

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ANTIVIRAL DRUGS ADVISORY COMMITTEE
MEETING

MONDAY, APRIL 14, 1997

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The meeting took place in the Conference Room, The Armory Place, 925 Wayne Avenue, Silver Spring, Maryland 20910, at 8:30 a.m., Scott M. Hammer, MD, Chairman, presiding.

PRESENT:

Scott M. Hammer, MD, Chairman
Rhonda W. Stover, RPh, Executive Secretary
Sandra Hernandez, MD, Consumer Representative
Wafaa El-Sadr, MD, MPH, Member
Judith Feinberg, MD, Member
James J. Lipsky, MD, Member
Henry Masur, MD, Member
William Christopher Mathews, MD, MSPH, Member
Mary Dianne Murphy, MD, FAAP, Member

ALSO PRESENT:

Janet Elashoff, PhD, Guest Statistician
Virginia Kan, MD, Consultant
Alan M. Sugar, MD, Consultant
Brian Wong, MD, Consultant
Donald Armstrong, MD

FDA REPRESENTATIVES PRESENT:

David Feigal, MD
Donna Freeman, MD
Teresa Wu, MD
Liji Shen, PhD, FDA Presenter

SPONSOR REPRESENTATIVES PRESENT:

Marc Gurwith, MD
Frank Martin, PhD
Carole Miller, MD

PUBLIC REPRESENTATIVES PRESENT:

Thomas J. Walsh, MD

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1 P-R-O-C-E-E-D-I-N-G-S

2 8:30 a.m.

3 CHAIRMAN HAMMER: Good morning. I'd like
4 to call this open session to order. This session is
5 to deal with the application by Sequus for Amphotec.

6 I'd like to begin by asking the people
7 around the table to introduce themselves, please,
8 starting to my right.

9 DR. KAN: Virginia Kan.

10 DR. WONG: I'm Brian Wong.

11 DR. SUGAR: Alan Sugar.

12 DR. ELASHOFF: Janet Elashoff.

13 DR. MATHEWS: Chris Mathews.

14 DR. HERNANDEZ: Sandra Hernandez.

15 MS. STOVER: Rhonda Stover, FDA.

16 CHAIRMAN HAMMER: Scott Hammer.

17 DR. EL-SADR: Wafaa El-Sadr.

18 DR. MURPHY: Dianne Murphy.

19 DR. LIPSKY: Jim Lipsky, Mayo Clinic.

20 DR. WU: Teresa Wu, Division of Antiviral
21 Drugs, FDA.

22 DR. FREEMAN: Donna Freeman, Antiviral
23 Drugs, FDA.

24 DR. FEIGAL: David Feigal, Office of Drug
25 Evaluation for FDA.

1 CHAIRMAN HAMMER: Thank you.

2 I'd also like to announce that Dr.
3 Feinberg will be arriving a little bit late this
4 morning, around 9:30.

5 Personally, for the Committee's sake and
6 for the record, I'd like to acknowledge, Dr. Wayne
7 Greaves who has left this Committee after a good deal
8 of terrific service to join industry. We wish him the
9 best.

10 Without further ado, Rhonda, did you have
11 any opening comments?

12 The first issue on the agenda is the Open
13 Public Hearing. We have one individual signed up.

14 Sorry, Rhonda corrects that. She does
15 have a statement.

16 MS. STOVER: This is a conflict of
17 interest statement. The following announcement
18 addresses conflict of interest issues associated with
19 this meeting and is made a part of the record to
20 preclude even the appearance of a conflict.

21 Based on the submitted agenda and the
22 information provided by the participants, the Agency
23 has determined that all reported interests in firms
24 regulated by the Center for Drug Evaluation and
25 Research present no potential for a conflict of

1 interest at this meeting with the following exception.

2 In accordance with 18 US Code 208(b)(3),
3 a limited waiver has been granted to Dr. Alan Sugar
4 which permits him to participate in the Committee's
5 discussions concerning Amphotec. Dr. Sugar will,
6 however, be excluded from any vote concerning this
7 product. A copy of this waiver statement may be
8 obtained from the Agency's Freedom of Information
9 Office, Room 12A15 of the Parklawn Building.

10 In the event that the discussions involve
11 any other products or firms not already on the agenda
12 for which an FDA participant has a financial interest,
13 the participants are aware of the need to exclude
14 themselves from such involvement and their exclusion
15 will be noted for the record.

16 With respect to all other participants, we
17 ask in the interest of fairness, that they address any
18 current or previous financial involvement with any
19 firm whose product they may wish to comment upon.

20 CHAIRMAN HAMMER: Thank you.

21 Again, now moving to the Open Public
22 Hearing, we have one individual signed up. That's Dr.
23 Thomas Walsh, the senior investigator and chief of the
24 Immunocompromised Host Section at the National Cancer
25 Institute.

