

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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Frank Gigliotti, M.D.
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P R O C E E D I N G S

1
2 DR. MASUR [Presiding]: Good morning. I am Henry
3 Masur. I would like to call this meeting of the Antiviral
4 Drugs Advisory Committee meeting to order.

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

9 Jeff?

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

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

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

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

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

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

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

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

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

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

5 MS. STOVER: Rhonda Stover, FDA.

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

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

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

12 DR. ELASHOFF: Mike Elashoff, FDA.

13 DR. FLYER: Paul Flyer, FDA.

14 DR. CVETKOVICH: Therese Cvetkovich, FDA.

15 DR. KUKICH: Stanka Kukich, FDA.

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

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

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

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

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

8 In accordance with the provisions of 1896 Code
9 208(b), full waivers have been granted to Dr. Hamilton, Dr.
10 Masur, and Dr. Mathews. In addition, Dr. Bertino has been
11 granted full waiver under Section 505(n)(4) of the FD&C Act.

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

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

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

1 involving Ziagen. In the event that the discussions involve
2 any other products or firms not already on the agenda in
3 which an FDA participant has a financial interest, the
4 participants are aware of the need to exclude themselves
5 from such involvement, and their exclusion will be noted for
6 the record.

7 With respect to our other participants, we ask, in
8 the interest of fairness, that they address any current or
9 previous involvement with any firm whose products they may
10 wish to comment upon.

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

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

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

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

1 to meetings of this Advisory Committee in general.

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

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

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

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

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

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

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

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

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

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

1 and discussion and would be presented.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 Therefore, both the sponsor and the Division will

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

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

8 Thank you.

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

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

17 May I have the first slide, please?

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

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

1 hypersensitivity and will offer concluding comments.

2 Abacavir is the first new nucleoside reverse
3 transcriptase inhibitor to be considered by the FDA since
4 1995. It is a carbocyclic nucleoside analog, which is
5 activated to the triphosphate by a novel pathway. It's a
6 potent HIV reverse transcriptase inhibitor shown in man to
7 lead to the 1.6 to 2.1 log viral load reduction in multi-
8 dose mono-therapy trials over 12 weeks.

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

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

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

21 We have worked closely with the FDA over the
22 development program of Abacavir and listed here are the key
23 regulatory milestones. The IND was submitted in June of
24 1994. In January of 1997, an end-of-phase II meeting was
25 held with the Agency, and the following month, in a closed

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

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

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

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

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

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

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

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

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

9 It is worth taking a minute to discuss our
10 rationale for investigating triple therapy with
11 abacavir/3TC/zidovudine. Wherein, the potency of abacavir
12 was demonstrated in Phase I-II trials, we elected to try it
13 in combination with a dual nucleoside regimen of
14 3TC/zidovudine, just as we have done with drugs of other
15 classes and other sponsors have done with drugs of other
16 classes. In vitro abacavir is synergistic with zidovudine,
17 an additive with 3TC. It does not compete with 3TC or
18 zidovudine for activation by way of phosphorylation. Each
19 of these three drugs terminate DNA at different sites.

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

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

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

11 MR. LaFON: Thank you, Dr. Smiley.

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

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

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

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

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

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

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

1 ongoing at this time, no data available.

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

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

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

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

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

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

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

25 Indeed, we were pleased and surprised to find that

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

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

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

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

1 part of our submission. The first three trials on this list
2 our treatment-naive superiority trial in adults, 3003; our
3 treatment-experienced superiority trial in children, the
4 3006 trial; and our study in adults with AIDS-dementia
5 complex, 3001, were all submitted as part of our original
6 NDA package in June of this year.

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

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

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

25 This diagram summarizes the basic clinical design

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

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

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

25 Because of the results of that trial, we amended

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

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

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

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

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

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

10 On a separate as-treated analysis, the 86 percent
11 of patients on the triple group versus 43 percent of
12 patients on the double group had plasma HIV-RNA less than
13 400 copies per mL.

14 This next slide summarizes the results of the Week
15 24 study. As we indicated earlier, this was an unplanned
16 analysis that we worked closely with the FDA to be able to
17 supply.

18 As you can see from this trial, the patients
19 randomized originally to abacavir/3TC/zidovudine continued
20 to maintain their viral load response out through 24 weeks
21 of treatment. In addition, as you can see, there is an
22 upturn in those patients originally randomized to receive
23 3TC and zidovudine after Week 16 of treatment. This is
24 primarily due to the fact that most of these patients did
25 choose to switch to open-label abacavir/3TC/zidovudine.

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

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

13 We have looked at this very closely, done analysis
14 and worked with the FDA on subsequent analysis of this data.
15 We believe this is an anomalous result, and that it is
16 primary due to the fact that at Week 12 there is no
17 difference in the two treatment groups and, indeed, at Week
18 20 and 24 there is no difference in the two treatment
19 groups.

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

25 In conclusion from this study,

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

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

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

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

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

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

5 This study is an ongoing, randomized, double-blind
6 trial in which 205 treatment-experienced children received
7 either abacavir, 3TC, and zidovudine all in their liquid
8 formulation form or abacavir placebo in a combination with
9 3TC and zidovudine. Children were stratified at baseline by
10 age and by prior 3TC/zidovudine use. The primary end point
11 for this study is response of HIV RNA and CD4 cell counts.
12 However, in addition in the study, we are collecting
13 neuropsychological end points and development milestones.
14 While today this data is not available, it will be available
15 at the time of the 48-week analysis.

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

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

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

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

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

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

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

5 I want to make particular focus on this time point
6 for just a minute because I mentioned earlier the primary
7 efficacy analysis of the proportion of patients less than
8 10,000 copies per mL, at this time point, without adjusting
9 for baseline viral load, had a P value of .054. So
10 marginally statistically significant. However, when
11 baseline plasma HIV-RNA was accounted for in the statistical
12 analysis, the P value adjusted for that variable was .006.

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

17 This slide summarizes the CD4 cell response in the
18 two treatment groups. The patients who received abacavir,
19 zidovudine, and 3TC had a superior CD4 cell count rise over
20 24 weeks of treatment compared to those children who
21 received 3TC and zidovudine alone.

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

1 group.

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

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

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

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

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

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

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

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

1 Finally, as I mentioned earlier, we now are in a
2 position today to present preliminary results from our
3 study, our adult treatment-naive equivalence trial, our 3005
4 trial. I have mentioned earlier that this is an ongoing
5 study, and we have worked closely with both the Agency and
6 with the investigators to be able to present this today.
7 This is an ongoing, randomized, double-blind trial. 562
8 treatment-naive adults were randomized to either receive
9 abacavir, 3TC and zidovudine or indinavir, administered at
10 800 milligrams every eight hours, and 3TC and zidovudine.

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

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

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

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

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

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

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

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

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

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

6 Just to contrast this study with our 3003 trial,
7 the trial I presented earlier, these patients, in general,
8 had slightly higher plasma HIV-RNA at baseline, the 3003
9 median baseline, plasma HIV-RNA was approximately 4.5 logs
10 and, indeed, had lower CD4 cell counts at baseline, and the
11 3003 results median CD4 cell count were approximately 450.

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

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

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

1 below 400 copies per mL.

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

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

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

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

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

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

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

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

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

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

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

25 So, in conclusion, from our efficacy studies,

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

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

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

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

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

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

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

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

1 We also learned in clinical virology studies that
2 no single baseline RT mutation predicts a lack of response
3 to abacavir. And, indeed, this is especially true of the
4 184 mutation, which we have extensively studied.

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

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

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

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

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

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

1 abacavir, and I will cover both recognition and management.

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

7 Among those 723 patients, 578 have experienced
8 treatment with abacavir for at least 24 weeks and another
9 144 patients of these have been treated for a minimum of 48
10 weeks.

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

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

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

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

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

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

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

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

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

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

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

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

25 I would now like to turn to the treatment-

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

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

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

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

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

9 Again, the 3001 trial allows us to look at the
10 frequency of laboratory abnormalities among patients
11 receiving twice the dose of that received in the adult trial
12 3003. There are 49 patients in the abacavir arm and 50 in
13 the background arm. And, again, you will see for evidence
14 of bone marrow suppression, really, no difference between
15 the two treatment groups, no difference in elevation of
16 liver function tests across the groups, no difference in
17 elevations of CPK or amylase. Again, you do see elevation
18 of triviscerides [ph.]. We believe that this is related to
19 the background therapy, since the incidence is identical in
20 both the abacavir and in the placebo-receiving arm.

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

1 1997. At that time, we had safety data on only
2 approximately 200 patients.

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

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

18 Let's look only at the open-label program, since
19 this data was collected in a far more far-reaching manner
20 than the expanded access program. Again, we had just over
21 2,000 patients enrolled. Of those patients, we have follow-
22 up data available on 1,677 patients at the time that we
23 submitted our new drug application. 376 of those patients
24 have permanently discontinued. The most common reason was
25 an adverse event, and then there are a scattering of reasons

1 that you see below.

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

9 You will note the incidence of rashes appears at
10 15 percent. These patients were receiving broad categories
11 of therapies, multiple drugs, including non-nucleoside
12 reverse transcriptase inhibitors in approximately 40 percent
13 of the cases. This incidence, by the way, is identical to
14 the placebo arm in one of the early zidovudine control
15 trials. So we do not believe that that 15 percent is
16 particularly unusual.

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

1 368, and the pediatric and AIDS dementia expanded access
2 programs, which were far smaller than the major expanded
3 access program.

4 What you will see is that, during the randomized
5 phase for all of our Phase 2 and 3 studies, there were an
6 equal number of deaths that occurred in the abacavir and in
7 the control arms. I want to point that one patient in the
8 3005 trial did die of an abacavir-related hypersensitivity
9 reaction upon rechallenge of the drug, and I will give you
10 more details on that in a little bit.

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

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

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

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

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

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

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

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

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

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

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

25 So what are the symptoms and signs of abacavir

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

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

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

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

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

6 Let's look at the time to onset of abacavir
7 hypersensitivity because this is very useful. Again, I am
8 showing you the definite cases. We have times recorded for
9 27 of those, and among the probable cases, 67 have the time
10 of onset noted.

11 All of the definitive cases occurred within the
12 first five to six weeks of therapy. Similarly, you see the
13 vast majority of probable cases occurring in that time
14 frame. The median time to onset for all of these cases is
15 11 days.

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

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

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

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

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

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

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

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

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

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

4 Secondly, stopping abacavir leads to a very rapid
5 resolution in the hypersensitivity symptoms, and this is
6 quite remarkable how much improved these patients are within
7 24 to 48 hours. Restarting abacavir after stopping for a
8 hypersensitivity reaction may lead to more severe and
9 potentially life-threatening events, including death,
10 associated with a recurrence of a hypersensitivity reaction.

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

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

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

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

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

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

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

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

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

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

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

4 There are no dietary restrictions for the use of
5 abacavir, and it's been shown in preliminary data from the
6 3005 trial suggests that the triple nucleoside reverse
7 transcriptase inhibitor combination strategy may be
8 reasonable for some patients.

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

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

20 Thank you very much. That ends our presentation.

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

25 DR. GIGLIOTTI: No.

1 DR. MASUR: Nothing. Ron?

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

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

11 DR. YUEN: There were three.

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

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

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

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

1 identify yourself.

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

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

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

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

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

1 because otherwise I think we are comparing mono-therapy.

2 MR. LaFON: There were more than two years of
3 prior treatment with anti-retroviral therapy, not
4 necessarily 3TC and, actually, we did look--actually, more
5 than 80 percent of the patients had received 3TC, and I
6 think more than 50 percent had received--I am sorry, had
7 received zidovudine and more than 50 percent had received
8 3TC.

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

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

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

23 DR. MASUR: Pam?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 pretty much the same. Maybe I misunderstood you.

2 DR. DIAZ: Just rash.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 His past medical history is also notable for
17 aortic cyanosis and he was an IV drug user. In June of
18 1998, approximately four months after starting his abacavir
19 he develops shortness of breath, cough, fever, and chills.
20 And he's taken to the emergency room where his temperature
21 is 101.4. His blood pressure is 138 over 54 and in a
22 previous clinic note it is reported as being 128 over 77.
23 His respiratory rate is 46 and he's anxious, he's
24 disoriented and there is no rash. His chest X-ray shows
25 bilateral infiltrates, and a white blood cell count of

1 29,000.

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

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

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

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

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

23 So--

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

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

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

10 His medical history is significant for IV drug use
11 and hepatitis A, B and C. He developed PCP in February of
12 1998 and he also had a rise in viral load which led to a
13 switch in his treatment to abacavir, d4T, ddI, hydroxyurea,
14 saquinavir, and ritonavir in March of 1998.

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

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

25 Now, what's unusual about this case for

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

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

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

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

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

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

1 DR. HEATHERINGTON: Okay.

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

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

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

19 Two days later her SGOT and SGPT increased. She
20 is transferred to hospice care and she expires on March
21 13th. This patient did have an autopsy. The examination of
22 the liver showed central lobular necrosis but no
23 inflammation, no ise infiltration. The spleen had infarcs.
24 The lungs showed bronchial pneumonia with micro-colonies of
25 organisms found on microscopic examination.

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

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

12 DR. POMERANTZ: What was in those bone lesions?

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

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

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

25 There was a confirmed diagnosis of C-dificile

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

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

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

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

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

1 together really hold together a picture of abacavir
2 hypersensitivity reaction.

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

8 CNB retinitis in November of 1997. Neutropenia,
9 pneumococcal sepsis, and he's receiving foscarnet
10 intravenously for his CNB retinitis. His abacavir was
11 initiated as a part of the open label program in October of
12 1997, along with d4T, 3TC, and nelfinavir.

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

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

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

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

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

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

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

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

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

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

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

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

17 Yes, Dr. Pomerantz?

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

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

23 DR. POMERANTZ: Yes, sorry.

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

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

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

6 DR. POMERANTZ: But he never had an LP?

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

11 DR. POMERANTZ: Okay.

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

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

17 Let's go on to the next case. This is a 25-year
18 old female with AIDS who is receiving abacavir, ddI and
19 nelfinavir beginning in October of 1997. Approximately two
20 months later she is admitted to the hospital with a history
21 of progressive fever, shortness of breath, cough and nausea.
22 Her ABG shows a PH of 7.16 with a PCO2 of 26 and a PO2 of
23 64. She was intubated and received ventilatory support.
24 Treated with vancomycin, santazomine, doxycycline,
25 pentamidine, and steroids; the latter two for presumed

1 pneumocystis carinii pneumonia.

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

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

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

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

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

3 DR. MASUR: Pam, other issues?

4 DR. DIAZ: No.

5 DR. MASUR: Okay.

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

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

10 DR. HEATHERINGTON: That's true.

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

12 DR. HEATHERINGTON: That's true.

13 DR. EL-SADIR: Okay.

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

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

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

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

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

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

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

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

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

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

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

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

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

21 MR. LAFON: We have no data, no.

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

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

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

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

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

14 DR. HEATHERINGTON: No, there's not.

15 DR. MASUR: And lipid abnormalities?

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

22 DR. MASUR: But in the other studies--

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

25 DR. MASUR: Okay.

1 DR. LIPSKY: Thank you.

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

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

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

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

1 decreased glucoronization in neonates with this drug?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 DR. HEATHERINGTON: That's exactly true.

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

15 DR. HEATHERINGTON: Thirty that we have presented
16 today.

17 DR. LIPSKY: Thank you.

18 DR. MASUR: Roger?

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

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

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

4 Do you have that data?

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

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

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

22 DR. POMERANTZ: You don't?

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

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

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

8 DR. POMERANTZ: Thanks.

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

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

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

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

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

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

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

16 DR. POMERANTZ: Interesting.

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

1 well in quiescent cell types?

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

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

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

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

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

25 The data on hydroxy urea and abacavir is really

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

6 DR. POMERANTZ: Thank you.

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

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

11 DR. MASUR: John?

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

14 DR. MASUR: We are.

15 DR. HAMILTON: Will we have another chance?

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

19 DR. HAMILTON: Okay.

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

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

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

6 Am I correct in that assumption?

7 DR. HEATHERINGTON: No. Actually all these were
8 very advanced disease patients. Because they were all
9 enrolled in the expanded access orphan label program. And
10 even the cases in the--I don't think there were any cases in
11 time frame where they were actually started in the expanded
12 access. So, they would have been under the more stringent
13 criteria of open label. That is viral load greater than
14 30,000 and CD4 count below 100 and having failed prior
15 therapy with at least one protease inhibitor.

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

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

23 DR. HEATHERINGTON: Well, I think just to clarify.
24 The one death which was in a rechallenge was actually in the
25 3005 study. And as I had mentioned in the presentation that

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

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

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

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

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

25 In spite of that fact, the principal of use of

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

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

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

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

1 nucleoside RTs.

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

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

10 DR. MASUR: John? Other questions?

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

12 DR. MASUR: All right.

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

16 So, we will take a 10-minute break.

17 [Recess.]

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

19 DR. MATTHEWS: Okay.

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

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

3 Could you comment on that?

4 MR. LAFON: I would be happy to.

5 That study was designed so that after four weeks
6 of treatment patients were getting an inadequate response to
7 change therapy. And, indeed, as I showed on the slide, 25
8 percent of patients in both of the two high-dose arms, the
9 300 milligrams twice a day and the 600 milligrams twice a
10 day, discontinued the study.

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

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

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

1 equivocal when you looked across studies but it did suggest
2 that the higher dose was, indeed, less tolerated than the
3 300 milligrams BID dose.

4 DR. MATTHEWS: Thanks.

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

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

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

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

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

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

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

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

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

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

1 question.