1 Dr. Walsh?

2 DR. WALSH: Members of the Committee, my
3 name is Dr. Thomas Walsh. I'm senior investigator,
4 Chief of the Immunocompromised Host Section of the
5 National Cancer Institute, and a member of the
6 Steering Committee of the Mycosis Study Group. I am
7 a participant in the previous FDA workshops and open
8 sessions concerning antifungal drug development trial
9 for empirical antifungal therapy.

10 The goal of empirical antifungal therapy
11 in persistently neutropenic patients is the early
12 treatment of invasive fungal infections and systemic
13 prophylaxis of virus patients. Empirical antifungal
14 therapy is the widely utilized indication for
15 parenteral antifungal therapy in neutropenic patients.

16 The two initial randomized studies of
17 empirical antifungal therapy reported it by the
18 National Cancer Institute and the EORTC in the early
19 '80s were placebo controlled and preceded the use of
20 fluconazole prophylaxis for bone marrow transplant
21 recipients. The sample sizes were small and study
22 endpoints of microbiologically proven infections were
23 achieved with placebo arm and no fluconazole
24 prophylaxis. Amphotericin B has since remained the
25 standard of care for empirical antifungal therapy in

1 persistently febrile neutropenic patients for the past
2 15 years.

3 With the advent of liposomal formulations
4 of antifungal compounds, an open workshop was
5 conducted by the FDA on April 20, 1994. The workshop
6 was widely attended by members of industry,
7 universities and government. A panel was charged with
8 the following question: "Is there a need to
9 standardize protocol design, analysis and reporting on
10 empirical antifungal management of neutropenic
11 patients?" A panel consisting of the members, the
12 following members was convened. Those representing
13 members of the National Institute of Allergy and
14 Infectious Diseases, Fred Hutchinson Cancer Center,
15 the FDA, UCLA, the Veterans' Administration Medical
16 Center, University of Alabama, Stanford University,
17 the National Cancer Institute, and Indiana University.

18 In setting the theme of the ensuing
19 discussion, Dr. Feigal emphasized that demonstration
20 of reduced toxicity is not sufficient in itself in an
21 empirical antifungal study drug design. A study must
22 assure the FDA and medical community that reduced
23 toxicity is not the result of giving effectively less
24 antifungal compound. In studying this challenge for
25 a high level of certainty, the FDA was fulfilling its

1 goal of protecting the public health.

2 A high level of certainty is also
3 important since resolution of fever, rather than
4 proven infection, was being used as the determinant
5 for sample size. Thus, a higher level of certainty in
6 declaring equivalency was necessary for study design
7 of empirical antifungal therapy in persistently
8 febrile neutropenic patients. Perspective and sample
9 size of randomized clinical trials and treatment of
10 proven invasive fungal infections, randomized trials
11 of fungemia and cryptococcosis typically have enrolled
12 200 to 400 patients for proven infections.

13 Among the additional guidelines
14 articulated for an equivalency trial between a
15 liposomal antifungal and amphotericin B, the most
16 pivotal and intensely discussed issue was the need for
17 a sample size sufficiently large to detect response
18 differences of ten percent between study arms.
19 Depending upon the anticipated response rates in each
20 arm, total sample size would range from approximately
21 600 to 800 evaluable patients. With such predictive
22 power, the question arose also, "would we also be able
23 to detect differences in proven invasive fungal
24 infection?"

25 The need for such predictive study design

1 was reaffirmed again in the open session of the FDA
2 Advisory Committee hearing on April 3, 1995. Given
3 these guidelines, the Steering Committee of the NIAID
4 mycosis study group agreed with the following study
5 design: An equivalency trial of liposomal
6 amphotericin B versus conventional amphotericin B with
7 the power to detect differences and response rates of
8 ten percent between study groups. Six hundred, 60
9 evaluable patients, 330 per arm were considered
10 necessary for such a trial. The study was double-
11 blind of both the bag and the tubing. The tubing was
12 important because lipid formulations of amphotericin
13 B could be readily distinguished from conventional
14 amphotericin B and a composite response was also
15 considered appropriate.

16 The composite response for success in the
17 study design was resolution of fever, recovery from
18 neutropenia, the absence of breakthrough fungal
19 infections, discontinuation of study drug and
20 survival. The study was able to complete enrollment
21 in 14 months with 31 centers in which 700 patients
22 were enrolled. The data are currently under review.
23 However, we have learned that the outcome of
24 implementation of the FDA workshop recommendations
25 provided results that had:

1 (1) The power to predict differences in proven
2 invasive fungal infections documented histologically
3 or by culture;

4 (2) The power to detect differences in
5 mortality due to fungal infections;

6 (3) The power to detect differences in fever
7 within ten percent confidence interval;

8 (4) The power to detect differences in safety.