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

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

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

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

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

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

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

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

20 DR. MASUR: Brian?

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

1 the rechallenge was positive.

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

7 DR. HEATHERINGTON: All right.

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

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

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

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

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

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

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

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

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

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

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

25 We have actually conducted a number of studies

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

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

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

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

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

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

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

13 Our first study we attempted in a small pilot
14 study--this is the study I was referring to in my talk--to
15 evaluate adding abacavir to patients who have been on six to
16 12 months of either zidovudine, 3TC zidovudine, ddI or D4T.
17 And abacavir was added to these patients and the medium
18 plasma HIV-R in any of the groups were monitored. And we
19 saw a very good response in most of the populations with one
20 and a half to even almost two load drops in viral load when
21 added to D4T specifically.

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

1 if no response at all.

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

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

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

25 And, indeed, the median baseline viral load in the

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

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

11 Caring our observations further, I mention in the
12 two previous trials that actually this is the 3003 study
13 which we mentioned earlier when at 16 weeks patients were
14 allowed to change their therapy to open label, abacavir and
15 3TC. So, indeed, patients on the 3TC, zidovudine group
16 while they had an initial good response, they had a rebound
17 in their treatment. And, indeed, most of these patients, I
18 showed you the slide earlier, had switched to abacavir, 3TC,
19 zidovudine. They had a concomitant drop back in their
20 median viral load back to approaching and at the levels that
21 were seen from the patients originally on abacavir, 3TC, and
22 zidovudine and that response was maintained.

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

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

13 When abacavir was added, we saw a very good
14 response by week 8 and week 16 in these patients that these
15 differences are not statistically significant and indicate
16 that patients regardless of whether they have a 184M or a
17 184V actually have a very good response to abacavir therapy,
18 at least, short-term, after short-term exposure to AZT and
19 3TC.

20 Briefly we have done collaborative studies in
21 which we evaluated abacavir as part of an additional
22 treatment regimens for patients who have already failed
23 prior therapy. Of note are a couple of studies. One, ACTG-
24 372-B, which I mentioned earlier, was a roll-over study of
25 patients who had been on the ACTG-320 trial and specifically

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

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

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

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

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

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

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

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

1 low viral load, and non-nucleoside naive.

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

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

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

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

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

4 Our findings, our general conclusions from this
5 set of studies is that in vitro and clinical data indicate
6 diminished activity of some nucleoside pre-treated subjects
7 to abacavir. Long-term exposure to nucleoside RTs which can
8 lead to 3 or more zidovudine mutations, with or without a
9 184 mutation, is clearly associated with a poor virological
10 response. However, short-term prior therapy even to 3TC and
11 zidovudine and a lesser number of NRTM mutations seems to be
12 associated with a better virological response to abacavir
13 therapy.

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

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

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

3 DR. MASUR: All right.

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

7 [Laughter.]

8 DR. POMERANTZ: Never mind.

9 DR. MASUR: Go ahead, Roger.

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

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

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

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

1 does show a resisted virus.

2 DR. POMERANTZ: How high?

3 MR. LAFON: Plus CDB mutations. That's why we
4 need Dr. Lanier up here. So, the constellation of CDB
5 mutations and the 69 insertion. I just misspoke. It is the
6 69 insertion plus the zidovudine mutations that can result
7 in a resistant virus and how high.

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

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

15 And very similar to the 151 constellation of
16 mutations.

17 DR. POMERANTZ: That holds for abacavir as well?

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

20 DR. POMERANTZ: Yes. Thanks.

21 DR. MASUR: Okay. Dr. Woolson?

22 DR. WOOLSON: Thank you.

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

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

6 DR. HEATHERINGTON: Right.

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

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

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

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

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

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

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

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

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

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

13 As far as the less than 10,000 or greater than
14 10,000, that wasn't a pre-stratification, first of all, that
15 was a post-study finding. When we looked at the proportion
16 of patients who dropped below 10,000, indeed, those who were
17 below 10,000 approximately 90 percent in both treatment
18 groups stayed below 10,000 through the 16 weeks of
19 treatment.

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

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

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

4 DR. WOOLSON: Okay. Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. MASUR: Other questions?

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

1 included in the traditional application.

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

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

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

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

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

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

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

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

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

1 a virological event.

2 But once they've met the switch criteria, they've
3 indeed met an endpoint. Indeed, we will also do in the
4 analysis the proportion of patients who are below the cutoff
5 limits defined in the protocol at week 48. For 3005, it's a
6 different endpoint. It's the proportion of patients at week
7 48 in the blinded study whose viral load remains below 400
8 copies. So we'll, of course, do the secondary analysis,
9 time to virological event, but the primary analysis for that
10 study is proportion of patients less than 400 copies at week
11 48.

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

19 MR. LaFON: Yes.

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

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

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

5 DR. HOGAN: I think I didn't really phrase my
6 question correctly. Let me just ask it this way: If a
7 person meets HIV--they meet the RNA less than 400 criteria,
8 and they're on the ZDV/3TC arm, so now they're less than
9 400, are they then allowed to switch after week 16 to the
10 ABC arm?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Now I'll ask Dr. Cutrell to come in and talk about
23 some--

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

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

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

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

11 MR. LaFON: There is no specific algorithm beyond-

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

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

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

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

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

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

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

17 MR. LaFON: Sure.

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

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

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

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

10 DR. CUTRELL: Yes.

11 DR. HOGAN: Okay. I have just two or three more
12 questions. I know it's kind of running along, but one more
13 about the statistical comparison in the pediatric study, and
14 this kind of follows up Dr. Woolson's questions. That is,
15 in the pediatric comparison, the decision was made to
16 stratify on less than 10,000 viral load or greater than
17 10,000 viral load, and the comparison of proportion of
18 children attaining less than 10,000 viral load at week 16.
19 Is that--

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

21 DR. HOGAN: Oh, I'm sorry.

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

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

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

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

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

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

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

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

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

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

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

12 DR. CUTRELL: I think there are a few things going
13 on to derive the p value to present such different results.
14 It is a complicated story, and what you said is true. If
15 you look at the patients who entered with viral load below
16 10,000 copies, the effect was essentially the same in the
17 two treatment groups: 89 percent in one group versus 88
18 percent in the other.

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

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

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

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

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

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

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

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

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

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

11 DR. HOGAN: Thank you very much.

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

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

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

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

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

1 There were no findings in rabbits.

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

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

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

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

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

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

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

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

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

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

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

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

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

4 We have looked at the effect of gender in terms of
5 pharmacokinetics, and it's an ongoing trial. Let me see if
6 I can find the slide. Yes, BE-21. These are relatively
7 small numbers. In the 2001 trial, we observed a difference
8 in women who had--and these women had higher exposures than
9 men, even correcting for weight. They had a Cmax that was
10 30 percent higher and an AUC that was 54 percent higher.
11 Given the safety profile for abacavir, we do not feel that
12 these differences are clinically significant.

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

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

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

1 gender with regard to either efficacy or safety parameters
2 measured.

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

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

9 DR. BERTINO: The same question for ethnic
10 differences.

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

15 DR. MASUR: Okay. Jeff?

16 MR. BLOOM: Thanks, Henry.

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

1 in naive patients?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 When I did that, I had truly nearly reached the
8 end of my ability to tolerate the daily nausea that I
9 experienced, the numbness of mouth, numbness of tongue,
10 lips, my teeth actually hurt every day just--if you've ever
11 been coming down with a cold and the cold gets into your
12 teeth, well, that's how my teeth felt every day. And after
13 14 months of that, I had really gotten to the point where I
14 just didn't think I could continue that regimen, although I
15 didn't seem to have any other place to go.

16 I've been aware of Ziagen since it was known as
17 1592, and I was concerned early on that when it became
18 available, there will be very little data available to me or
19 my physician about its possible efficacy in patients like
20 myself. So I must tell you that I am indeed very grateful
21 that my doctor had data available on Ziagen as applied to
22 experienced patients to help us support the decision for a
23 need to replace my protease inhibitors with this new drug.
24 And I truly believe that it's important for FDA to continue
25 to encourage companies to gather this kind of data so that

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

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

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

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

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

1 my quality of life.

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

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

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

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

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

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

1 3TC, and a protease inhibitor is premature, and to price it
2 in the same range is outrageous. And our greatest hope for
3 the drug is that this would be helping patients with more
4 experience, drug experience, and the data doesn't show that
5 this drug is that much better either. So although Act Up
6 Golden Gate supports the approval of the drug eventually,
7 I'm not sure there's compelling evidence that was presented
8 today for an accelerated approval of this drug. But we do
9 support the drug, and hopefully they will give us some more
10 data with other drugs from other companies, not just their
11 own. It seems that abacavir, AZT, 3TC, all owned by Glaxo
12 Wellcome, was a convenient drug combination to test, and
13 unfortunately, they haven't looked at the real-world issues,
14 and ignored the real-world use of the drugs.

15 Thanks.

16 DR. MASUR: Thank you for your perspective.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 [Luncheon recess.]

AFTERNOON SESSION

[1:17 p.m.]

1
2
3 DR. MASUDA: Again, I apologize for being off
4 schedule. There are a number of committee members who have
5 early planes to catch, so we are going to try to move
6 expeditiously. And as I mentioned before, if any of the
7 three people who made statements at the open public hearing
8 wants to have a follow-up after the agency presentation, if
9 they'll let Rhonda Stover know, we'd be happy to provide
10 them that opportunity.

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

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

15 Good afternoon. Welcome back. I'm Therese
16 Cvetkovich, the medical reviewer for this application, NDA
17 20-977 for abacavir sulfate. The FDA presentation will
18 focus on our analysis of the efficacy and safety of abacavir
19 for the treatment of HIV infection.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 and 20 percent of subjects started below 10,000 copies.
2 Thus, the response rates, 12 percent on the abacavir arm and
3 2 percent on the control arm, are quite low. Further,
4 examination of the subjects who were responders at week 16
5 revealed that about half of them had started below 1,000
6 copies at baseline.

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

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

22 I'll now turn to the adult naive study, 3003.
23 This compared the same treatment combinations as the
24 pediatric study. While designed as a 48-week study, after
25 16 weeks subjects were given the option of receiving open-

1 label triple therapy. Most subjects availed themselves of
2 this option. In particular, this included subjects from
3 both arms who were being successfully suppressed to below
4 400 RNA copies. Since most subjects in the two arms were
5 receiving the same treatment after 16 weeks, we will be
6 focusing on the 16-week time point as the most important for
7 assessing relative efficacy.

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

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

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

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

1 data shortly.

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

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

17 The first baseline factor we examined was the one
18 used to stratify the study. There were three strata of
19 baseline RNA: less than 10,000 copies, between 10,000 and
20 100,000 copies, and greater than 100,000 copies. You can
21 see that as you move from the low baseline RNA values to the
22 high baseline RNA values, CD4 responses increase in both
23 groups. However, the difference between the groups was
24 essentially constant across each of the three strata.
25 Similar analyses subset the results by baseline CD4, gender,

1 and race, as seen in the next figure.

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

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

16 As noted before, missing data was roughly uniform
17 between the groups, with 13 subjects on the control arm and
18 9 subjects on the abacavir arm having missing CD4
19 measurements at week 16. To investigate the potential
20 impact these missing values may have had, we looked at the
21 last CD4 measurement prior to week 16 for the subjects who
22 had dropped out. You can see that subjects with missing 16-
23 week CD4 data, this slide here, tended to have smaller
24 increases than those with observed data, minus 19 compared
25 to 47, and 46 compared to 113. However, again, we see that

1 the differential between the arms is fairly similar.

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

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

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

22 After identifying the concerns raised by Study
23 3003, we asked the applicant for an early look at the
24 results from their ongoing equivalence study, 3005. This
25 study was deemed to be relevant to potentially address the

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

4 Recently, the applicant provided a summary report
5 and a preliminary data set. This data set includes CD4 and
6 HIV-RNA data, but does not yet include many things that are
7 necessary for a complete analysis, such as demographic
8 variables, center, and concomitant antiretroviral therapy.
9 Given this, we must not view the preliminary analysis of
10 3005 as definitive.

11 Although many subjects had data to week 20 or 24,
12 due to the preliminary nature of the data it was not
13 possible to determine the disposition of all patients past
14 16 weeks. For this reason, we will focus on the week 16
15 results.

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

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

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

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

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

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

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

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

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

25 ACTG 368 is our first look in a large study at

1 abacavir in a combination other than with ZDV/3TC. This is
2 a placebo-controlled study of abacavir, indinavir, and
3 efavirenz versus indinavir and efavirenz. The study design
4 and sample size are comparable to the principal studies from
5 this application. The preliminary ACTG analysis identified
6 no difference between the abacavir- and placebo-containing
7 arms for the proportion reaching the failure endpoint at
8 week 16, 27 percent versus 31 percent, p value 0.43. There
9 was also no difference identified for CD4, 59 cells versus
10 60 cells.

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

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

1 this assessment of efficacy for this population.

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

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

10 DR. CVETKOVICH: Thank you.

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

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

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

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

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

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

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

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

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

25 Our review of the preliminary data submitted from

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

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

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

25 Importantly, the applicant followed through with

1 their commitment to pediatrics and conducted one of their
2 Phase 3 studies of abacavir in the pediatric population. We
3 believe that this study contributes much to the NDA. Just
4 as efficacy results in HIV-infected adults apply to
5 children, likewise we conclude that these results in
6 pediatrics apply to adults. The apparent lack of a
7 clinically meaningful effect in these heavily pretreated
8 children can reasonably be generalized in the adult
9 population for extensively nucleoside analogue experienced
10 and is, in fact, supported by other studies in adults and
11 children.

12 In addition, this study demonstrates that it is
13 feasible to conduct Phase 3 studies in the HIV-infected
14 pediatric population, and we encourage other sponsors and
15 applicants to view this approach as one that the agency
16 regards favorably.

17 The 12-week results from the study in subjects
18 with AIDS dementia did not support efficacy for this
19 indication, and the applicant has not sought an indication.

20 We believe that studies of resistance have
21 implications for both safety and efficacy. I would like to
22 review our conclusions about the resistance studies
23 submitted to the abacavir NDA.

24 The applicant has submitted results of both
25 preclinical and clinical virologic studies evaluating the

1 development of resistance to abacavir. We have drawn the
2 following conclusions regarding these data:

3 First, the mutations detected in cell cultures
4 were also observed in HIV isolates from abacavir-treated
5 patients.

6 Second, that the multiple reverse transcriptase
7 mutations detected in nucleoside inhibitor experienced
8 patients' isolates may affect abacavir efficacy.

9 And, finally, that the correlation of a particular
10 mutation or mutations with the loss of abacavir activity has
11 not been established.

12 The results of several Phase 1 and 2 studies laid
13 the groundwork for the clinical observation that nucleoside
14 experienced patients may be unlikely to respond to abacavir.
15 However, at this time we do not have adequate data derived
16 from clinical isolates with which to make clinical
17 correlations.

18 DR. CVETKOVICH: I would now like to turn to our
19 review of the safety database. Our review of the safety
20 profile of abacavir will address stats, hypersensitivity,
21 other clinical adverse events, and laboratory abnormalities
22 associated with abacavir treatment.

23 As of the cutoff date in July 1998, the applicant
24 reports that approximately 7,900 patients are included in
25 the safety database for deaths and serious adverse events,

1 and that 149 deaths have occurred among all subjects in
2 studies of abacavir. The majority of the deaths have
3 occurred in the expanded access study; in the rest, 14
4 deaths have occurred in the Phase II and III studies.

5 While no imbalances in deaths between treatment
6 arms in these studies were noted, the numbers are too small
7 to evaluate either the benefits of treatment or risk from
8 adverse events. With the exceptions of deaths potentially
9 related to hypersensitivity that I will discuss, these
10 deaths have been primarily related to the subjects'
11 underlying HIV infection.

12 The most serious adverse event that has been
13 associated with abacavir treatment has been a
14 hypersensitivity reaction. These reactions were noted early
15 in the development of abacavir. Though the constellation of
16 symptoms associated with this reaction appear recognizable,
17 considerable overlap with multiple common syndromes in HIV-
18 infected patients will be evident.

19 The most common presentation of abacavir
20 hypersensitivity reactions have included the symptoms of
21 fever, rash, malaise, and GI symptoms such as nausea and
22 vomiting. Myalgia, arthralgia, and paresthesia are also
23 reported, but somewhat less commonly. If the reaction is
24 not recognized and dosing continues, symptoms both
25 accumulate and worsen. More severe reactions have included

1 anaphylaxis, hypotension, respiratory symptoms, liver
2 failure, and renal failure.

3 Soon after these reactions were identified, it
4 became apparent that re-challenge was associated with the
5 rapid return of symptoms, and that the symptoms after re-
6 challenge were much more severe. While the majority of
7 reactions occur early in therapy, it should be noted that
8 some have occurred after many months of treatment.

9 Laboratory abnormalities associated with these
10 reactions have included increased liver function tests,
11 elevations of creatine phosphokinase and serum creatinine,
12 as well as neutropenia and lymphopenia.

13 I will now present two cases taken from the
14 serious adverse event case narratives that represent fairly
15 typical hypersensitivity reactions. The first case is of a
16 42-year-old white male who has a history of rash allergies
17 to sulfa and nevirapine. He was treated with abacavir, 300
18 milligrams b.i.d.

19 Five days after initiating study treatment, the
20 patient developed symptoms of upper respiratory infection
21 and fever. Abacavir was temporarily interrupted and the
22 event resolved over five days. When abacavir was restarted,
23 the following day he developed fever and rash. One day
24 later he was hospitalized when he was noted to be weak,
25 lethargic, and febrile to 102 degrees.