9 Now, such a trial clearly requires more
10 patients than were enrolled in the NCI and EORTC
11 trials. But this is not unexpected given that many
12 high risk patients now receive fluconazole prophylaxis
13 and that a placebo arm is no longer part of the study
14 design.

15 In conclusion, the guidelines for study
16 design for empirical antifungal therapy outlined in
17 the two previous FDA 1994 and 1995 meetings, when
18 implemented in a randomized double-blind trial, permit
19 assessment of differences in documented fungal
20 infection and fungal related mortality as well as
21 fever and safety. Thus, the MSG recommends that the
22 predictive study design outlined in the FDA workshops
23 and implemented in 1995 and '96 be sustained as a
24 standard in conducting randomized trials of empirical
25 antifungal therapy in persistently neutropenic

1 patients.

2 Thank you.

3 CHAIRMAN HAMMER: Thank you very much.

4 Are there any questions for Dr. Walsh from
5 the Committee?

6 Please, Dr. Lipsky?

7 DR. LIPSKY: Would you comment on doses
8 chosen for amphotericin and liposome in comparison?

9 DR. WALSH: Yes. I think in trying to
10 establish a study design that is workable, I think
11 it's pivotal to appreciate that these patients are
12 often critically ill. One needs to have the protocol
13 to be workable to fit appropriately within the context
14 of how patients are managed on a day-to-day basis.
15 Accordingly, the dosages of empirical amphotericin B,
16 conventional amphotericin B, initially was .6 mg per
17 kg. The initial starting dose of the liposomal
18 formulation was three mg per kg.

19 However, following very characteristic and
20 strict guidelines that were agreed upon by the 31
21 institutions there was opportunity, if patients
22 progressed either with fever, clinical deterioration,
23 pulmonary infiltrates, that there would be option in
24 the course to increase the dosage at the clinician's
25 discretion following those guidelines in the following

1 manner: 4.5 mg per kg or 6 mg per kg on the liposomal
2 formulation; or on the conventional amphotericin B, .9
3 or 1.2 mg per kg. So that there was flexibility
4 initially after the initial starting dosage.

5 CHAIRMAN HAMMER: Please?

6 DR. WONG: Could you expand a bit on what
7 you said about ability to demonstrate efficacy in
8 proven fungal infection?

9 DR. WALSH: Okay.

10 DR. WONG: Exactly what were the kind of
11 criteria and the findings?

12 DR. WALSH: The criteria, Brian, were
13 those of histologically proven, literally open lung
14 biopsy for pulmonary invasive fungal infections, or
15 demonstration of organism on bronchoalveolavage of
16 filamentous fungi. Any candidative recovery from BAL
17 was discarded as not being infectious. We considered
18 that as possible but none of those were considered
19 documented or proven. Only the filamentous fungi
20 recovered from a bronchoalveolavage or an open lung
21 biopsy or percutaneous needle aspirate were considered
22 proven for invasive pulmonary infections. Deep tissue
23 biopsies from liver, spleen or positive blood cultures
24 for candida or Fusarium, or skin biopsies
25 demonstrating Fusarium or candida.

1 Insofar as the actual differences in the
2 clinical trial, those data -- in the specific data,
3 those data are currently under review by FDA at this
4 point. Because those data specifically are under
5 review, they can not be presented here.

6 DR. WONG: Well then, why do you say that
7 there was sufficient power to demonstrate a
8 difference?

9 DR. WALSH: The key is is that one can
10 design clinical trials sufficiently strong to be able
11 to predict differences. At the time that we conducted
12 our FDA workshops in '94 and '95, we dealt in the
13 realm of detecting fever and we wanted to achieve a
14 high level of certainty with regard to fever as a
15 marker. What we have learned and what neither the FDA
16 nor the advisory panel has been fully apprised about,
17 but the MSG has this information now from the multi-
18 center trial, is that we can, with the type of study
19 design that was laid forth, be able to detect
20 differences in proven invasive fungal infections.

21 At that point, I can not legitimately give
22 you additional information. It's not a question so
23 much as to what a particular study shows specifically
24 of drug A versus drug B. The key is, is that
25 irrespective of those differences, the fact is is that

1 the study design can predict differences in invasive
2 fungal infection. That's the pivotal issue. That has
3 never been shown previously for the last decade and a
4 half. All of the previous empirical antifungal trials
5 have been strictly based on fever.

6 DR. WONG: Tom, am I missing something
7 here?

8 CHAIRMAN HAMMER: I think the point is
9 that he can't really reveal the data.

10 DR. WONG: But your conclusion must be
11 based on having a certain number. Is that a fair
12 inference?

13 DR. WALSH: The conclusion would be, for
14 example, if you had taken --

15 DR. WONG: If there were no proven cases
16 of invasive fungal disease, you would not have made
17 the statement you made.