1 On admission to the hospital, he was hypotensive
2 and had a low urinary output. Subsequently he developed
3 renal failure and progressive respiratory failure. The
4 event was diagnosed as anaphylaxis. Laboratory tests
5 performed at admission revealed an elevated creatine
6 phosphokinase. Abacavir was discontinued and he was treated
7 with intravenous vasopressors and required intubation. The
8 respiratory distress resolved over five days, and the acute
9 renal failure and elevated CPK level resolved over three
10 weeks.

11 Case two: This 43-year-old white male had a
12 history of Pneumocystis pneumonia and previous hepatitis B
13 infection. He was treated with abacavir, 300 milligrams
14 b.i.d. Concurrent medications included delavirdine,
15 trimethoprim sulfa, fluconazole, azithromycin, diazepam,
16 alprazolam, and amitriptyline.

17 Two weeks after initiating study treatment, he was
18 hospitalized when he developed a fever of 105 degrees,
19 nausea, diarrhea, weakness, and abnormal liver function
20 tests. Abacavir was interrupted, along with delavirdine and
21 most of his other medications. His condition gradually
22 improved, and the fever resolved over a four-day period.

23 He was discharged from the hospital and resumed
24 use of all medications except delavirdine and abacavir. One
25 week later he was re-challenged with one dose of abacavir.

1 Approximately one hour after re-challenge, he developed
2 hypotension, nausea, vomiting, and a generalized pruritic
3 erythematous rash. His condition continued to deteriorate
4 and he subsequently presented in the emergency room with a
5 blood pressure of 60/40. On evaluation, azotemia,
6 hepatitis, and hyperkalemia were also detected.

7 Abacavir was discontinued and the patient's
8 condition was stabilized in the medical intensive care with
9 dopamine therapy and aggressive intravenous hydration,
10 diphenhydramine, and steroids. The patient was diagnosed
11 with a probable severe allergic drug reaction which resolved
12 over eight days.

13 These cases illustrate the potential difficulty in
14 making the initial diagnosis, the severity of the reactions,
15 increased severity after re-challenge, as well as the
16 potential reversibility of the events.

17 To date, the applicant has reported that
18 approximately 3 percent of patients in clinical trials of
19 abacavir have been recognized to develop these reactions.
20 Due to the nature of the safety reporting, at this time we
21 do not have complete access to the safety database used by
22 the applicant to define the incidence of hypersensitivity
23 reactions. Therefore, we have been unable to verify the
24 incidence reported by the applicant. In addition, we are
25 unable to identify potentially important risk factors such

1 as association of these reactions with gender, race, degree
2 of immunosuppression, or other important medical history.

3 As indicated in the applicant's presentation, we
4 have identified eight cases of deaths that we view as
5 potentially associated with hypersensitivity reactions.
6 These cases were identified from our review of all the
7 serious adverse event case narratives submitted to the NDA
8 and safety updates. We included a death as potentially
9 associated by virtue of either the identification of
10 characteristic signs, symptoms, and clinical course, or
11 investigator designation of the death as a potential case of
12 hypersensitivity. Six of these deaths took place in
13 patients enrolled in Study 3008, the expanded access
14 program. Two of the deaths occurred after re-challenge.

15 We believe that identification of these
16 potentially related deaths are useful in demonstrating the
17 uncertainties in attribution while underscoring the
18 potential severity of outcomes.

19 When increased severity of these reactions upon
20 re-challenge was detected in October of 1997, investigators
21 were informed about the importance of avoiding re-challenge.
22 Wallet cards were provided to subjects in abacavir studies
23 that described the common symptoms of hypersensitivity
24 related to abacavir treatment, instructions for seeking
25 care, and the potential for fatal reactions. In addition,

1 the agency requested increased reporting of these events and
2 that all potential cases of hypersensitivity be reported as
3 serious adverse events. As the review progresses, we are
4 working with the applicant to explore ways to effectively
5 disseminate this important safety information to patients
6 and practitioners.

7 Other adverse events more frequently associated
8 with abacavir treatment in the Phase III trials have
9 included nausea and vomiting, headache, and malaise or
10 fatigue. The majority of these reports have been Grade 1 or
11 2, and few of the events have resulted in treatment
12 discontinuation.

13 In all three Phase III studies, mild elevations of
14 blood glucose were more frequently in subjects on abacavir-
15 containing arms. Increased ALT, CPK, or triglyceride levels
16 were associated with abacavir arms, each one of them in one
17 of the Phase III studies.

18 It should be noted that distinguishing adverse
19 events associated with abacavir therapy in these studies is
20 complicated by the use in combination of abacavir with other
21 nucleoside analogs, as well as the comparison to nucleoside
22 analogs.

23 Now I would like to summarize our conclusions
24 about the safety and efficacy of abacavir. A
25 hypersensitivity reaction to abacavir was identified in

1 clinical trials as the most serious adverse event associated
2 with its use. Because it is impossible to predict the
3 occurrence of this reaction, and because prompt recognition
4 and discontinuation of abacavir are of paramount importance
5 to patient outcome, it will require a major commitment by
6 the applicant to disseminate this safety information to the
7 community of providers and patients. How this is
8 accomplished will be critical for the safe use of this
9 product.

10 The long-term adverse event profile of abacavir
11 remains to be determined. In the short term, it appears
12 that the surrogate marker changes seen in the clinical
13 trials that we have presented support the antiviral efficacy
14 of abacavir. Long-term efficacy, that is, durability of the
15 antiviral response or effect on clinical outcomes, is
16 unknown.

17 This afternoon, in addition to your thoughts on
18 the safety and efficacy of abacavir for the treatment of
19 patients with HIV infection, we will ask for your advice on
20 some of the following unresolved issues: the triple
21 nucleoside combination; the risk/benefit ratio of abacavir
22 in clinical use; the overlap in toxicity profile with other
23 antiretroviral agents; as well as the adequacy of the
24 applicant's traditional approval proposal.

25 Given the agents currently available to treat HIV

1 infection, we recognize that it is not always possible to
2 achieve the goals of providing potent combinations that
3 utilize more than one molecular target and mechanism of
4 action, as well as having toxicity profiles and resistance
5 patterns that do not overlap. However, it is not clear
6 whether the combination of three nucleoside analogs
7 represents appropriate therapy, and if so, for what
8 population this would represent a reasonable combination.

9 How this agent will be utilized in clinical
10 practice of course is yet to be determined. We have to date
11 very little information on its use in combinations other
12 than with zidovudine and lamivudine. In addition, we do not
13 know what the implications for future treatment with
14 lamivudine and didanosine will be, given the known
15 overlapping resistance patterns with abacavir. It appears
16 that treatment-experienced patients have very limited
17 responses to abacavir, though this is the group for whom new
18 agents are particularly needed. And, finally, the balance
19 of risk versus benefit, given what is known about
20 hypersensitivity to abacavir, is not known.

21 As a practical issue, the management of patients
22 who developed rash while being treated with combinations of
23 antiretroviral agents, each of which may cause rash, is also
24 of interest. It seems unlikely that a rash associated with
25 hypersensitivity to abacavir and a rash associated with

1 other antiretroviral agents will be easily distinguished,
2 though the outcomes for each of these may be quite
3 different.

4 And, finally, the results of adequate and well-
5 controlled studies confirming clinical benefit are required
6 for traditional approval. The division recommends that the
7 applicant have at least two adequate and well-controlled
8 studies that will provide 48-week durability data underway
9 at the time of accelerated approval.

10 Given these requirements, we are concerned about
11 the adequacy of the applicant's proposal for traditional
12 approval. The adult/naive study, 3003, because the majority
13 of subjects on the comparator arm switched to open label
14 therapy after 16 weeks, will not provide 48-week durability
15 data. In the pediatric study, because a very low response
16 rate at 24 weeks has already been identified, it does not
17 seem likely that this study will provide 48-week results
18 supportive of the durability of effect.

19 Therefore, we can identify a single study, the
20 adult equivalence trial, 3005, that appears likely to
21 provide controlled, blinded durability results, and so have
22 recommended that the applicant consider initiation of
23 another study to support traditional approval.

24 In conclusion, we appreciate the opportunity to
25 provide our perspective on this application. We believe

1 that open discussion of these issues will be useful to both
2 the applicant and to us. We look forward to your comments
3 and your recommendations. Thanks.

4 DR. MASUR: Thank you. While you're at the
5 podium, are there questions from committee members or
6 advisors on the agency presentation?

7 Dr. Kweder, do you have any comments for Professor
8 Jolson? Jim?

9 DR. LIPSKY: I'm just slightly confused. On the
10 summary slide when you talked about, you know, the safety
11 and efficacy, about the sixth one back, I guess, from the
12 end, you said short-term surrogate marker changes support
13 antiviral efficacy, yet it seemed to be the flavor of the
14 earlier part of the talk that you were saying that that
15 wasn't the case. Would you clarify? The statistical
16 analysis was giving a strong overtone that you weren't
17 supporting efficacy on the surrogate markers, and your
18 concluding side said yes. Which is it?

19 DR. CVETKOVICH: I think that, you know, the
20 discussion reflects what we have gone through in trying to
21 figure out what the CD4 results from 3003 meant, and we did
22 spend quite a bit of time trying to tease this out. And I
23 think our conclusion was that we really needed more data to
24 come to any conclusion, and that we felt somewhat reassured,
25 not completely but somewhat reassured, after we saw the

1 results of 3005.

2 So I think that the presentation probably
3 reflected our concern, particularly given the fact that for
4 quite some time we had no other data to look at, and that
5 the results of 3005 really have only been very recently
6 received. So in a way it's a work in progress, and our
7 thoughts are certainly--we're certainly open to your
8 thoughts on this whole issue.

9 DR. LIPSKY: Okay.

10 DR. MASUR: Dr. Elashoff?

11 DR. ELASHOFF: Yes. I think in naive, the naive
12 population, there was antiviral activity as evidenced by HIV
13 RNA. However, the net efficacy is pretty hard to determine,
14 since CD4 and RNA are both surrogate markers, and how you
15 weigh those, I'm not quite sure. I think it was pretty
16 clear in treatment-experienced patients, from all of the
17 studies we looked at, there was consistently no effect.

18 DR. MASUR: I guess one of the issues, I guess
19 this wouldn't have come to a committee presentation if this
20 were all completely straightforward.

21 Let me ask one procedural issue of Dr. Jolson.
22 One of the first questions that we will get to has to do
23 with whether or not the data are sufficient to support
24 accelerated approval, and yet there are a variety of
25 criteria that have been described for accelerated approval.

1 One is that there be sufficient studies in place for
2 traditional approval.

3 If a committee member were not convinced that
4 there was more than one study in place that would provide
5 such data, can the committee vote in favor of approval, or
6 would there have to be a study already underway?

7 DR. JOLSON: Well, I think that there's some
8 flexibility there. In the past we've heard from this
9 committee a strong mandate that there be two adequate and
10 well-controlled studies, reasonably likely to demonstrate
11 clinical benefit, that are already approved at the time that
12 a product is approved. And that has been in the past
13 because of concern that once a product is approved, it may
14 be less enticing for patients to enroll in the study if the
15 product is readily available. That was, at least initially,
16 historically the concern.

17 I think for this particular committee, if you felt
18 that on balance that you were in favor of approval, but felt
19 that the traditional approval package was less than
20 adequate, that you could provide a recommendation for--that
21 the sponsor conduct an additional study, and you could
22 additionally use it as an opportunity to say what other
23 questions could an additional study answer that you feel
24 aren't addressed in the current package.

25 DR. YOGEV: Just maybe comment about the 10,000

1 viral load that it seems like that you don't like. This
2 number is coming from other pediatric studies that suggested
3 that less than 10,000 within about four and a half years,
4 and a good average age was about three and a half years,
5 it's a good surrogate marker for death.

6 And the ACTG, pediatric ACTG chose that as another
7 marker, because we were quite impressed on the variation
8 that we see just here between viral load and the CD4, and
9 just hope you will support what I am saying, because I'm not
10 sure I'm citing it right, that 65 percent of predictability
11 is for the viral load and about 35 is for the CD4, a one log
12 reduction in viral load and I think 7 percentage of the CD4.
13 So you have already another study which is showing PI even,
14 that there is some discrepancy between those, and we started
15 using those as a parameter, that maybe the 10,000, if we
16 have a change in CD4, would be unacceptable like study 338
17 and so forth, suggests why that 10,000 came around.

18 DR. MASUR: Again, we're going to go around and
19 take questions. These are some procedural issues we're
20 addressing to Dr. Jolson et al.

21 DR. EL-SADR: Another question is, what about
22 accelerated approval, and I thought that for accelerated
23 approval the requirements are for two studies with--two
24 controlled studies, right? Sixteen-week data with potential
25 for 24-week data, correct?

1 DR. JOLSON: Well, the standard of evidence for
2 accelerated approval and traditional approval are really the
3 same. In other words, there needs to be substantial
4 evidence from adequate and well-controlled studies that the
5 drug is reasonably likely to have the effect that is
6 claimed.

7 The only distinction is that for accelerated
8 approval the endpoints can be based on changes in surrogate
9 markers that are reasonably likely to predict clinical
10 benefit. And the way that the regulation has most recently
11 been implemented is with either 16 or 24 weeks of surrogate
12 marker data and with a follow-up application for traditional
13 approval that had previously been based on clinical endpoint
14 studies when those were feasible, and is now and in the
15 foreseeable future would be based on 48-week demonstration
16 of viral suppression, durability of response.

17 So the standard of evidence is the same, that the
18 evidence needs to come from at least two adequate and well-
19 controlled studies. It's just that the surety of the
20 endpoints is somewhat different.

21 In terms of the distinction between 16 and 24
22 weeks, previously the division has told the sponsor that
23 they could submit their application based on 16 weeks of
24 data, with the understanding that 24 weeks would be
25 submitted sometime during the review cycle, sometime during

1 the six-month review period. And that's what the sponsor
2 has done in this case. Additionally, other data has been
3 provided because it was felt that the two studies alone
4 still raised significant issues and didn't provide, alone,
5 compelling evidence of efficacy.

6 In the future we will probably ask the sponsors,
7 when they submit their initial applications, to provide us
8 initially with a minimum of 24 weeks of data, because of the
9 difficulties in trying to interpret shorter-term viral
10 suppression and differences between treatment groups.

11 DR. MASUR: Let me ask you one other procedural
12 issue that I think has probably been an issue for many of
13 the committee members. When there were inquiries about how-
14 -about patients, I think that in some ways the patients who
15 had died, the details could have been more substantial in
16 terms of what was known and what was not known.

17 In terms of, at least from my personal
18 perspective, when we inquired about what the efforts were
19 going to be to educate consumers and physicians, the plan
20 was quite general and vague. Now, again, it may be that
21 that's, in this kind of hearing, all there was time for.
22 Are we to presume that this will be the subject of much more
23 detailed negotiation as to what that will be? Or I wonder
24 if it would be useful to have some more concrete comments
25 from the sponsor about what exactly they plan to do other

1 than "educate" the patients and physicians.

2 DR. HETHERINGTON: Give me a second to turn this
3 on here, get rewired.

4 Thanks for the opportunity to add some more
5 clarity to the question. We recognize, by the way, that
6 this is one of the specific questions that's going to be
7 asked to the committee, but just to give you some basic
8 ideas, some of the activities around hypersensitivity
9 reactions in clinical trials are actually quite extensive.

10 For instance, it has been our policy for over a
11 year and a half now that at every scientific meeting when a
12 presentation on abacavir is given, that there is a
13 discussion about hypersensitivity and it is related to the
14 study at the time. We have also done letters to physicians.
15 We have done interviews with not just newspapers but
16 community newsletter writers in the activist community that
17 have been very helpful in disseminating information. We
18 also have put out letters to physicians concerning it, and
19 updated our investigators brochure.

20 Now the kinds of things, the kinds of activities
21 after approval that would be appropriate, first of all in
22 the labeling discussions with the agency we have proposed a
23 physician package insert with a boxed warning at the very
24 beginning to describe the hypersensitivity reaction and a
25 rather extensive description of the syndrome further on in

1 the package insert, but there is the information right up
2 front to at least direct the physician to additional
3 information.

4 Secondly, we have proposed a patient package
5 insert with a tear-off card which would summarize the
6 reaction the patient could carry with them, and this is
7 really a follow-on to what we have used in the expanded
8 access program. I notice Dr. Matthews has his yellow card
9 with him. It has been very useful. It basically provides
10 information on one side for the patient, information for a
11 physician, so that a patient on one of our studies, if they
12 happen to go to a clinic or emergency room, would produce
13 the card and give somebody who is not familiar with the
14 experimental protocol at least some background information
15 and a way to get in contact with somebody, as well.

16 Other kinds of items that could be done, first of
17 all, simply a web site showing the FDA-approved labeling and
18 whatever agreed-upon wording for hypersensitivity could be
19 included. Letters to physicians could continue, including
20 those directed specifically to emergency room physicians,
21 general practitioners, or physicians who might not be in the
22 mode of keeping up to date with all the fast-moving pace of
23 the HIV treatment world.

24 We already have a 24-hour 1-800 number which is a
25 medical information line. It is being used now in expanded

1 access, and it's available of course post-approval for all
2 products that are marketed by Glaxo Wellcome. We also
3 propose educational programs in conjunction with the patient
4 community to continue our dialogue with them to help
5 disseminate the word to patients, because I think it's
6 critical that patients understand the potential for this
7 reaction right up front.

8 A patient instructional brochure has been actually
9 proposed and actually sketched up, although we don't have
10 comments back that I'm aware of from the appropriate body
11 with in the FDA to make comments on that, but that is in the
12 words.

13 And, finally, we could propose continuing medical
14 education programs in the treatment of HIV that would
15 include specific verbiage and information about the
16 hypersensitivity reaction, including illustrative cases like
17 the ones that I presented earlier and that Dr. Cvetkovich
18 presented later on as well.

19 But these are the kinds of activities that
20 certainly can be done and that Glaxo Wellcome would commit
21 to. It certainly is in everybody's interest that the
22 information is disseminated and that an accurate picture of
23 hypersensitivity is known to all physicians out there. And
24 obviously that means that we have an obligation to continue
25 collecting the data and to update that information to

1 physicians as it becomes available, because it is a very
2 changing clinical picture which is dependent upon the body
3 of evidence that we do collect.

4 DR. MASUR: Just while you're up there, I don't
5 think any of us minimize the amount of effort and
6 imagination it takes to come up with an effective program.
7 But one further issue is, obviously many of these programs
8 are logical, do you have any plans to look at the efficacy
9 of the programs to see whether you're reaching your target
10 audiences and whether they understand the information that's
11 being provided?

12 DR. HETHERINGTON: Right. I think that's an
13 important part. You're basically talking about verification
14 of the penetration of the educational initiatives, and
15 that's something that we can certainly incorporate. I think
16 that would be very useful.

17 DR. MASUR: While Dr. Hetherington is up here, do
18 we have any other questions for him?

19 DR. YOGEV: What part of your education is to the
20 emergency room? See, everything here is between the patient
21 and the doctor who is giving it, but unfortunately others
22 are also going to see them in terms of the emergency room,
23 other physicians, and is there any special program for them?

24 DR. HETHERINGTON: Well, I did mention, Dr. Yoga,
25 we have letters to physicians specifically directed at

1 emergency room physicians, as well as the patient tear-off
2 sheet so that a patient has something with them they can
3 carry into the emergency room when they are seen, or an
4 urgent care center, or if they're outside at another city
5 and seeing a physician that's never seen them before and may
6 not be familiar with the care of HIV patients.

7 So, yes, that is I think the important part, and I
8 think that also ties back to Dr. Masur's question about
9 being able to verify the penetration of the educational
10 initiatives that we know and have a gauge of how well we're
11 doing.

12 DR. MASUR: Okay. John?

13 DR. HAMILTON: In these days of surrogate marker
14 endpoints, I think it's well not to lose track of what it is
15 we're trying to accomplish here, and obviously I'm referring
16 to clinical events that attend these treatments, and to some
17 extent those are reflected in the adverse event rates and so
18 on. There are some, I think, softer measures and then some
19 extremely hard measures that we try not to reach, actually,
20 but inevitably these things do happen.

21 So I have actually contributed my share to this
22 surrogate marker epidemic, but I wonder if the company, I
23 wonder if the company, the sponsor, has made any effort to
24 assess any of these softer endpoints? We heard some
25 impassioned testimony today from Mr. Breitman and others as

1 to the benefits of this particular drug, tangible things on
2 their life. It would seem that this would be an important
3 measure to keep track of, at the very least, and should not
4 necessarily I think impede the science that the sponsor has
5 pushed forward.

6 So I guess my question is, are there in fact any
7 measures of, let's call it quality of life, for lack of a
8 better term, on these patients who are enrolled in these
9 clinical trials?

10 MR. LA FON: I assume this is on? That's a very
11 appropriate question, and let me just review some of our
12 thoughts along those lines.

13 First of all, we understand or at least believe
14 that the issue of traditional clinical endpoint trials in
15 today's era of antiretroviral therapy and changing therapy
16 in response to specific surrogate markers has become a very
17 difficult issue in the traditional of ages ago. Now
18 mortality trials are probably a thing of the past, or at
19 least become a very difficult program.

20 We have attempted, and I think we mentioned it
21 specifically around the AIDS dementia study and our study in
22 pediatrics, to try to monitor some other clinical events.
23 Unfortunately, in our AIDS dementia study we were not able
24 to demonstrate any efficacy in that population, probably we
25 believe the result of the fact that most of those patients

1 indeed were harboring resistant virus after chronic therapy.
2 But indeed the pediatric trial is still ongoing and the
3 neurological and developmental milestone data is yet to be
4 collected on that.

5 In some of our programs we do have quality of life
6 measures. I think one issue to bring up here is the issue
7 about the validation of quality of life measures and whether
8 that indeed as a stand alone would be appropriate as a
9 clinical endpoint trial. But we are open to suggestions of
10 the committee. If there are ideas or proposals that we can
11 examine along the lines of a more traditional clinical
12 endpoint type trial, we will obviously take those under
13 consideration.

14 DR. MASUR: Dr. Jolson, did you have a comment?

15 DR. JOLSON: Yes. Again, this gets back to just
16 procedural issues, and I thought just for the sake of having
17 done it, it might be worth reviewing very briefly the
18 difference between accelerated and traditional approval and
19 exactly what the agency means by accelerated approval.

20 It used to be when, shortly after the regulation
21 was enacted in 1992, that we would routinely do this every
22 time we presented an application for accelerated approval,
23 and after a while it got kind of old and the committee got
24 kind of tired of hearing about it. But since there are many
25 new faces around the table, I'd like to just at least

1 clarify exactly what we mean by accelerated approval and how
2 it's implemented.

3 The slide that you showed, shows where it's from
4 in the CFR. It's called subpart H because it's subpart H of
5 the NDA regulations, and it applies exclusively to
6 treatments for serious and life-threatening illnesses that
7 presumably provide meaningful therapeutic benefit over
8 existing treatments, and the regulations cite examples, such
9 as those unresponsive to or intolerant of available therapy,
10 or improved patient response over available therapy. Those
11 are just examples, and there certainly is flexibility in
12 terms of how we define "meaningful therapeutic benefit."

13 And again, it's based on a surrogate endpoint that
14 we believe is reasonably likely to predict clinical benefit.
15 Here, where the committee has discussed in July of '97 that
16 clinical benefit can be indicated by long-term viral
17 suppression and by that we as an arbitrary point have chosen
18 48 weeks, so in these studies if you believe that a
19 surrogate marker response has been demonstrated through 24
20 weeks, we would say, "Well, that's reasonably likely to be
21 indicative of a longer-term response and a longer-term
22 clinical benefit."

23 The regulations go on to further describe the
24 implementation of this type of approval, and it differs from
25 traditional approval in two important respects. One is that

1 advertising is supervised in a different way than other
2 advertising.

3 And also, it's the only regulation, the only type
4 of approval that has mandatory Phase IV commitments. All
5 other Phase IV commitments from regular approvals are
6 voluntary. These are mandatory, and these are the
7 traditional approval studies that we've spoken of, for if
8 they were not to have been done or if they failed to
9 indicate clinical benefit, products would be withdrawn from
10 the market, and those are some things spelled out in the
11 regulations.

12 So that is why the studies that we have--that we
13 will ask you about, the traditional approval studies, are
14 different in how they can be enforced by the agency than
15 other Phase IV studies that might address other issues.

16 Let me just ask if there are any questions or any
17 other points of clarification.

18 DR. MASUR: Well, let's start. Again, for each of
19 those categories, accelerated and traditional, one needs two
20 independent studies, correct?

21 DR. JOLSON: They can be the same studies. For
22 example, there's nothing to say that sponsors couldn't
23 initiate 48-week studies, submit an analysis between 16 and
24 24 weeks in support of accelerated approval, and continue
25 them on. So it can be the same two studies.

1 I think in this case the concern that was raised
2 by the review team was that of the three studies, there was
3 really only one study that was reasonably likely to provide
4 confirmation, and that the package may be somewhat lacking.
5 And so that was a point for you all to discuss.

6 DR. MASUR: Right. Let's move on. Let me, just
7 to indicate what's going to happen after this, we will read
8 the questions, we'll go over the voting members, and then if
9 the voting members, maybe we could pass around something,
10 Rhonda, so I know what time all the voting members are
11 going, so we make sure that anybody who has to leave early
12 has a chance to give his or her comments.

13 So start with Jeff.

14 MR. BLOOM: Dr. Jolson, this is a procedural
15 question. I believe in the past, and I can think of at least
16 two examples where accelerated approval has been granted
17 pending acceptance of a second acceptable protocol or a
18 final end of a protocol, with the FDA and the sponsor
19 agreeing to another trial that would be agreeable to meet
20 the definition for traditional approval. But the
21 accelerated approval was conditional upon that protocol
22 being followed and accepted, or other conditions have been
23 put in place where not accelerated approval which was voted
24 but certainly things had to happen first for the accelerated
25 approval to be given.

1 Because one of the things that's troubling, I
2 think, and in talking to some of the people sitting next to
3 me, the one trial that you're citing as the trial that meets
4 that standard has the 24 percent dropouts, and as pointed
5 out, depending on what happened with those 24 percent
6 dropouts really does affect how that data is in those two
7 different arms of that trial. So there are ways--I'm asking
8 you, I guess--there are ways of putting conditions on the
9 approval, there are ways of doing that so that it's a way of
10 moving forward but also placing certain conditions prior to
11 granting accelerated approval.

12 DR. JOLSON: I think my response would be not just
13 for this application but for any application, there is a lot
14 of work that goes on between an advisory committee
15 discussion and the product's approval. And that's why we
16 try to time the advisory committee at least a month or so
17 before the actual action date, to allow time for that kind
18 of work.

19 And the sorts of things that would have to be
20 agreed upon would include labeling, all Phase IV
21 commitments, and in particular the adequacy of the
22 traditional approval study plans. So those would be things
23 that would need to be agreed upon for us to take an
24 affirmative action.

25 MR. BLOOM: I'm sorry. Maybe you aren't

1 understanding my question clearly.

2 In the past, advisory committees have recommended
3 accelerated approval pending acceptance of a second protocol
4 that was agreeable by the sponsor and the FDA. It was
5 conditional based upon the agreement on a subsequent
6 protocol. And I think that was--I can think of two examples
7 of that, and I was wondering if that's still the case.

8 DR. JOLSON: Where it would be--

9 MR. BLOOM: The committee's recommendation.

10 DR. MASUR: Well, in other words, Jeff, you're
11 saying that if we said there has to be a second study that's
12 agreeable to the agency, that might be a condition for our
13 providing approval--

14 MR. BLOOM: Exactly.

15 DR. MASUR: --depending that--

16 MR. BLOOM: Exactly.

17 DR. MASUR: That would be one option for us to
18 recommend?

19 DR. JOLSON: Yes. Yes. Oh, absolutely.

20 DR. MASUR: Without specifying exactly what the
21 trial was?

22 DR. JOLSON: Right, right. If you had
23 suggestions, for example, that you'd like to see another
24 study designed to provide comparative efficacy data, 48
25 weeks, that could additionally address unanswered questions

1 X, Y and Z, we would then work with the sponsor to at least,
2 you know, get some agreement on the conduct of that sort of
3 study.

4 DR. MASUR: Jim?

5 DR. BERTINO: Just to clarify, in my mind Dr.
6 Lipsky's question before for the medical reviewer and the
7 statistical reviewer, are you saying that based on 3005, the
8 sixth slide from the end is where you say short-term
9 surrogate marker changes support antiviral efficacy, but
10 then we heard the statistical reviewer say there was 24
11 percent dropout, and we're not sure after you take that into
12 account what the--

13 DR. CVETKOVICH: No, I think the--

14 DR. BERTINO: I'm not trying to pit you folks
15 against each other, but--

16 DR. CVETKOVICH: No, no, no. I think that's--I
17 mean, that's a very fair question. I think that I guess
18 what we hesitate to do is really overstate our evaluation of
19 the preliminary results from 3005. However, we have to
20 balance that with the fact that when we requested that data,
21 we knew that what we would have would be preliminary, and we
22 felt that this was required to support or to help flesh out
23 questions we had based on the review of the first two
24 studies.

25 So it is kind of a delicate balance that I think

1 you're seeing kind of go on before you. I guess I feel that
2 we did need to make a cut and a decision about what our
3 thoughts on this were, but that we are here today in order
4 to hear whether that can be supported or not. So, you
5 know, --

6 DR. BERTINO: So then are you saying that of the
7 studies presented today that you reviewed with us, only 3005
8 supports antiviral efficacy by surrogate marker?

9 DR. CVETKOVICH: No, I think 3003 did also.

10 DR. BERTINO: 3003 did that, too?

11 DR. CVETKOVICH: Yes.

12 DR. MASUR: And clearly what our role is, as I'm
13 sure you well recognize, is we have to balance what the FDA
14 has said, what the sponsor has said, and our own perspective
15 of the role of importance of various issues, as to whether--
16 which side of the line we vote on, and we'll find out where
17 you stand in a few minutes.

18 DR. BERTINO: Could I ask one more question about
19 the hypersensitivity, and this is both for the FDA and for
20 people at this table that treat HIV patients. Are there any
21 other antiretrovirals that you see a significant rate of
22 hypersensitivity reaction as discussed here today, other
23 than a couple of reported cases somebody mentioned for
24 indinavir?

25 DR. CVETKOVICH: I'm unaware of any others,

1 although I haven't probably gone through every single
2 antiretroviral, but it's not my impression that this is a
3 common adverse event. I mean, this is--rash and that other
4 direction, we have dealt with--but this again I think is a
5 different--

6 DR. BERTINO: Life-threatening.

7 DR. MASUR: Well, we can talk about there are
8 life-threatening complications for a number of the drugs.
9 For instance, Stevens-Johnson syndrome, we could probably
10 point to a number of drugs, and I guess what we have to
11 assess is where this frequently of this life-threatening
12 complication fits into the spectrum, as one of the questions
13 that really goes into what the risk/benefit is.

14 Joe?

15 DR. HOGAN: I'm still trying to clear up the
16 surrogate marker issue, because in the slide that was just
17 up here it said treatment needs to demonstrate efficacy on a
18 surrogate marker, and yet there seems to be--there seems to
19 be a sense that the new drug should be held to a standard of
20 improving two surrogate markers.

21 And so I would be wondering, just from the
22 clinicians here, and the statistician, Mike Elashoff,
23 brought up that we're trying to weigh the relative benefits,
24 and I wonder how those are weighed in a clinical sense,
25 because it seems like there is maybe demonstrated efficacy

1 viral-wise for the adult trial, sort of debatable in the
2 pediatric trial, but maybe CD4 has held the same in both,
3 and so I don't know how we are supposed to evaluate that.
4 If we can maybe make a case or we think in our minds that it
5 does affect one surrogate marker, not the other, is it one
6 surrogate marker we have to hold it to, or two?

7 DR. MASUR: Well, I would suspect that that's
8 going to come out in the discussion, but I guess we had all
9 hoped several years ago that these would always go together.
10 I guess we're finding out that there are some situations
11 this isn't unique where they don't, and that it is, at least
12 from my own perspective, very difficult to know where to put
13 an agent that affects one and not the other. And
14 fortunately, we're not the Center on Biologics; we don't
15 have to deal with that from another perspective.

16 DR. YOGEV: But you have to admit that
17 unfortunately we are realizing, when we get to the point
18 that we don't have any other options, that the option of
19 only one marker doesn't change. Because in pediatric we are
20 more now accepting because we have only two options, that if
21 at the end of the second one, either the viral goes up or
22 doesn't come down, if CD4 is changed, we are now collecting
23 data to see if that is really also a good marker for
24 extension of quality that it is at that point in time, to
25 buy time, so-called. So this is a very important question,

1 which I had an impression in pediatric we are now moving
2 into looking into those naive coming back, and so forth,
3 without viral load being changed.

4 DR. MASUR: Well, I agree with that. I was trying
5 to be neutral in terms of where I stand on that position.

6 DR. HOGAN: Just to be more specific and not sound
7 too legalistic, the letter of the law says one surrogate
8 marker and yet we're considering two surrogate markers, so
9 I'm just looking for an interpretation of the mandate for
10 early approval.

11 DR. MASUR: Yes. Well, I'd be surprised if Dr.
12 Jolson can clarify this, but we ought to give her a chance.

13 DR. JOLSON: You just want to see how I'm going to
14 answer. That's actually a very good question. Well, that's
15 that flexibility thing, that I think it's--sort of overall,
16 it's the surrogate marker database that we're looking at
17 now. When the law went into effect, there was really only
18 one surrogate marker, so it was kind of easy. CD4 was the
19 clear preference at the time, and everything else, you know,
20 P24 antigen and all those other things, were a little less
21 interpretable.

22 I don't think you should feel restricted that it's
23 an either/or, and that's really why it's here in front of an
24 advisory committee, because in at least one study there's
25 somewhat conflicting results in terms of the magnitude of

1 the treatment effect. And that really I think is up for
2 clinical judgment in terms of how those are interpreted and
3 how the different results are integrated together, but you
4 all don't have to worry about the letter of the law in terms
5 of your interpretation of it.

6 DR. MASUR: Yes, and I presume that, again, one of
7 the reasons it's at this advisory committee is that the
8 agency would like our advice on what to do, and clearly it
9 isn't a very clear-cut issue.

10 Are there other procedural issues? Because,
11 again, I do want to get to the questions. Linda, do you or
12 Steve have a solution to this. Not that we necessarily--

13 MR. LA FON: Well, we do appreciate the complexity
14 of this, and obviously we have been working with the agency
15 to try to address some of these issues. I just want to make
16 some points in discussion here.

17 One, we are in agreement that 3005 is an
18 appropriate traditional approval study, with the agency. We
19 are also in agreement that 3003 will only be supportive. As
20 a matter of fact, we have 48-week 3003 data which may help
21 with the CD4 discussion.