18 DR. WALSH: If we had no proven cases of
19 invasive fungal infection in conducting the trial with
20 700 patients, we would conclude that we have no more
21 predictive power than being able to detect differences
22 in fever.

23 The implication that we can go beyond
24 differences in just fever, which has been considered
25 by many to be an uncomfortable and soft surrogate

1 marker, has profound implications for study design.
2 It then says that like we have with fungemia, like we
3 have with proven invasive fungal infections, now with
4 the appropriate study design, we can with empirical
5 antifungal therapy, use more than just fever. We can
6 use proven invasive fungal infections as a documented
7 marker. That has been one of the key criticisms to
8 empirical antifungal therapy which, with the proper
9 study design, would not have to be leveled anymore.

10 CHAIRMAN HAMMER: Thank you.

11 Dr. Masur?

12 DR. MASUR: I'm trying to decide if I
13 understand the implication of this. I think that this
14 is a group that has a lot of experience and that
15 commands considerable national and international
16 respect. Yet, on the other hand, are we being told
17 that we should take your word for this? That you're
18 not going to show us the data; you can't show us the
19 data, but that we should take your word that this is
20 true?

21 I find that a little bit difficult to make
22 any decisions on because that's not the way science is
23 generally done, that we should take your word for this
24 based on data that we can't see. I mean, is there
25 some other interpretation of this?

1 CHAIRMAN HAMMER: Well, I would think
2 since that sounds like it's the implication. This is
3 the open hearing. It's for our information to gather
4 this as we will, and to judge it as we will, if I may
5 take Dr. Walsh off the spot on that question for a
6 moment.

7 DR. WALSH: But I would say, just to
8 clarify, that I was requested not to present this data
9 until the mycosis study group hearing. I could very
10 easily, Dr. Masur, have not presented anything to you
11 and left the advisory committee with the current
12 status of where we were in '95 and '96. The FDA has
13 all these data. It certainly would be up to them and
14 their discretion to share it with you. It is my
15 discretion, sir, to share that with you. It will be
16 revealed at the mycosis study group meeting that will
17 be conducted in closed door session according to our
18 policies and guidelines. The FDA has had the data to
19 which I'm referring and you can certainly ask them for
20 that data. I'm not privy to be able to release that
21 data on a public forum.

22 CHAIRMAN HAMMER: Excuse me. We'll just
23 take three more questions and then we need to move on,
24 please.

25 Dr. Lipsky and then Dr. Masur.

1 DR. LIPSKY: Okay. But can you say, did
2 you find differences in --

3 CHAIRMAN HAMMER: I don't think we should
4 press Dr. Walsh anymore. I think he's made it clear.
5 He really can't --

6 DR. WALSH: Sir, I have made the point
7 both on the slides and several times now, there are
8 differences. There are differences in proven invasive
9 fungal infection and that's the critical issue that we
10 can go beyond just fever as an endpoint, as a marker.
11 And this has profound implications for future study
12 designs.

13 Empirical antifungal therapy is the most
14 widely used role for antifungal therapy in neutropenic
15 patients. If we stay with study designs that do not
16 have the predictive power, we run the risk of
17 utilizing agents that may not have the potential to
18 impact on invasive fungal infections. We know from
19 the previous FDA study guidelines, now, that we can
20 see differences. It is not my position here to say
21 whether drug A or drug B is superior. The key is is
22 that you can see differences and in fact, we have seen
23 differences between the amphotericin B and the
24 liposomal formulation based on proven invasive fungal
25 infections. That sets a new standard in study design.

1 DR. LIPSKY: Well, in fairness to the
2 sponsor, perhaps the FDA would like to state whether
3 or not the Committee can make reasonable judgments
4 without the information which may be available to it.

5 CHAIRMAN HAMMER: Well, the FDA
6 introduction will be coming in a moment. I'd like to
7 finish up this section.

8 Dr. Elashoff?

9 DR. ELASHOFF: I have one request for
10 clarification and then a comment.

11 The request for clarification is because
12 I'm new to the whole antifungal thing. The study
13 that's being talked about here is comparing the same
14 two drugs as we're looking at in this submission, the
15 Amphotec and the --

16 CHAIRMAN HAMMER: I don't believe so.

17 DR. ELASHOFF: It's different drugs?

18 DR. WALSH: No. I've endeavored --

19 DR. ELASHOFF: I'm sorry. I just missed
20 it.

21 DR. WALSH: I've endeavored to keep this
22 above the level of one drug versus another in terms of
23 marketing issues. That is not the point. The point
24 is the science of the study design.