22 3006 is a little bit more complex, and I think Dr.
23 Yoga was bringing it up. We seem to find that result where
24 the viral load response, significantly different, not
25 significantly different, the response is not near as

1 profound as we have seen in adult naive patients. However,
2 we did see a CD, a positive CD4 response, and while the
3 FDA's review indicated there was numerically an advantage,
4 as a matter of fact our analysis showed a statistically
5 superior response to CD4 in that group.

6 I think thirdly, and probably most importantly, as
7 we mentioned earlier, that trial is collecting
8 neuropsychological endpoints and development milestone
9 endpoints which will be available at 48 weeks. So that data
10 may be appropriate for discussion around the traditional
11 approval package.

12 I want to just briefly, and I appreciate, and
13 we'll talk about the caveats of this, want to show the 48-
14 week CD4 data for 3003.

15 DR. MASUR: Steve, let me just--for everybody
16 speaking, we need to truncate this, because otherwise some
17 of the voting members are not going to have a chance to make
18 any comments. But ago ahead at 78 speed.

19 MR. LA FON: Okay. This is the absolute CD4 cell
20 count through 48 weeks of treatment. We have provided this
21 just very recently to the agency, and so will accept that it
22 has not been reviewed and has not been discussed. And this
23 right here is the--let me find it--this is the 16-week
24 point.

25 The bottom line is that both groups--and again I

1 mentioned earlier, most patients switched on the double to
2 open label abacavir/3TC/zidovudine, and both groups are
3 showing a similar CD4 increase through 48 weeks. The bottom
4 line is, and unfortunately we don't have this plot, the
5 median increase in CD4 cell counts through 48 weeks of
6 treatment was 152 cells in both treatment groups. So while
7 at 16 weeks we were showing, you know, less than 100 cells
8 or possibly a 100-cell increase, that continues to increase.

9 DR. MASUR: Are there other procedural issues
10 before we move ahead?

11 [No response.]

12 DR. MASUR: All right. Let me then read the
13 questions for the advisory committee, and then we'll start
14 with the individuals who have to leave first. There are
15 seven questions that have been proposed to us:

16 Number one, are the available data sufficient to
17 support accelerated approval of abacavir for treatment of
18 HIV? If no, what additional studies are recommended? If
19 yes:

20 Number two, the principal abacavir-containing
21 regimen studied in Phase III trials consisted of three
22 nucleosides. Please comment on the appropriate use of this
23 regimen and the appropriate patient population..

24 Number three, please provide your assessment of
25 the risk/benefit ratio for abacavir and the implications for

1 clinical use.

2 Number four, several marketed antiretroviral
3 agents associates with rash are likely to be used in
4 combination with abacavir. Please provide your
5 recommendations for the management of patients developing
6 rash while receiving abacavir in combination with these
7 agents.

8 Number five, please provide recommendations for
9 disseminating information on abacavir-associated
10 hypersensitivity to patients and providers, and what further
11 studies of these reactions should be recommended.

12 Number six, please comment on the applicant's
13 proposed traditional approval package.

14 And, number seven, please provide recommendations
15 for any additional Phase IV studies.

16 So those are the seven questions, and again, in
17 the interest of making sure that we get the comments
18 particularly of five individuals who have to leave before 4
19 o'clock, why don't we start with Dr. Pomerantz?

20 DR. POMERANTZ: Thank you for allowing me to go
21 first. First, I do think that I would support--I will
22 support the accelerated approval of abacavir for treatment
23 of HIV infection. So I guess since I said yes, I should go
24 on with the other questions, or do you want to take a vote
25 around the table for one and then go back to the comments?

1 DR. MASUR: All right. Let's see if we can do
2 that expeditiously. Do you want to make any comments, any
3 other comments about number one?

4 DR. POMERANTZ: No. I say yes, and then I'll go
5 into why I say yes and two through seven.

6 DR. MASUR: all right. Well, this is actually--I
7 thought we would do through all of them, but I think that's
8 a more reasonable idea. Why don't we--we'll start there and
9 just go around the table on number one. And then again, if
10 we start running out of time, we will get Dr. Pomerantz go
11 through all of them, but let's do number one.

12 DR. HAMILTON: I would say I'm reluctant to
13 support the approval for traditional--or for accelerated
14 approval.

15 DR. MASUR: Do you want to make any comments,
16 John, any editorial comments?

17 DR. HAMILTON: I have some I can make, but--

18 DR. MASUR: Why don't you make them briefly, and
19 then again we will move on.

20 DR. HAMILTON: Well, it seems to me it hinges on
21 question number six: Are there the appropriate elements to
22 accept this in the usual framework? The message I've gotten
23 today is that 3005 is the only one that's currently
24 constituted to answer the question. That's one study. The
25 others are either not going to provide that data for sure or

1 are very marginal. My sense would be that there needs to be
2 some additional work to support that proposal.

3 DR. MASUR: John, if I understood--again, maybe we
4 ought to ask Dr. Jolson to clarify this--but if the agency
5 could come to an agreement with the sponsor as to two
6 studies that would support traditional approval, even if
7 they're not underway, if the agency were satisfied that
8 there were two traditional studies that could be gotten
9 underway, would you feel the same way? In other words, if
10 there is another study negotiated.

11 DR. HAMILTON: It would all depend on what the
12 study was that they were proposing. I'd like to see what--
13 you know, what there is. Where's the beef here? And so it
14 just seems like we're pushing back the approval process
15 further and further without a compelling reason to do so.
16 We're proposing to approve this drug so that it can be
17 accessible to patients who need it desperately, and the fact
18 is that there certainly are patients who do need it
19 desperately.

20 However--I'm not trying to get in the way of their
21 having access to it, now that by the good graces that it has
22 been made available for some number of people on expanded
23 access, and they are to be applauded for that. I don't
24 think, however, that licensing it or recommending that it be
25 licensed provisionally necessarily is going to have a major

1 impact. I mean, think of where we are thinking of using
2 this drug.

3 We're thinking of using it in a population of
4 people who already have gone a long ways down the line.
5 They've tried a lot of drugs, and what have we gotten from
6 it? What we've gotten is a whole lot of resistant drugs.
7 Granted, we've also had some major benefits in the form of
8 what seem to be dramatic changes in survival. Those
9 benefits have been attributed to the protease inhibitors. I
10 don't know if that's true. I have some doubts that that is
11 the entire explanation.

12 But I think to prematurely put another agent out
13 there without a compelling reason, one that I guess lives up
14 to the standards that have previously been set by this
15 committee, I think would be--to me it would be a mistake.

16 DR. MASUR: All right. Let's go--we are going
17 around getting each person's decision. Then we will do a
18 formal vote, and again, I'll read the list at the end of
19 this as to who the voting members are, but there are 10
20 voting members today.

21 Dr. Matthews?

22 DR. MATTHEWS: I believe adequate evidence of
23 efficacy has presented, particularly with the 3005
24 preliminary data. I have major concerns about safety, not
25 so much within the trials and expanded accesses that have

1 been described, but potentially in a much looser context
2 once the drug is available by prescription. On balance, I'm
3 going to vote "yes" with assurances that an adequate safety
4 package is put together subsequently.

5 DR. MASUR: Dr. Wong?

6 DR. WONG: I guess I would just like to make a
7 comment and maybe a question to the FDA reviewers. When I
8 read the results of the pediatric trial, I really came to a
9 different conclusion: that these data do show efficacy, or
10 at least that if this study is carried out until the end,
11 that there is a reasonable chance that they will demonstrate
12 efficacy that is durable.

13 And I understand, you know, that the less than 400
14 endpoint was not the one that was originally included in the
15 protocol, but that doesn't mean that it's not relevant
16 information. And I think I would like to hear why it is
17 that your bottom line conclusion is that this study is
18 unlikely to be supportive of efficacy for this drug, in
19 light of these graphs, especially with the less than 400
20 endpoint showing to me a clear superiority of the triple
21 combination as compared to the double.

22 DR. CVETKOVICH: We have--perhaps we haven't made
23 our position as clear as it might be. I believe that we're
24 not quite sure what do with this protocol-specified endpoint
25 of 10,000. Clearly when the study was designed, time has

1 passed, we know more now. Hopefully we're moving toward
2 more and more effective treatments for kids.

3 So we're kind of looking at two endpoints and
4 somehow trying to say what this means in terms of efficacy.
5 I think that clearly there are patients who have benefited
6 from this treatment in the pediatric study. I suspect that
7 those are the ones who have received the shortest previous
8 treatment and the least exposure to zidovudine/3TC.

9 And so I think that we do have pieces from this
10 study which are supportive of efficacy, but on the whole,
11 given that we only have 12 percent at 16 and 24 weeks in the
12 abacavir-containing arm versus 2 percent in the ZVD/3TC arm,
13 and the study isn't even halfway through, it's very hard--or
14 it is halfway through and has halfway to go--it's very hard
15 for me to see that with another six months that's going to
16 give us a whole lot more.

17 DR. WONG: I guess my reaction to this is that,
18 you know, I'm afraid that we might have put ourselves in the
19 position of being almost prisoners of the criteria, and
20 since we're going to--you know, since we will have numerical
21 data that's continuously variable on efficacy, why not
22 analyze it that way, rather than say, you know, count up the
23 yeses and noes at 10,000 and count up the yeses and noes at
24 400.

25 Why not just ask the question at the end of the

1 study, or at interim points through the study, you know,
2 what is the net reduction in viral load per individual over
3 time, comparing the two groups? It would seem to me that
4 although we can't predict the outcome at 48 weeks, I think
5 it's too strong to conclude from the data we've heard today
6 that this study is not going to support efficacy. I think
7 it's an open question. And for that reason I would say that
8 the sponsor has shown what they need to show today, and I
9 would vote for accelerated approval.

10 DR. MASUR: Okay, and we'll come back to that
11 before 3:40. Let's see if we can get around relatively
12 quickly.

13 Skip?

14 MR. O: I'm probably the newest member here.
15 Well, I'm not a member, I'm a consultant. But I'm not
16 really compelled by the data that have been presented here
17 today, and I think if I had to vote right now, I probably
18 would vote against it.

19 Very quickly, I am bothered by the so-called
20 anomalous result in the adult study, the 3003, and I am also
21 a little bit bothered by the very high fraction of people
22 who were enrolled in the study, the pediatric population,
23 who actually were less than 10,000. Twenty percent of the
24 individuals actually had the endpoint at baseline. And I am
25 troubled by the 24 percent dropout rate in one of the

1 studies that's going to be used to actually support the
2 traditional package.

3 DR. MASUR: Okay. All right, and again, we'll
4 come back to some of these issues.

5 Joe?

6 DR. HOGAN: I'm not actually a voting member
7 today.

8 DR. MASUR: But I'd like everybody's position, and
9 then again we'll get back to the voting members, to vote.

10 DR. HOGAN: Well, my position would be not quite
11 binary, more of a conditional yes, and I know that that
12 probably reveals my being a rookie here, to give an answer
13 like that. But here are some of the concerns that I have.

14 DR. MASUR: Actually, Joe, if you don't mind, if I
15 could come back, if we can come back to you, because if it's
16 going to be conditional, that will have to do with some of
17 the things in two through seven, I think.

18 DR. HOGAN: Yes.

19 DR. MASUR: So if I could, we'll come back to
20 that.

21 DR. HOGAN: Yes. Okay. So I would say it would
22 be a yes, but under some strong conditions.

23 DR. MASUR: Okay. Joe?

24 DR. BERTINO: Something on Dr. Jolson's memo that
25 she sent to us, under "Issues": "For accelerated

1 approval...effect on surrogate endpoints sufficient to
2 conclude that the drug may provide meaningful therapeutic
3 benefit over existing therapies." Using that definition, I
4 would vote "no" unless Dr. Jolson wants to tell me
5 different, that I am interpreting that wrong.

6 DR. JOLSON: Well, I think that there is a couple
7 ways that you could look at this product as at least being
8 consistent with that criteria. In terms of providing
9 meaningful therapeutic benefit, it's in someone or in some
10 population, so whether it's in patients who have limited
11 options, that this might provide benefit through
12 demonstration of an antiviral effect, or by virtue of being
13 used in a triple combination it would provide another
14 treatment option. So those are at least two possible ways
15 that you could say that it is providing benefit, and the
16 sponsor may be able to add to that in terms of what the
17 argument would be for how their product fills those
18 criteria.

19 DR. MASUR: Okay.

20 DR. BERTINO: Then I'll vote "yes."

21 DR. MASUR: Okay, and we'll come back to this.

22 Jeff?

23 MR. BLOOM: I think it's rather unfortunate the
24 way they actually have done these studies. I think it
25 doesn't meet the threshold for accelerated approval simply

1 because we do have a lot of therapies on the market now. We
2 have a lot of people that are pretreated with AZT and 3TC,
3 that may use this with other nucs in a triple-nuc regimen,
4 but we really have no idea how it would work in that regard,
5 and it's unfortunate they really didn't study it with a
6 wider variety of antivirals, nor are their follow-up plans
7 currently to study it with a wider variety of antivirals.

8 And when asked this question before, the answer
9 was basically, "Well, it's convenient four-pro regimen."
10 There is a current five-pro regimen that is available with
11 combavir and sustiva that's pretty convenient and available
12 as of now. So given that, and given the fact that there
13 really is only one study with that 24 percent dropout, I
14 would think that gives me pause to concern. Because if
15 throwing another--people do need more treatments and people
16 need more therapies, but we need effective therapies, not to
17 just throw them out there.

18 DR. MASUR: Okay. We'll come back to some of
19 these issues that need to be followed up.

20 Frank?

21 DR. GIGLIOTTI: I guess one of the key things is
22 whether the pediatric trial suggests efficacy or not, and
23 again, I would agree with Dr. Wong's assessment, that as I
24 look at this, that I think while a 20 percent rate of having
25 less than 400, a viral load of less than 400, isn't

1 terrific, in the population studied I think it is
2 significant, and the control group is approaching zero. So
3 if you look at it the other way, 10 times as many people
4 have success virologically. That's a small number, but I
5 think that does indicate efficacy.

6 And as I look at these numbers, it looks--there
7 was concern this morning that there are not going to be
8 enough because that offer of a switch-over at 16 weeks,
9 although blinded, was going to interfere with the analysis.
10 As I'm looking at the numbers on the slide, it looks like
11 there's at least 90 people in each group that have passed
12 the 16-week point, and so you have that--and I don't know if
13 that's because the rest of them have switched or that the
14 others have not reached that marker, but it looks like
15 there's going to be a least 180 kids who will be followed
16 for the full 48 weeks, and I think that will give you some
17 data. So I would be inclined to favor it, although I am not
18 fully--

19 DR. MASUR: Okay. Well, again, we will come back.
20 Ram?

21 DR. YOGEV: I'm a little bit different on
22 pediatric. I think we are seeing--people compared to
23 others, because there were too many patients on those AZT
24 and 3TC, and that's basically on--300 or 150 to ACTG. So I
25 don't think on science I approve it.

1 On the other hand, I think compliance is a major
2 issue which we somehow avoided. In pediatric it is a major
3 problem to supply a combination that will give us the same
4 efficacy, at least for a short period of time, until we get
5 the trust of the patient, until the patient is getting used
6 to taking those drugs or taking few, getting the same
7 efficacy, make a point that you might consider.

8 So on science, no; for patient convenience, maybe
9 have compliance, yes.

10 DR. MASUR: Okay. Pam?

11 DR. DIAZ: There are some very concerning issues,
12 but I feel that I probably would approve it based on
13 efficacy and safety, but again, somewhat conditional in the
14 sense that in particular the 3005 study, which is the one
15 study that we're all sort of hinging on getting data in the
16 long run on, our 16 and 24 week data is not really
17 finalized, and I think that would in my mind have to be more
18 succinctly put together in order to give accelerated
19 approval.

20 I too am not as skeptical about the pediatric
21 study not showing anything in the long run. I think that it
22 might provide some additional data, but I certainly wouldn't
23 hinge everything on that. I would expect a second study to
24 be instituted and conceived for traditional approval, and
25 again, I think it would depend on what that study was as to

1 whether approval should be given unconditionally at this
2 point in terms of accelerated approval.

3 In terms of the safety, again, I think it would in
4 my mind depend upon the package that's designed for the
5 education and demonstration of this drug in terms of its
6 safety. And again, I think the Phase IV commitments would
7 be--I would need to see those in my mind, but I do believe
8 that there are a group of patients out there that would
9 benefit from this drug, and because of that I would vote
10 "yes."

11 DR. MASUR: Okay. I'll come back to my comments
12 in a moment. Wafaa?

13 DR. EL-SADR: I'm glad I'm not voting today. This
14 is very difficult.

15 I guess it's just a little bit concerning that we
16 are hinging everything on the equivalent study, 3005, where
17 the--we didn't have really a chance to look in detail at the
18 study, and the agency didn't have a chance to review it in
19 detail, but I think that's the one study that's reassuring.

20 I'm very concerned about 3003, with the
21 discrepancy between the HIV RNA and the CD4 cell count, and
22 also about the pediatric study, because I'm not sure that
23 this study will demonstrate any superiority of abacavir in
24 the arm where it's being used.

25 I also am concerned that we haven't really seen

1 good data on any efficacy in the experienced adults. So a
2 lot of ifs, and--

3 DR. MASUR: All right. We will come back to your
4 "ifs," and there are going to be a number of "ifs" to come
5 back to.

6 Jim?

7 DR. LIPSKY: Okay. I won't "if." I would say
8 approve it for accelerated approval. By the nature of that
9 approval process, that is a conditional approval, and once
10 this committee by your predecessor pointed out that there
11 have been so few times when drugs haven't gone on to, you
12 know, the traditional approval, that maybe we are a bit too
13 stringent. We are, you know, too stringent, or even having
14 the drugs brought forward.

15 So anyway, yes, I think there is antiviral
16 efficacy there, enough for--on one surrogate marker, which
17 is enough for accelerated approval. There is the worrisome
18 aspect of the toxicity. In general, toxicities are often
19 worse in situations where they are out of controlled
20 clinical trials. I mean, I think that's aware of everybody--
21 -to everybody, including the manufacturer.

22 DR. MASUR: And my position is to favor approval
23 with a number of caveats. I guess, as with everybody else,
24 I'm troubled by the apparent discrepancy between immunologic
25 and virologic response, and would like to be assured that we

1 will have the safety program and the traditional approval
2 studies in place before accelerated approval were given.

3 But I agree with Jim that we need to--I think that
4 this is an appropriate indication where we don't have all
5 the data we would like, but I think we have enough data to
6 put this out. And I would hope that the agency has the
7 courage of its convictions, that if it approves a drug for
8 accelerated approval and either efficacy is not ultimately
9 shown or there is more of a safety problem than was
10 initially recognized, that they would withdraw their
11 approval, and I guess that has not happened yet but
12 potentially could happen.

13 So, again, so that we can get some of the comments
14 from other people in a moment, the voting members today are
15 Drs. Diaz, Hamilton, Masur, Lipsky, Pomerantz, Hamilton, and
16 consultants--oh, I'm sorry--and Drs. Bertino, Matthews,
17 Wong, and Woolson. So if those individuals could answer the
18 first question: Are the available data sufficient to
19 support the accelerated approval for abacavir? We will take
20 a yes/no vote, and then we will come back to issues two
21 through seven.

22 So of those nine individuals, how many vote in
23 favor of question number one?

24 [A show of hands.]

25 DR. MASUR: And how many vote opposed?

1 [A show of hands.]

2 DR. MASUR: So fortunately the math comes out.
3 It's seven in favor, two opposed.

4 With that initial--or with that vote, with that
5 final vote, the issue is now about addressing questions two
6 to seven, and we'll do that in order of which people have
7 travel commitments. And again, we do appreciate the
8 committee members and the consultants for taking a day out
9 of their lives to come to this meeting.

10 Dr. Pomerantz?

11 DR. POMERANTZ: Yes. Thanks again. As you heard,
12 I voted "yes" with some of the problems that each of us have
13 faced. I mean, it's clear that this wouldn't come to
14 committee unless there was a difficult series of choices.

15 And that being said, going to number two, where
16 it's asked, "Please comment on the appropriate use of the
17 three nucleoside analog regimens," well, this is not just
18 for abacavir but it seems to be a general question in the
19 field, and it's one that remains somewhat unanswered.
20 Abacavir is interesting not only because of its resistance
21 profiles but also because of the strength of its
22 monotherapeutic effect.

23 This--if one of the three nucleoside analog
24 regimens is really going to hit the full tilt of comparing
25 to a protease inhibitor regimen, it may be this one, but I

1 fully agree it's not been shown conclusively. I actually
2 thought that the company would be showing more data today
3 than they actually did, even though they hit the level that
4 I found necessary to make accelerated approval.

5 Three nucleosides, as I said, have been over the
6 last year somewhat anecdotally stated to be not as intense
7 or to have the duration of effect of a protease inhibitor
8 containing regimen. I think that a number of studies are
9 going to have to be done here, and I'm not fully convinced
10 that in the long term, as you heard from my earlier
11 questions about is this less than 50, how long have you
12 carried this out to, whether it will be truly equivalent or
13 not.

14 So I wouldn't say up front that in patients of
15 mine, that I might use this as protease sparing initial
16 effect, but that's not what we're being asked today. I
17 think for certain patients who can take protease inhibitors,
18 or those that have not had good results with them, both with
19 side effects and others, that this is a perfectly reasonable
20 second regimen. I'd like to see it become a first regimen,
21 but I certainly don't think that's there yet.

22 Number three, where it asks for the risk/benefit
23 ratio for abacavir and its implications for clinical use,
24 that's sort of an open-ended question that you've heard a
25 lot today. This is really the first drug, as you all know,

1 that has a hypersensitivity effect that is more commonly
2 involved with having such serious effects, rather than
3 typical rashes we're used to with some of the drugs that we
4 give both to inhibit HIV and otherwise.

5 I think that the risk/benefit, there is a higher
6 risk/benefit ratio here than in most of the drugs that we
7 give out to patients who are HIV-infected, but I don't think
8 it reaches the level where it should not be part of the
9 armamentarium of the United States at this point. But, as
10 we'll get to in a minute, this is not a trivial issue, as a
11 variety of people, including Dr. Hamilton, had mentioned.

12 I think, though, that this can be taken care of by
13 very critical attention by the company, not only by
14 announcing it at meetings but also doing what you're doing
15 now, which is to go out to the grassroots. As was brought
16 out before, it's not just the experts in infectious disease
17 or in HIV therapeutics that need to know about this, it's
18 the people in the walk-in clinics, it's the people in the
19 emergency rooms who will come--who will see these patients
20 on weekends when they get their flu-like illness, and this
21 is something that should be generalizable, as I think and
22 hope that you will continue to do.

23 Number four, several marketed antiretroviral
24 agents are associated with rash, although if you look in the
25 PDR, I would say that you couldn't find a drug that doesn't

1 have rash somewhere in that list. So we go through very
2 commonly in patients, either HIV-infected or otherwise, who
3 have rash, to prune away the usual candidates.

4 This is a different story, obviously. This isn't
5 a rash that will slowly go on to Stevens-Johnson at the
6 worst, or erythema chronicum major at the best, but this is
7 something that could kill you. And obviously, therefore, as
8 we have talked about before, I think that this is absolutely
9 necessary to bring out into the community outside of the HIV
10 experts.

11 And I think that as well, one group that I forgot
12 to mention is the pharmacists, not just those in the
13 tertiary care centers but the pharmacists in the small
14 pharmacies throughout the country that need to learn about
15 this. I've been very impressed with how they have kept
16 physicians such as myself out of trouble in the
17 multipharmacoepia of patients. So I would again stress that
18 the company try to work on pharmacists, not only in the
19 tertiary care institutions.

20 And I think I've dealt with number five as I
21 talked about number four. You know, again, I think that
22 it's important that the traditional approval not be thrown
23 aside, as has been brought up by a number of people,
24 including Dr. Hamilton. But if something could be developed
25 between the company and the FDA to make absolutely sure that

1 happens. Clearly we don't want abacavir to be the first of
2 the drugs to get accelerated approval and then get into
3 trouble because no studies were designed to look well for
4 traditional approval, although I doubt that Glaxo Wellcome
5 will do that, but I think that the FDA will keep good look
6 on that and make sure that it gets accomplished
7 appropriately.

8 Phase IV trials for abacavir, clearly one of the
9 things that was brought up at the other end of the table is
10 that it would have been nice to have seen more data on other
11 combinations with drugs that are out there besides combavir.
12 Knowing that there are protocols out there, both in the
13 United States and in Europe, I was not overly taken back to
14 the fact that I couldn't approve the drug on that count, as
15 was discussed, although again, I would have thought that
16 some of those trials would have been near completion, which
17 I guess they are not.

18 There are a number of drugs, both on a molecular
19 biological level that I had mentioned earlier, that may have
20 theoretical reasons why they may do better than combavir
21 with abacavir, but I think that most of the people at Glaxo
22 that I've heard present here and around the country have
23 those drugs in mind, and I would imagine that there will be
24 other studies that will change the way we even look at this
25 drug within the next six months.

1 And those are the feelings that I had in moving
2 forward with an accelerated approval.

3 DR. MASUR: Okay. Well, I appreciate, we
4 appreciate those comments.

5 Dr. Matthews, your plane is next.

6 DR. MATTHEWS: I'll make some accelerated
7 comments.

8 On question two, I don't think the long-term
9 comparability of a triple nucleoside regimen has been
10 established vis-a-vis the PI or NNRTI-containing regimens,
11 and so I wouldn't use it up front. On the other hand, there
12 are some definite populations where I would view this kind
13 of a regimen very favorably, and those are the populations
14 who have various contraindications to drugs that affect the
15 P450 system, so that would include people who are on
16 anticonvulsants for either psychiatric disorders or seizure
17 disorders, and despite the fact that the latest MMWR has
18 anointed rifrobutin as the candidate for tuberculosis
19 treatment regimens, I think a regimen like this may have a
20 role in people who are either being ruled out or have
21 tuberculosis.

22 One other comment I wanted to make. A number of
23 people have commented on the pediatric trial being brought
24 forward as part of the package, and I want to not only echo
25 that but also the notion that trials can be brought forward

1 as part of the approval package in salvage regimens, which,
2 you know, if you think about it is quite a daring thing to
3 do. And having been at ICAC recently and listened to a
4 whole session on salvage, it's pretty dismal, the results
5 that have accumulated.

6 I think while the venue here is different, we
7 clearly can't approve a drug based on good intentions in
8 treating populations which have a low probability of
9 response no matter what you give them, still I think it's
10 important that these kinds of trials be continued. That's
11 more or less as an aside.

12 With regard to question three, the risk/benefit
13 ratio, the risk is the issue in my own mind, and I think
14 that there need to be additional analyses done to identify
15 predictors of the hypersensitivity reaction, and these
16 analysis need to be in particularly--using particularly
17 challenging subsets of data. It's not just enough to say a
18 person is, say, on two other nucleosides and has abacavir
19 and then has a particular syndrome within six weeks of
20 starting, because the fact is that most of these patients,
21 at least in expanded access, are started on multiple drugs
22 simultaneously, and it is not an easy problem to distinguish
23 efavirin reactions from this reaction.

24 I have been to meetings where doctors get up and
25 give testimonials on how they can distinguish these things,

1 but I don't think we've heard any data about how accurate
2 physicians are, particularly when there are cases that
3 cannot be resolved very easily in terms of what is a
4 reaction and what isn't a reaction and this large group of
5 nebulous, maybe kinds of people. So I think, you know, the
6 definitive cases and the people, as Dr. Wong pointed out,
7 who were considered as potential reactions but didn't have
8 reactions on re-challenge is an opportunity to apply some
9 statistical modeling to identify these predictors.

10 I was pleased to hear about the physician hot
11 line, although I think that once the drug is made available
12 for prescription, that that really needs to be promoted and
13 publicized both for providing information for physicians on
14 how to manage a patient and how to recognize--as well as how
15 to recognize it, and to continue to accumulate data, at
16 least until the time of traditional approval, on the full
17 spectrum of this syndrome. Because, you know, I'm not
18 convinced at all, and Dr. Hetherington acknowledged this,
19 that we understand the full spectrum from the least severe
20 to the most severe, as well as the perhaps uncommon
21 reactions that may not have been present yet.

22 Let's see. With regard to rash management, there
23 are several subsets of syndromes that I think clinically
24 have to be dealt with. One is the person who has rash
25 alone, and in that sort of situation I think it's reasonable

1 and many people would just continue treatment, follow the
2 patient closely, and see what happens.

3 The constellation of rash and fever in my own mind
4 would lead probably, if the patient is on abacavir with or
5 without other drugs that could produce rash and fever, that
6 one would tend to stop all drugs.

7 The more problematic groupings of symptoms would
8 be rash and just fatigue and malaise, or rash and nausea and
9 vomiting. What does that mean? Because those, the latter
10 symptoms are so common and could be due to almost anything.
11 So one would have to use "clinical judgment" in that
12 context, but what is clinical judgment, and is clinical
13 judgment, and is my clinical judgment the same as yours?

14 You know, I think one of the things the company
15 needs to do is to study groups of physicians presented
16 various scenarios and see how much uniformity of opinion
17 there is on what people would do in managing these kinds of
18 patients.

19 With regard to question six, the approval package,
20 I agree that another trial needs to be mounted. The
21 question in my own mind is that, you know, ideally the
22 greatest shot for showing efficacy would be in a naive
23 population. If it's going to be in an experienced
24 population, then I think there should be a prospective
25 stratification on genotypic resistance so that we could get

1 some useful information on what subsets of patients with
2 various mutation patterns are likely to respond. And there
3 was a very instructive article in JID in September that
4 Scott Hammer co-authored, that illustrated how resistance
5 testings could be included in a factorial design to study
6 agents like this.

7 And I don't have any additional comments on
8 question seven right now.

9 DR. MASUR: Dr. Jolson, I missed the fact that you
10 had a comment you wanted to make. Do you have any comment
11 you want to make now?

12 DR. JOLSON: Well, it's again just back to the
13 traditional approval package in terms of the studies, and I
14 don't think that we're saying that it would be impossible
15 for the pediatric study to demonstrate a treatment
16 difference at 48 weeks. I think that our concern was that
17 it's somewhat risky, given what the analysis at 16 and 24
18 weeks looks like, that at least with the less than 10,000
19 cutoff, that the arms are approaching each other, and that
20 if you look at the less than 400 cutoff, the rate, the
21 overall rate in both arms is very, very low.

22 So from looking at it from that standpoint, even
23 if we believe that there is evidence of some limited, you
24 know, evidence of efficacy during that period of time, it
25 becomes somewhat risky for the sponsor to assume that we're

1 going to see a robust treatment effect at 48 weeks. It
2 seems somewhat unlikely.

3 And that's not at all to diminish the importance
4 of a pediatric study or 48 weeks of pediatric data. We
5 definitely want to see that data. We want to see the study
6 completed and submitted and incorporated into any labeling,
7 but it just is somewhat risky to bank on that as one of two
8 pivotal studies, because it can't be assumed that the
9 equivalent study either is going to pan out.

10 So again, it's risk, and it's not in any way to
11 say that it's not an important study or doesn't contribute
12 to our understanding. So I just sort of wanted to put that
13 into the context of thinking.

14 DR. MASUR: What procedurally would occur if six
15 months or a year from now, one study supported efficacy at
16 48 weeks and the other did not? At what point would you
17 feel obliged to pull the plug on the accelerated approval?

18 DR. JOLSON: Well, this would be the--whatever
19 application, accelerated approval application comes in with
20 the first traditional approval package based on 48 weeks of
21 viral load data, that will be the first. And I would think--
22 -and, you know, we also might entertain bringing it to the
23 committee.

24 I don't know that--I don't know what the sponsor's
25 plans are in terms of the timing of the studies, if both

1 studies would come in at the same time or if they would be
2 staggered, because sometimes we'll see traditional approval
3 applications that are staggered, that will only include--

4 DR. MASUR: Right, but I guess what I was
5 suggesting is if one is--if the pediatric study in fact
6 turns out to show no difference--

7 DR. JOLSON: Uh-huh.

8 DR. MASUR: --for the reasons you indicated, the
9 other study does show a difference, then you're faced with
10 the fact that you have to start another study that will take
11 a year, two years, three years.

12 DR. JOLSON: Well, I think we would probably be
13 back here in a setting like this at a Holiday Inn, you know,
14 somewhere in Montgomery County, and we would sort of
15 probably be asking the committee, given the totality of the
16 evidence, do we believe that clinical benefit has been
17 demonstrated?

18 My preference would be not to assume that studies
19 are all positive or all negative, even if they don't--
20 because even if they don't reach a certain p-value,
21 sometimes we can get important information, and I think in
22 the pediatric study some of the maybe differences between a
23 biometrics review and the clinical review is based on the
24 fact that even if a particular endpoint wasn't reached in a
25 robust way, we can still conclude that there is some

1 evidence of efficacy there.

2 DR. MASUR: Okay. Quick comments, Ram?

3 DR. YOGEV: I just wanted--I am a little bit
4 confused, and maybe you can clarify to me. Nobody in your--
5 until just recently there was a recommendation how to treat
6 a pediatric patient, and do a therapy on a patient who is
7 experienced with any one is not indicated, and are we saying
8 that in taking a study which is basically close to placebo,
9 monotherapy, to compare this treatment, and if it show even
10 efficacy, we accept that?

11 My problem is that the study design at this point
12 in time is not appropriate, and one would like to see
13 something else, not even to wait for those results, because
14 if you show efficacy, it's what happened to us in 152. We
15 said that ddI is as good as ddI/AZT because we didn't
16 realize we are dealing with a placebo.

17 DR. MASUR: Dr. Jolson, we'll ask for a quick
18 response, because one thing, I'd like to make sure that with
19 Dr. Wong, Dr. Lipsky, and Dr. Hamilton if he's coming back,
20 that we get their comments in before 3:40.

21 DR. JOLSON: Yes. I guess I think your point is
22 well taken, and just in a one-sentence response, I think
23 that is what we would hope to hear when we ask you to
24 evaluate the adequacy of the traditional approval package,
25 would be to take those issues into account in terms of the

1 types of questions that studies can answer and how
2 clinically relevant that information will be.

3 DR. MASUR: Okay. Well, for those of us who are
4 staying a little later, we'll come back to that, but Jim?

5 DR. LIPSKY: Okay. Thank you. First, I would
6 also like to congratulate the sponsor on the pediatric
7 studies and complement them for bringing them forward at
8 this time. This committee in the past, as some remember,
9 heard an impassioned plea from the public to not ignore the
10 pediatric population. I'm glad to see that that plea has
11 been listened to.