25 DR. ELASHOFF: I understand that. I'm

1 just asking, was this trial with these drugs or some
2 other drugs?

3 DR. WALSH: It was a liposomal formulation
4 of amphotericin B. It is not with the current product
5 that is under review.

6 DR. ELASHOFF: Thank you.

7 As a statistician, I wanted to comment on
8 some of the -- the power issues are largely sample
9 size issues. I understand part of the point to be
10 that if you want to detect differences of the sort
11 that he's talking about, and especially in those that
12 you know actually had an infection, you have to have
13 a big sample size. When you have a big sample size,
14 then you can find things out. As a statistician, I
15 took that as to be the main point.

16 CHAIRMAN HAMMER: Thank you.

17 I just have one question. Could you
18 clarify the definition of fever resolution used in
19 this study?

20 DR. WALSH: Yes, the resolution of fever
21 was considered fever to have resolved during the
22 course of antifungal therapy and upon recovery from
23 neutropenia.

24 CHAIRMAN HAMMER: And total resolution for
25 X period of time? What about issues of working out

1 intercurrent problems that relate to fever, blood
2 transfusions, and fusion reactions, those sorts of
3 things? Those were all --

4 DR. WALSH: The febrile response rate,
5 because of all that background, is 50 percent. Thus,
6 by the time patients recovery from neutropenia, 50
7 percent will still have some fever by the definitions.
8 It reflects all of that background which all the more
9 is the reason why one has to power it to a level
10 beyond fever. That was the reason why everyone felt
11 so uncomfortable with using a definition of fever,
12 understandably.

13 CHAIRMAN HAMMER: Thank you.

14 Last question on this.

15 DR. EL-SADR: For some of the other
16 endpoints other than fever, are you using response
17 during therapy, or for how long beyond the completion
18 of treatment?

19 DR. WALSH: That's a good point as well.

20 The evaluation for fever stops upon
21 recovery from neutropenia particularly, for example,
22 in allogeneic bone marrow transplant recipients. We
23 find that the frequency of fever will start recurring
24 again. So, fever is a very soft marker and we
25 certainly used it for sample size determination,

1 anticipating having the power to determine a ten
2 percent difference. Ultimately, it then generates a
3 sample size that's sufficiently large that then tells
4 us we can determine differences in proven invasive
5 fungal infections which everybody has wanted to
6 ascertain from the very beginning. It turns out that
7 with 600 to 800 patients enrolled, it is possible to
8 discern those differences and go beyond fever.

9 CHAIRMAN HAMMER: Is the occurrence of
10 fungal infection or survival censored at some point
11 after? I think that's your point.

12 DR. EL-SADR: When do you censor for these
13 events?

14 DR. WALSH: Upon recovery from
15 neutropenia. The patients were followed up only
16 formally for protocol for three days. Then it became
17 irrelevant after that because of the philosophy of
18 dose intensity. Many of these patients were started
19 once again on cytotoxic chemotherapy on yet another
20 cycle.

21 CHAIRMAN HAMMER: Okay, thank you.

22 Thank you, Dr. Walsh.

23 DR. WALSH: Sure, you're welcome.

24 CHAIRMAN HAMMER: I think it's very
25 helpful to the Committee to know about this study

1 design that's going to help the discussion later this
2 morning.

3 There are no other speakers signed up for
4 the open public hearing. Is there anyone who wishes
5 to come forward and speak? If not, the open public
6 hearing part of this program is closed.

7 The next point on the agenda is Dr. David
8 Feigal, who will give the FDA introduction.

9 DR. FEIGAL: Well, good morning. I'd like
10 to welcome everyone here. I believe this is the 29th
11 meeting of this Committee. We've had trouble keeping
12 an exact count. Every time I think we've discovered
13 every large conference room in the northern part of
14 Washington, when we need to schedule something at last
15 minute, we find another one. So, I'd like to thank
16 all of you who not only found this place, but found a
17 way to park.

18 There are a series of things that I think
19 are challenging about this topic of empiric antifungal
20 therapy. I'd just like to begin this morning by
21 making some comments on what I see some of those
22 challenges are. Then you'll have an opportunity to
23 see how they're addressed by this particular
24 application.

25 The first challenge comes from the fact

1 that these are empiric therapies. By definition, all
2 of the patients won't need treatment. If you could
3 wait until the diagnosis was confirmed, you wouldn't
4 need empiric therapy. And so, the corollary to this
5 is that when you use an empiric therapy, there are
6 some patients who are treated who don't need
7 treatment, who won't benefit. And of course, we're
8 concerned about the safety of treating patients for a
9 therapy that they don't need. But the older studies
10 in the literature when this was still an open question
11 that were placebo controlled, clearly showed that
12 there were survival benefits to empiric treatment with
13 amphotericin B for neutropenic patients.