12 On the use of three nucleoside analogs, well, it
13 would seem that theoretically a more rational approach would
14 be try to hit the virus at two different targets. Of course
15 there is the issue of mutation resistance which at least
16 dual nucleoside therapy has demonstrated. But what one
17 would--one would think that this probably wouldn't be the
18 answer of a long-term therapy, but again, that is
19 theoretical. And I think that several people have already
20 talked about, you know, appropriate use, and it probably
21 wouldn't be an initial therapy although it might be part of
22 it, or it might be useful to some people to have a twice-a-
23 day regimen.

24 The risk/benefit ratio in part may have something
25 to do with question two, in other words, who are you going

1 to use it in? If there are other drugs available which
2 have, in combination, good antiviral response, and you have
3 another combination but one of the drugs may be associated
4 with fatality, which is different than the others, then that
5 may--that may change the risk/benefit ratio. I think,
6 though, it's a little bit confusing with multidrug regimens
7 exactly--exactly what's going on, so it may be--I think it's
8 a bit premature to see where that will--where that will come
9 out.

10 The recommendation of managing patients with rash,
11 it looks like this drug may be the first one that you'd want
12 to discontinue if you had a variety of agents and developed
13 what looked like a hypersensitivity problem.

14 We talked about recommendations and the proposal
15 for a traditional approval package. Well, I don't think the
16 sponsor is naive and I believe that they would be looking
17 very carefully to see what is going to make the best package
18 and would work with the FDA. It's hard to, you know, come
19 up, here's the study, here's the study to do, but I'm sure
20 the company doesn't want to see this--you know, the efforts
21 of this drug go to waste, and I think that will be an
22 important, probably an important task which they are
23 probably undertaking at this very moment, and I'll end
24 there.

25 DR. MASUR: John?

1 DR. HAMILTON: It's great following Dr. Pomerantz
2 and Lipsky and Matthews, and I don't have to say that much,
3 but in this case since I voted differently, perhaps I could
4 say just a few words, supplement what I said earlier.

5 I think underlying my position here today is that
6 I don't consider the undetectable plasma viral load as being
7 the Holy Grail of treatment of HIV, a view that I'm happy to
8 see some pretty prominent AIDS investigators are supporting
9 as well, including Jay Levy in The Lancet a few months ago,
10 including David Cooper very recently, and others. I think
11 there's a larger picture here. Efficacy is one thing.
12 Effectiveness, effectiveness is another.

13 So I guess perhaps then I intentionally, and
14 certainly unintentionally as well, hold the sponsors to
15 something of a higher standard than perhaps they have been
16 given marching orders for, and I know that's possibly not
17 fair also. They have been given a task and, as you saw,
18 seven of nine agreed that they had done so. And I don't
19 altogether disagree with those votes, though I would
20 continue to say I think there are some supplementary pieces
21 of information that I think we would all profit from, and
22 hopefully those will be provided in the follow-up period, in
23 the course of pursuing the traditional approval.

24 Those comments having been said, I think my
25 interpretation of the risk-benefit ratio here would probably

1 be self-evident. It depends on what you mean by "benefit."
2 We are instantly attaching some risk here in the form of a
3 new drug with a potentially serious side effect, perhaps
4 not.

5 But I'm always concerned when something serious
6 happens in a smaller number of patients and you then put it
7 out in that larger number of patients, with health care
8 providers who perhaps are not as well informed, who may
9 inadvertently re-challenge these patients and have a much
10 larger problem than we see in clinical trials. I think that
11 wouldn't be all that unexpected.

12 In addition, efficacy traditionally falls when one
13 puts a product in the general population, so this drug too
14 is not a miracle. On the other hand, it may well provide
15 some benefit. We heard, as I said earlier, some impassioned
16 testimony from one of my duramites today, and he means it.
17 And I'll say that I have known this man for some time, and
18 he looks a lot better, there's no doubt about it, and I'm
19 glad for that.

20 But I think efficacy or cost/benefit here is
21 highly dependent on the definitions that one imposes. If
22 one requires actual quality of life benefits and, you know,
23 feeling better from day to day, well, there are ways to
24 measure that. Symptoms are included. Simple pill-taking
25 can be an adverse side effect of sorts. In this case they

1 may have simplified that. That's good. It's not reason
2 enough, however, in my view to provisionally license this
3 drug. Nonetheless, it's good.

4 So risk/benefit, yes. I don't know. I don't
5 think we're going to have a fair measure of that. I would
6 be reluctant to use three nucleoside analogs, personally.
7 It just doesn't make much sense to me. Have I done it?
8 Probably. Will I do it again? Probably. Would I recommend
9 it? No. The problem is, we're running out of drugs here.
10 To that extent, I am extremely grateful for Glaxo Wellcome's
11 commitment to this area of research and drug development.

12 The rash, potentially serious. I already
13 mentioned that I think it's going to potentially get worse
14 once this gets out into the community. That remains to be
15 seen. I think to take all the appropriate advisory,
16 educational efforts that have been outlined, and others, is
17 completely appropriate and I hope will be done.

18 Inevitably, however, people don't always get the
19 message. I mean, those of you who have been in the AIDS
20 field for any period of time whatsoever realize very quickly
21 that even the message of transmissibility and infectivity
22 never seems to reach receptive ears somehow. It's always
23 astounding to me that that's the case, and I can imagine
24 that this message too will fail to reach a lot of people.
25 Hopefully they'll keep track of it, though, "they" being

1 Glaxo Wellcome, and if there's anything serious, why,
2 something will be done, and I have confidence that that will
3 happen.

4 And I've addressed briefly the dissemination of
5 information. I'm not certain I have any idea what to
6 recommend for Phase IV studies. I'd like to see us get
7 through Phase III, and then--and then think about it.

8 DR. MASUR: Well, that's the virtue of being an
9 advisor, not a member of the agency.

10 Dr. Wong?

11 DR. WONG: I guess I voted for accelerated
12 approval. I agree with virtually everybody else that I
13 would have liked to have seen a more complete set of data to
14 justify that, though, but I guess on balance I came down on
15 yes.

16 You know, with respect to these specific
17 questions, you know, triple nucleoside analogs, I guess it
18 should be an option, since we don't have that many options.
19 And then I considered questions three through five really
20 all to be the same, in the sense that we don't have enough
21 information to draw any conclusions on these points, and I
22 would put it right back to the sponsor, that I think it
23 should be up to Glaxo Wellcome to generate clear data on the
24 benefits and risks, and particularly about how to handle
25 possible adverse effects.

1 I don't think we really saw enough information to
2 draw any firm conclusions about what really is this
3 syndrome. For example, there were no controls, and I think
4 that we need some--you know, some careful and rigorous
5 clinical research here to describe this syndrome and also to
6 work out what the best way to handle this syndrome should
7 be, even if it takes prospective studies to address that
8 point.

9 I don't think I have anything to add on the
10 traditional approval package. I hope the pediatric study
11 works out to be definitive, but if I were in the sponsor's
12 shoes, I would not count on that and would mount another
13 study. And I think I agree with Dr. Hamilton on Phase IV.
14 We need to finish Phase III.

15 DR. MASUR: Okay. Skip?

16 MR. O: Sure. I'm one of the two that came down
17 on the other side of the coin, although it was a very
18 difficult call for me. I would--as we move forward here, I
19 think it would be very helpful if we could see some plans in
20 the future or something worked out with the agency with
21 regard to formal analyses of the risk/benefit, and
22 particularly the safety analyses. We talked a little bit
23 about that today, but I think that there are a lot of
24 analyses that can be undertaken to take a look at factors
25 that might predict hypersensitivity, and I think it would be

1 very useful for those things to be undertaken and for those
2 things to be part of the traditional package that comes
3 forward.

4 The issue of the 24 percent dropout, not to keep
5 mentioning that, but since this is one of the pivotal
6 studies now for the traditional package, I think it really
7 would be important for the agency and the sponsor to get
8 together on that matter, and I'm sure that they have, for
9 the reasons mentioned here, but I am concerned. The point
10 made by Dr. Elashoff that the 24 percent dropout in an
11 equivalent study tends to make the groups more comparable,
12 so in a sense that's a little more problematic than it is
13 with an efficacy study, and I think that that issue will
14 need some careful attention.

15 I still do believe that the data that were
16 presented here today largely support a benefit, if anywhere,
17 in the group that is treatment-naive. In particular in the
18 adult and then even among the pediatric population, it's
19 those individuals who had no prior--I realize it was both
20 therapies. That's where the effect seemed to be seen. And
21 so the experienced population is one where the likelihood of
22 benefit really is going to be small.

23 I'm not sure I have anything. I think that's
24 about all I have here, Henry.

25 DR. MASUR: Okay. Thank you. I guess the next,

1 going in an order known only to me, Wafaa?

2 DR. EL-SADR: I'll go to question number two. I
3 think the question of three nucleoside analog therapy is a
4 question that's an unknown, and probably the ongoing study
5 will demonstrate whether this is a viable strategy, since
6 this is the study that's comparing triple nucleoside versus
7 a PI-containing regimen. So I'm sure this study will be
8 very important, because I think it will be the first one
9 that may provide answers to this potential strategy.

10 The risk/benefit ratio, I am concerned because of
11 one issue that many people today mentioned, that this is a
12 very convenient regimen, and it is a convenient regimen, and
13 therefore it's going to be--people will be really tempted to
14 use it or a lot of people will be tempted to use it.
15 Providers who are not very experienced with HIV care will be
16 tempted to use it, and the patients may get into trouble if
17 they don't really know the risks that may be associated with
18 this drug.

19 So I think for the sponsor, they need to be very
20 careful in how they teach and how they talk to the providers
21 and to the patients. Say yes, it is convenient, but on the
22 other hand there's a very important caveat, which is the
23 potential for a serious side effect. So I think the
24 convenience is very helpful but the convenience can also
25 tempt a lot of people to misuse this drug and for problems

1 to develop.

2 I think the key to dealing with the side effects
3 and the hypersensitivity issue, I believe is reaching the
4 patients. I always feel that the patients are the ones who
5 really teach the provider, so we have to somehow be able to
6 reach all of our patients and be able to inform them of this
7 potential side effect, and to think of reaching the
8 providers and to think of the providers as a whole team.
9 Now with this focus on adherence, we're thinking more and
10 more of sort of all the team of providers taking care of the
11 patients, to go beyond the doctor and try to maybe get the
12 nursing staff and other people involved in managing our
13 patients to know about this potential side effect, as well.

14 I think the problem with the rashes, I think
15 mistakes will be made. It's inevitable that people will
16 think that the rash or the manifestations are not the
17 hypersensitivity reactions. Mistakes will be made. I hope
18 that people will be rather cautious and they will err on the
19 side of caution and discontinue medication if they suspect
20 that this may be a hypersensitivity reaction to abacavir.

21 As for dissemination of information, I mentioned
22 what I thought about dissemination of information. I think
23 the idea of wallet cards is a very, very useful, especially
24 for patients who need to go to an emergency room in the
25 middle of the night or on a weekend or when they can't reach

1 their provider.

2 Number six, question number six, the traditional
3 approval package, again I think it's risky with just the
4 pediatric study. It would be really nice to have studies in
5 patients with advanced disease, an experienced population,
6 because I think we've seen all these reports and posters and
7 presentations on salvage therapy, as I think Dr. Matthews
8 mentioned, and it's very difficult to interpret the results,
9 and it would be very nice if there were some studies that
10 really tried to, in an organized manner, look at people who
11 are experienced and with advanced disease.

12 Finally, on Phase IV studies of abacavir, I think
13 the convenience of the regimen may provide an opportunity to
14 really look at adherence in some Phase IV studies, as well
15 as quality of life issues as well.

16 Finally, I think coming back to where we started
17 today, about 16-week data versus 24-week data versus 48-week
18 data, I guess I, in thinking about the data presented today,
19 I think for the population that's treatment-naive, what I'm
20 really looking for in a study is the durability of the
21 effects, of the antiviral effects, and 16 weeks does not
22 make sense to me for a naive population. I think at a
23 minimum a 24-week population would make sense to me, because
24 it is a naive patient population.

25 And I would feel much more comfortable for naive

1 studies to be looking at 24-week data, because I'm really
2 more interested in durability. I think for advanced--in
3 patients who are experienced, who have multiresistant virus,
4 then I think the earlier data may be quite useful. As we
5 noted, the effect is more likely to be limited and not
6 likely to be as durable. And I'll stop here.

7 DR. MASUR: Okay. Thank you, Wafaa.

8 Let's--why don't we just go in order. We can
9 start over here, Ram, and go around, since I think the
10 urgent travel issues are taken care of.

11 DR. YOGEV: Just for the record, next time I'm
12 leaving at 2:30.

13 I think identified lists of new population that
14 this triple combination, because of b.i.d. two tablets, are
15 very limited, will be very effective, if as long as we agree
16 that we can have an induction like or a shorter period of
17 time using it, because we know after 16 or 24 weeks it might
18 lose its effect, and then move to a better therapy. Where
19 for example a pediatric patient, when we have a problem with
20 compliance, IV drug user, adolescents, and other groups who
21 have a decreased compliance and an increase in dropout, that
22 might be a very important mechanism to start therapy, to get
23 the effect of that specific one, with the understanding and
24 hopefully part of the education to the physician that this
25 one is really temporary and you have to change in its

1 approach.

2 I have a problem, that I sat here for six, seven
3 hours now, and I still don't think that hypersensitivity is
4 well defined, and I hope you approve the drug only in the
5 spring because we don't what to do with influenza in the
6 winter, and it's going to be a major problem, because over-
7 education is a disadvantage.

8 Every time a person would come to me now with a
9 runny nose and a fever and maybe a rash, and pediatric have
10 six of them per year, we are going to stop this drug. So we
11 are going to stop many more times than we are going to
12 start, and then we have to form yes or no to restart. So I
13 think a major effort has to be put by the company to define
14 this hypersensitivity better, so we know how to deal with
15 it, because otherwise that will pose the risk versus
16 benefit.

17 To me the population, that there is enough that--
18 for accelerated approval, is the naive population. The
19 problem is the pediatric, as I mentioned, is working on, as
20 far as I am concerned, too many patients monotherapy. I was
21 especially impressed when you had more than 10,000, if you
22 took away those who were not treated with AZT or treated--
23 CD4, you didn't find any difference between the two groups,
24 whether it be triple or dual, and you do see that so much in
25 between 152 and 300, led us to believe that dual therapy is

1 good when we look at 16, even 24.

2 So I am not sure 24 is the right one for
3 accelerated, but you need to give some points for 16, give
4 you at least some indication. If it's an excellent drug, I
5 think 16 might be good, and then we can change according to
6 what 16 is showing us is different. But to me the studies
7 in pediatrics are interesting at best, but I think the
8 design was not the one I would like to see.

9 I would like to see a design which will take
10 salvage as a protocol with other drugs, another triple,
11 working on the same mechanism, and on the naive maybe use
12 this one and showing it compared to another triple, to see
13 if really abacavir with its risk of hypersensitivity is
14 better than the ZVD/IDV and 3TC, for example. So another
15 triple nucleoside, if you want even to go in that direction.

16 And I would like also, there is a claim all the
17 time and we didn't touch on it, or touch on it and run away,
18 on this dementia CSF penetration. I think is very dangerous
19 to take three patient and to suggest there is 30, 40 percent
20 penetration. I don't know what the range is. I think it's
21 not enough, and any study which we are going to design,
22 especially in the salvage patient, should include in it CSF,
23 at least levels.

24 And some effort should be made if somebody goes
25 into the unfortunate brain of those patient, for pediatric,

1 whatever, to design a study which will give them for about
2 few, four or five drugs, to just support a study state and
3 then take some even brain tissue to see if it's really
4 working in the right place we want, and I'm not sure CSF
5 does represent it. So those will be my contribution to the
6 Phase IV, if you want to call it like that.

7 DR. MASUR: Pam?

8 DR. DIAZ: Most of what I would say has already
9 been said. I'll just make a couple of comments. In
10 particular the magnitude of the risk/benefit ratio is really
11 highly dependent on the group in which one is measuring it,
12 and there are some specific groups, many of which have been
13 mentioned here today, where I believe that risk/benefit
14 ration is high enough to merit the use.

15 But I would strongly encourage the FDA to work
16 hard with the sponsor to guide physicians and others in
17 which groups they feel this decision merits the use of the
18 drug in particular, and likewise along the lines of the side
19 effect with the hypersensitivity, in particular to work--for
20 the sponsor to work very diligently in developing a program
21 to really further delineate the risk factors associated with
22 this adverse event.

23 And also to provide physicians, once this is out
24 on the open market, a plan not only that includes recording
25 of any hypersensitivity adverse events, but in particular on

1 what is necessary and what should be done in terms of data
2 collections, specimen collections, God forbid, autopsy if a
3 death occurs, in being able to help further describe and
4 delineate this, this event, these events, when it occurs.

5 On the flip side of that, the patients with just--
6 who will present with just rash and perhaps no other adjunct
7 symptoms or signs perhaps associated with this syndrome, I
8 think to guide physicians in what to do in those scenarios
9 and how to monitor patients carefully, time line, et cetera
10 for patients with rash, and with the concern that that may
11 be a heralding event for progression, is also extremely
12 important.

13 I think some of the other topics have been
14 addressed adequately, as far as I am concerned.

15 DR. MASUR: Okay. Thank you. Let's go around to
16 Joe.

17 DR. HOGAN: My concerns are just mostly in some of
18 the--how the analyses relate to how the drug would be used
19 after the accelerated approval. The one issue that I
20 brought up during the question and answer with the sponsor
21 was about the analysis of the pediatric data, and I think
22 this is not entirely clear. I think it's debatable about
23 whether the drug is efficacious in the pediatric population
24 at large, or just in a specific portion of the pediatric
25 population.