14 Now with some empiric therapies, you can
15 confirm the diagnosis later. There are some empiric
16 therapies where the diagnostic tests will be available
17 within a matter of days and you can quickly stop the
18 therapy in the patients who don't need it. There are
19 other circumstances where even though you have to
20 continue the therapy for longer periods of time, you
21 can at least identify a subset of patients who clearly
22 needed the therapy and that's a particularly rich
23 group to look at for efficacy in that subgroup.

24 An approach to these kinds of dilemmas
25 presented by empiric therapy in this area has been to

1 consider a hierarchy of evidence. Rather than having
2 a single hypothesis chosen for a superiority design,
3 are taking a look at a hierarchy of evidence in a
4 number of different populations. The intent to treat,
5 or keeping the randomization groups intact is a way to
6 assure that there is no overall harm to the product
7 for the patients who didn't need it. It's conceivable
8 that there could be a product that's good enough in an
9 intent to treat analysis to demonstrate superiority,
10 even carrying along all of the patients in both groups
11 who won't demonstrate benefit. But usually that's not
12 the study design feature in these types of trials.

13 Fever is the next type of endpoint that's
14 considered. Here, the problem is the complexity of
15 the treatment of these patients. Many of them will
16 have changes in their therapy, dictated by changes in
17 their clinical course, which will give them other
18 reasons for resolution of fever. Many of these
19 patients will have, again, no diagnostic tests which
20 will confirm that either the study drug or the non-
21 randomized intervention had any effect. So, you'll
22 see analyses that attempt to deal with this by
23 identifying the patients who have no other reason than
24 the randomized study drug to resolve their fever,
25 other than the recovery of their neutropenia and other

1 things which we can not control.

2 Part of the reason for emphasizing fever
3 -- and I think the previous discussion identified some
4 of the dilemmas though -- is the fact that this is not
5 a treatment just for patients whose diagnostic tests
6 and cultures come back positive. This is not a
7 therapy that you give and then you stop if the
8 cultures are negative. These strategies are often
9 designed to treat patients until resolution of either
10 neutropenia or fever, even in the face of negative
11 cultures. Therefore, it's relevant to look at the
12 resolution of fever as an endpoint, per se.

13 The final group in the hierarchy of
14 evidence is to take a look at the patients with
15 confirmed fungal infections. In the meeting of about
16 a month ago looking at empiric treatment with a
17 cephalosporin, both alone and in combination for
18 bacterial infections, empiric treatment of bacterial
19 infections in neutropenic hosts, about 25 percent of
20 patients had identifiable bacterial infections. There
21 was adequate power to compare, with some level of
22 precision, the number of patients in each group that
23 had confirmed infections and what the outcome,
24 whether those infections were adequately treated or
25 not.

1 The difficulty, as you all realize, with
2 fungal infections is that even before the era of
3 prophylaxis against fungal infections with azole
4 therapies, fungal infections are much less common and
5 they're much more difficult to get diagnostic cultures
6 for. Many of the diagnoses are presumed. So, we have
7 an inherent difficulty, no matter what drug we're
8 studying in this indication, that we will have
9 difficulty having much power for the fungal infections
10 that occur.

11 Those are the series of challenges that I
12 wanted to begin with that relate to empiric therapy.
13 Another set of the issues with this drug relate to the
14 fact that it's amphotericin. This is a product line
15 extension of a different formulation of an active
16 drug. We assume that the active drug for this product
17 is amphotericin, and that it should have the same
18 spectrum of activity as the older formulation of
19 amphotericin. But there still remain questions about
20 how the formulation affects dose and distribution in
21 the body; issues that have been addressed perhaps more
22 directly in studies of confirmed infections.

23 Finally, we have the issues that this is
24 an equivalence design. Most of our study design
25 safeguards our design to be conservative for type 1

1 errors in superiority designs. Unfortunately, with
2 equivalence some of the relevant subgroups are some of
3 the more problematic where you need to identify
4 subsets who are only identified by events which occur
5 after randomization. Subgroups are even problematic
6 enough when they're based on pre-randomization
7 characteristics, but even more difficult when it's
8 post-randomization.

9 There have been suggestions and overall
10 guidances for anti-infective products from the
11 Division of Anti-Infective Drugs in their general
12 points to consider about how to approach equivalence
13 designs. These are based on, however, the assumption
14 that this equivalence will be met in all of the
15 hierarchy of evidence that's presented. Usually, the
16 intent to treat analysis with all patients included
17 for bacterials is easy to demonstrate a confidence
18 interval. The difficult one is demonstrating it for
19 the microbiologically confirmed subset which, even for
20 bacterial infections, is often only a fraction of the
21 total patients treated.