1 And unfortunately I don't think the trial really
2 addresses either of those questions. Number one, it doesn't
3 address whether it's efficacious in the general pediatric
4 population because the combined analysis is not significant
5 at the 5 percent level, even though the effect is dramatic.
6 When the adjusted analysis is presented, my feeling is that
7 the adjustment is improper in the sense that the treatment
8 effect is dramatic for those who start out with viral load
9 over 10,000 but not--there is no real treatment effect for
10 those who start out under 10,000. And in fact, it's just a
11 maintenance effect.

12 So I think that's a crucial issue, and I know a
13 lot of folks around the table got excited about the
14 pediatric study, and the FDA I think was properly cautious
15 about the result.

16 I think that the company in the traditional
17 approval needs to investigate this a little bit more
18 carefully. In particular, using the new drug on pediatric
19 patients where the viral load is already less than 10,000
20 seems to unnecessarily expose them to risk of side effects.

21 So that's a big concern, and I think that the
22 analysis that adjusts. that shows an overall p-value that's
23 highly significant, should simply be disregarded because it
24 is improperly applied. So on the flip side, if you think
25 there is some efficacy, it's just that it's in a population

1 with viral load that starts out higher than 10,000.

2 The problem is, when you do the subgroup analysis,
3 you're stuck with the quandary it's no longer a randomized
4 comparison. So there seems to be some hope there, but I
5 think the analysis needs to be done a little more carefully
6 and maybe even a new cohort started in the group, with a new
7 group over 10,000.

8 It's also troubling in the pediatric analysis that
9 the dropout rate, which wasn't really adjusted that
10 carefully, is twice as high on the new drug than on the
11 placebo. It's 11 percent versus 5 percent, from what I
12 recall, and I think that this points to a larger issue that
13 has been addressed by several of the panelists about dropout
14 in general.

15 In a lot of these long-term trials, dropout is a
16 problem. I think due to the hypersensitivity and the
17 possible ramifications of hypersensitivity, some sort of
18 protocol for following dropouts, people who drop out, is
19 warranted. Twenty-one percent dropout or 25 percent dropout
20 on the equivalency trial is extremely troubling, especially
21 since we don't know what the long-term ramifications of re-
22 challenge are; that is that if a person drops out of the
23 study drug and then goes off, maybe gets a study drug some
24 other way later on down the line, is that person also
25 exposed to a re-challenge effect?

1 So I was a little disappointed in the answer that
2 there is no well-defined protocol for re-following dropouts.
3 I think that needs to be explicitly developed for
4 traditional approval. I think that it may be possible to
5 find these 24 percent of people, and there needs to be some
6 sort of community outreach, re-phone calling, visiting
7 people at their home, something like that, to find these
8 people, because the issue of the hypersensitivity is serious
9 enough to warrant that.

10 DR. MASUR: I'm sorry. Go ahead.

11 DR. HOGAN: I just had a couple more comments, but
12 that's okay. I know it's late, but--

13 DR. MASUR: No, actually now we have an unlimited
14 amount of time.

15 DR. HOGAN: I see. Well, I won't exercise that
16 limit.

17 More on the safety issue and sort of tied in with
18 the dropout is, I'll admit that clinicians really are the
19 experts here, but my--I was just a little bit concerned that
20 the--that the labeling or the warning associated with the
21 possible side effects was not quite dramatic enough,
22 especially since this is going to be recommended for general
23 distribution, not within the well-controlled setting of a
24 clinical trial.

25 You know, it's one of those things that's a lot

1 easier to criticize rather than create. I really don't know
2 what the method of a more dramatic labeling procedure would
3 be, but I would certainly like to see one. I wasn't totally
4 convinced that a little wallet card would be enough, and
5 something a little more creative, a little more dramatic,
6 given the possible side effects, I think is also warranted.

7 So just some last notes on possible analyses. I
8 think in the traditional approval it's unfortunate that the
9 3003 trial, I think the long-term efficacy is really--this
10 sounds a little bit harsh, but I think it's really not going
11 to provide any information about long-term efficacy, and
12 that's too bad. But the switching option really I think
13 will prevent us from seeing anything meaningful long-term on
14 adults in that population.

15 I think that the investigators, not only do they
16 need to have a protocol for following people who drop out
17 but they also need to know what are the characteristics of
18 people who drop out. That is, if you think about the
19 placebo arm, if a patient enters a trial and they know
20 they've been randomized to either placebo or active drug,
21 and they don't notice that their viral load is dropping,
22 they might be more likely to leave the study.

23 And I was thinking during the analysis that that
24 might explain actually the differential in the CD4 effect in
25 the 3003 trial. If you have that the people who leave on

1 the placebo arm are the ones that are doing worse, then you
2 somehow have a more--a better selected, in terms of CD4
3 count, a better selected population on the placebo arm
4 because you've weeded out those who have low viral loads, if
5 there's any association between viral load and CD4.

6 And then finally with the analyses methods, I
7 think, you know, I read this with sort of a skeptical eye in
8 the sense that there were some places where I thought the
9 analyses were fishing. I think that the sponsors need to
10 define their analyses a little bit more clearly and use more
11 modern statistical methods.

12 The imputation methods that they used, filling in
13 the data with last value carried forward, are rather
14 arbitrary and there's a little more modern ways of dealing
15 with that, to be specific for the record, such as maximum
16 likelihood and generalized SMA equations, and Dr. Woolson
17 has developed several of these methods himself. Really they
18 can be implemented on any standard software package, and
19 there's no reason why the data can't be looked at that way,
20 and that will help us maybe understand a little bit better
21 what's happening with the dropouts.

22 So those are my comments, and also, thanks also to
23 the sponsor and to the FDA for the opportunity to be here.
24 I appreciate it.

25 DR. MASUR: Okay. Well, those are some useful

1 statistical considerations.

2 Joe?

3 DR. BERTINO: Well, my plane is not until 9:00,
4 and Jeff lives in Washington, so having the last two of us
5 go--I'm not going to comment on number two because I think
6 smarter people than me have already done that.

7 I think in terms of the risk/benefit for abacavir,
8 I'm very concerned about the hypersensitivity reaction. I
9 think if this drug was in a different class, such as an
10 antibiotic, it wouldn't be approved. I think that my
11 concern is, is what happens in the office setting when it's
12 one-on-one with the pharmaceutical representative and the
13 doctor, and I think people who are going to prescribe this
14 or follow patients who are on this agent really need to be
15 very hypersensitized, too, to this possible side effect.

16 I think in terms of number four, I think an
17 algorithm would be good, to provide to prescribers a very
18 detailed algorithm. If patients are on A, B and C, and C
19 happens to be abacavir and the patients develop a rash, you
20 do this; if they develop a rash and fever, you do this; if
21 they develop, you know, whatever constellation of symptoms,
22 here's what you would do.

23 Number five, I liked Dr. Pomerantz's comment about
24 disseminating the education to a lot of people, including
25 pharmacists, and I think patients tend to see their

1 pharmacists more because sometimes of restrictions, of only
2 being able to get a couple of months' worth of medications
3 at a time. So I think that that would be important
4 information, so the pharmacist can then either call the
5 patient's physician or have the patient go to their
6 physician right away, whatever.

7 Number six, I don't think the traditional approval
8 package is ready for consideration. I think we need to get
9 full analysis on the 3005 study.

10 And finally for number seven, just two comments on
11 Phase IV studies. One is, is that in terms of the
12 hypersensitivity mechanism, I think if you look at the data
13 with cefaclor, if you look at the data with phenytoin, the
14 mechanisms of these have been worked out now. I would urge
15 the sponsor to look at the mechanism and the epidemiology of
16 this hypersensitivity reaction, and maybe it could be easily
17 pinned down and you could decide who not to use this drug
18 in. That would be a huge, huge benefit.

19 One of the--the big concern I have is, and I go
20 back to this again, I know FDA has heard this from me for
21 four years now, is the data in men versus women. A number
22 of years ago in the Federal Register there were some
23 proposed guidelines on studies of drugs in men versus women,
24 including menstrual cycle effects, pre- and post-menopausal
25 studies. These, this publication generated a lot of comment

1 from big pharma.

2 And I think I would just say to the sponsor, as I
3 have said to other sponsors, it would be great if someone
4 would take the high road and do these studies in men versus
5 women. For this particular drug, a 54 percent increased
6 exposure of women based on AUC is very concerning to me. I
7 think I would say to the FDA that the reason that these
8 studies aren't done is because the FDA doesn't make the
9 sponsors do the studies.

10 Women are a huge majority of the population in
11 general in the United States, and certainly lots of women
12 have HIV disease, and I feel very strongly that sex
13 differences studies in terms of kinetics, dynamics, efficacy
14 and toxicity really need to be done for not just this group
15 of agents but in general for drugs. So that's my comments.

16 DR. MASUR: Good.

17 MR. BLOOM: I should be clear that the reason I
18 said no is not because I don't believe that this drug may be
19 a valuable drug. I do think it may be valuable, but I
20 really think the sponsor shortchanges themselves and
21 shortchanges the patients when they really don't study it in
22 a way that it's likely going to be used once it's approved.

23 Because not everyone that's going to be taking
24 this drug is going to be using it, obviously, with AZT/3TC,
25 particularly if they are previously experienced with

1 AZT/3TC. And I think that's an important point, as we did
2 learn today there are certain populations that this would be
3 inappropriate to use for. But also it would be good to know
4 if it was inappropriate to use for other previously
5 nucleoside experienced people.

6 But I think the thing that troubles me the most is
7 that I hope Glaxo and the other sponsors that are here and
8 the FDA understand that right now, when a patient decides to
9 start making the commitment to treatment, it's a lifetime
10 commitment. You don't have a choice of making a halfhearted
11 commitment or a partial commitment, but you make a
12 commitment for a lifetime of therapy at the moment.

13 And with this information given in this
14 application here, you can't possibly know whether this would
15 be your best choice if you are going to initiate therapy. I
16 think we owe it to the people that are treatment-naive, as
17 well as the unfortunately 40,000 new people that are still
18 getting infected every year, that are going to be coming
19 into the market looking for therapy, looking for treatment,
20 to be able to give them the best possible opportunity to
21 effectively treat their disease.

22 And we have learned, if nothing else, that the
23 first choice has serious consequences for your subsequent
24 choices, and with this kind of information it's very, very
25 difficult to say where this would fit in that dynamic of

1 choices, and I think that's unfortunate. I think it's
2 unfortunate because I think it shortchanges a drug that
3 potentially could be enormously beneficial, and I think it
4 shortchanges the patients to make educated choices.

5 I think the timing of this is a little difficult
6 for the hypersensitivity thing because it's flu season, and
7 in the real world there's probably doctors that are going to
8 have a very hard time differentiating between the flu and
9 the hypersensitivity reaction, as well as the rash reaction,
10 which NNRTI's have frequent rash reactions.

11 This probably is not an appropriate drug to start
12 if you're going to start therapy with one of the NNRTI's
13 that also create rash at the same time, unless there is
14 clearly a way of delineating what is causing the rash and
15 which one is not, particularly since one of the rashes is
16 life-threatening and the hypersensitivity is life-
17 threatening, so that would be two life-threatening
18 situations to start out with. That would be pretty risky.

19 And as far as disseminating information, I think
20 that's--you know, that's the key. One of the good things
21 about HIV and AIDS now, and this will be one of Henry's
22 challenges, is that there is the DHHS HIV/AIDS treatment
23 guidelines that make recommendations in terms of treatment.
24 And I hope that the fact that those guidelines exist will
25 give this sponsor and other sponsors incentives to do the

1 studies so that they can be recommended in the guidelines as
2 an appropriate treatment, and where it will fit in the
3 dynamics.

4 But it does give you an incentive to have it rated
5 as best treatment, better treatment, less effective
6 treatment. So hopefully everyone is familiar with those
7 treatment guidelines, and if companies aren't going to take
8 it upon themselves to do these kind of studies, hopefully
9 NIH will. But certainly the treatment guidelines have been
10 a godsend in helping people understand this.

11 And there's a lot of doctors--we all talk about
12 experienced patients--there's still a whole lot of people
13 that aren't experienced in treatment, haven't had treatment
14 at all. That's the majority of the population. So it's
15 really incumbent upon everyone to keep that in mind, and we
16 owe it to them to let them be able to make the best choice
17 possible so that they can live good, full lives and this can
18 be a manageable disease.

19 I've been living with AIDS for 12 years now. I'm
20 lucky, I've made very good choices. I don't have a lot of
21 resistant virus. I'm not the usual case. So I haven't
22 burned all my options. Other people shouldn't have to burn
23 all their options with bad choices, and make good choices up
24 front, and that's why I'm very disappointed in how this is.
25 I am glad to see that they did a pediatric. I will say that

1 there was another drug recently approved that also had a
2 pediatric indication, so it's nice to see that we're making
3 progress in that regard. That is something that has been
4 done and they should be commended on that.

5 As far as the Phase IV studies, you know, it's
6 learning how to use this drug as best as possible, with
7 given the other drugs. You know, those kind of studies
8 unfortunately aren't going to be just carried out by the
9 companies, but they will be carried out by the ACTG and NIH
10 and subsequent studies as that.

11 And I thank the FDA, and I thank you for letting
12 me be here today.

13 DR. MASUR: Thanks, Jeff. Fortunately, as far as
14 the antiretroviral guidelines are concerned, Orrin Cone, who
15 has been in the back, hopefully he will take up that
16 challenge, because I think it is important that the
17 information be available so that specific guidelines can be
18 given.

19 Let me make a few final comments. First of all,
20 as a longstanding committee member, I'm glad to see that the
21 criteria for accelerated and traditional approval are
22 changing as the situation changes, and I hope that we will
23 begin to see more 24-week data rather than just 16-week data
24 for accelerated approval consideration. It sounds like
25 that's the direction we're going, and I would certainly be

1 enthusiastic about that.

2 There's clearly a lot of concern with this drug
3 about the dichotomy between immunologic response and
4 virologic response. I was somewhat disappointed not to see
5 more data on--that might be able to separate out which
6 patients had a virologic response without an immunologic
7 response. I hope we will learn more about that, because
8 clearly there are some very important issues coming down the
9 road with other drugs where there is that dichotomy, and
10 with the immunomodulators, where other groups will have to
11 make that decision.

12 In terms of long-term efficacy, again, I share
13 skepticism that we're going to have more than one study of
14 the studies presented to us that will give us useful data at
15 48 weeks, and would hope that the agency is going to be very
16 definitive with the sponsor about what needs to be done and
17 how soon it needs to be done in terms of getting another
18 study started.

19 In terms of the dementia study, I was somewhat
20 disappointed that only three patients, and it wasn't clear
21 to me whether they were patients on the dementia study, had
22 drug levels in the CSF. To some extent, as data becomes
23 available, if there is a correlation between HIV viral load
24 and CSF and dementia, it would be useful to know whether the
25 patients--whether any patients who might have had a response

1 or appeared to have a response also had a drop in CSF viral
2 load, and happened to be ones who had higher CSF levels.
3 But it's very difficult to know whether there's anything to
4 look forward to in terms of a role for abacavir with
5 dementia or not.

6 In terms of strategy studies, it's heartening to
7 see that companies are beginning to work together to look at
8 sequential studies with different drugs, and hopefully we
9 will continue to see that.

10 In terms of safety, I was disappointed at the
11 safety database. While it's been said by a number of people
12 on the panel that it would be great to have some algorithms
13 that indicated what to do, it's not clear to me that the
14 data is there about what to do. We certainly don't have
15 enough data about the eight patients who died. There were
16 distressing holes in knowledge about what was known and what
17 was not known.

18 It's also not clear to me whether--what the
19 database is that says that continuing a patient on a drug
20 once they have a rash makes the syndrome worse. One of the
21 big issues is going to be, is if a patient has a fever and a
22 rash, on the one hand we're told not to stop and restart,
23 that's when you get into trouble. It's not clear to me how
24 often you get into trouble from just continuing the drug.
25 So the question is, if you're going to try to tough it out,

1 how long should you tough it out and when should you stop?

2 And I hope that that data will become available,
3 and that there will, as several people suggested, be some
4 focus studies on those who clearly have the syndrome because
5 they've been re-challenged and gotten into more trouble, and
6 that there will be some comparative studies looking at
7 patients who have fever or rash due to other drugs compared
8 to this hypersensitivity reaction, to see if we can develop
9 more data that would help identify this syndrome
10 specifically.

11 The mechanism of the adverse reaction, we didn't
12 hear very much about that, what the sponsor is doing to look
13 into the mechanism, but I would hope that at some of the
14 treatment sites that there will be a plan that if a patient
15 has this syndrome, there will be some specific studies
16 looking at immunology, looking at hemodynamics, depending on
17 the severity, so that we get some more information, because
18 right now when we have simply a random observational data
19 base, we are obviously not going to get very far in terms of
20 understanding what this is, how to treat it if it occurs, or
21 perhaps how to prevent it.

22 But in any event, I think that there is a lot of
23 useful data here, and we'll look forward to what the sponsor
24 negotiates with the agency and hope that the agency can come
25 up with a very concrete plan that will help us all have the

1 information that we need.

2 So unless one of the committee members has another
3 comment, we again appreciate the candor of the sponsor in
4 providing all the data and the pre-meeting material. We
5 appreciate the agency analysis. And on behalf of the
6 committee, we thank everybody for attending, and we'll look
7 forward to seeing you at the next meeting.


8 [Whereupon, at 4:12 p.m., the meeting was
9 concluded.]

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C E R T I F I C A T E

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.

A handwritten signature in black ink, appearing to read 'T.C. Bitsko', is written over a horizontal line.

THOMAS C. BITSKO

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