22 To conclude, just a couple of general
23 comments on the role of this Committee today and some
24 comments on past committees. It is not unique when
25 the Committee is considering one application, to hear

1 comments about other products, other studies, other
2 applications. However, the task today is just to
3 consider this study and application on its own merit.

4 The other comment is a bit on the workshop
5 which Dr. Walsh mentioned. He referred to some of the
6 recommendations from that workshop as guidance.
7 Actually, even if it was guidance, guidance is not the
8 same as a requirement. When general counsel has been
9 asked "what is a guidance mean?" they've said, "if
10 you follow a guidance, we're less likely to prosecute
11 you than if you don't."

12 Guidance is only one way to often
13 accomplish a scientific objective and it's considered
14 our best advice at the time, but it's not considered
15 the only way to accomplish a goal that's not a
16 requirement. However, this workshop actually didn't
17 even generate guidance. This workshop had a panel of
18 experts that made recommendations. There was
19 commentary by the FDA, and that workshop actually
20 served much the same role that you will today. The
21 Committee, actually, is an important way for us to
22 develop scientific guidance from our expert panels and
23 the previous workshops were held with very much that
24 same intent.

25 This is an increasingly important area for

1 us to have effective therapeutics with the advances
2 that have been made in transplantation and the more
3 wide use of transplantation in econology and other
4 areas. We look forward to your consideration of this
5 application and your guidance on developing drugs in
6 this area.

7 Thank you very much.

8 CHAIRMAN HAMMER: Thank you.

9 The next section is some background
10 information for the Committee and for the group. It
11 will be an overview of empiric antifungal therapy by
12 Dr. Alan Sugar from the Boston Medical Center.

13 DR. SUGAR: Thank you.

14 When I was originally given this topic to
15 speak about, I was told that I had about 40 minutes.
16 Then our second phone call, it was about 30 minutes,
17 and the agenda says 20 minutes. But I think we're a
18 little bit ahead of schedule, so I'll probably average
19 it out and be around 20, 25 minutes.

20 If I could have the first slide?

21 What I'd like to do in this period of time
22 is to just review some salient points of empirical use
23 of antifungal therapy in the persistently febrile
24 neutropenic patients because that's the group that
25 we're focusing on this morning. And then to, as a

1 global summary, to confirm that the use of an
2 antifungal drug in this situation is a legitimate
3 indication for which a sponsor can supply data and
4 which can be scrutinized in an effective way by the
5 FDA. As always, when I follow Tom Walsh in speaking,
6 I usually just have to reiterate much of what he has
7 just said. The foundation has already been presented.

8 When dealing with the febrile
9 granulocytopenic patient, there's really three issues
10 to treat a defined infection, to treat empirically or
11 to prophylax. I thought it would be very useful,
12 since there have been a lot of terms thrown around and
13 a lot of different ways of describing these scenarios,
14 to step back and go over some definitions so that we
15 all know what we're speaking about when we talk about
16 therapy either being empirical or prophylaxis or the
17 like.

18 So, these are the terms that you see in
19 the literature. You see empiric, empirical,
20 preemptive, presumptive -- and that's been spilling
21 outside of the neutropenic realm into the surgical
22 realm, but we still see that sometimes in treating
23 neutropenic patients and certainly prophylaxis. The
24 big question is, what are all these terms getting at?

25 Well, I went back to the dictionary to

1 just see what I could find. It's interesting that
2 empiric is a noun. I think Tom Walsh's recent
3 publications indirectly allude to this. Certainly the
4 second definition here, that unqualifiers -- to sign
5 this practitioner, Charlatan has no place in what
6 we're talking about here. But the term I think they
7 were going to focus on is empirical. It is an
8 adjective and the second definition is guided by
9 practical experience and not theory, especially
10 medicine. I think, and Tom has alluded to this very
11 eloquently this morning, that what we had been dealing
12 with has been experience, but that we are starting to
13 get some theory and some real scientific, or at least
14 more rigorous approaches to dealing with this tough
15 issue of how to deal with the persistently febrile
16 neutropenic patient.

17 Presumptive is another word that we can
18 use to describe this therapy, providing a reasonable
19 basis for belief or acceptance, or founded on belief
20 or presumption. So that, we treat people because we
21 believe that there's a fungal infection that's causing
22 the fever in the patient. The bottom line that I
23 think practitioners have to deal with is that our
24 diagnostic capabilities for making the diagnoses of
25 the types of fungal infections that infect neutropenic

1 patients are very poor. They really haven't kept up
2 to speed with the advances now being made in
3 therapeutics. This wouldn't be such a big problem to
4 demand our attention if our diagnostic capabilities
5 were as easy as doing cryptococcal antigens, for
6 example, and getting a definitive answer very quickly
7 about making diagnoses of fungal infections.

8 Now, another term that has been used
9 especially in the surgical venue, as I said, is that
10 of preemptive therapy. That's an action that's
11 undertaken or initiated to deter or to prevent an
12 anticipated usually unpleasant situation or
13 occurrence. This has a lot of military overtones.
14 Depending on your approach to medicine, if you like
15 that kind of analogy, then that's maybe an appropriate
16 term. I think there are other ways of looking at it.
17 Certainly, prophylaxis has been used in this
18 population of neutropenic patients to prevent the
19 development of a disease. And in this case, to
20 prevent the development of fungal infections which we
21 already know are very difficult to definitively
22 identify as causing disease in a particular patient.

23 So, what are we talking about here? I
24 would just propose that we really are speaking about
25 empirical therapy which is the same thing as

1 presumptive therapy. Some people will need the
2 therapy because they will have a documented invasive
3 fungal infection and other people will not need the
4 therapy. That gets to the issue of what's the
5 downside of unnecessarily treating patients?
6 Preemptive therapy is probably, at least on an
7 intellectual plain, the same thing as prophylaxis.
8 With that, I would just stop talking about the
9 terminology and from now on, at least I'll talk about
10 empirical antifungal therapy. I've been guilty in my
11 writing of using empiric as well and I think that will
12 be the last time that that happens.

13 Now, what is the real problem here? The
14 problem, as I mentioned, is diagnosis of fungal
15 infections. In the patient population that's up here,
16 the neutropenic patient who develops fever and who
17 does not defervesce despite some number of days of
18 broad spectrum antibacterial therapy. These are the
19 patients in whom we use broad spectrum, antifungal
20 therapy.

21 Now, how long should this window be? That
22 is a moving target. Some people say four days. Some
23 people even say less than four days. Other people
24 will say maybe it's longer than 10 days. I think that
25 disagreements arise predominantly because different

1 investigators treat different kinds of patients -- and
2 whether we are talking about someone who is getting
3 their first episode of neutropenia or somebody on
4 their fifth or sixth episode of neutropenia -- the
5 issues are somewhat different.

6 Now, just as an aside, the problem here in
7 terms of assigning this window is, if you delay the
8 institution of antifungal therapy in a patient who has
9 a documented fungal infection, the mortality of these
10 patients increases, as you can see here. If you delay
11 the therapy, the longer you wait when an invasive
12 fungal infection is present, the higher the likelihood
13 of death, and certainly of the presence of
14 disseminated disease from a focal source. This has
15 been demonstrated multiple times.

16 Another issue is what is the critical
17 number of neutrophils that puts patients at risk? And
18 again this differs from investigator to investigator,
19 and this has profound implications on clinical study
20 design because the patients at highest risk in whom
21 you want to use the empiric therapy. If patients are
22 not at high risk, you certainly are not going to treat
23 large populations with drugs that have a chance of not
24 being needed and various definitions of neutropenia
25 have been offered.

1 This is from Gerald Bodey's seminal
2 studies in the '60s which showed that the percentage
3 of patient days with infection significantly
4 increases, as you can see in the open circles
5 representing the total. He did separate out patients
6 in remission and relapse. But it significantly goes
7 up when the total neutrophil count reaches 500, when
8 it's 100 to 500, and certainly 100 and below. So,
9 there is a gradation of increased risk. And at 1,000
10 cells and above, there really is not a great increase
11 in risk. So, this kind of information which, again,
12 has been confirmed many times since the 1960s, can
13 indicate where prophylaxis or empirical therapy should
14 be used.

15 Just to show, this was another study that
16 was reported in the 1980s, in terms of the duration of
17 granulocytopenia and the duration of fever. I'd just
18 direct your attention to the far right column there,
19 the granulocytopenic days with fever. Again, it's
20 about 40 to 50 percent of days when patients have
21 neutrophil counts less than 1,000 in this case. Forty
22 to 50 percent of the days are going to be spent with
23 fever. These are the patients that are going to
24 command attention if they don't respond to broad
25 spectrum, antibacterial therapy. And the same thing

1 is seen here broken down between different numbers of
2 neutrophils. The duration of neutropenia in this
3 particular study was running around eight days, eight
4 to nine days. Again, on the days febrile percentage,
5 you can see in the third column here, with neutrophil
6 counts approaching zero, that at least three-quarters
7 of patients are going to have fever. And again, these
8 are the ones that we want to target.

9 These slides have a lot of different
10 messages to them, but I just want to point your
11 attention to the first row there, "duration of
12 neutropenia." This was one of the National Cancer
13 Institute studies directed by Phil Pizzo. In 1982, it
14 was published. The duration of neutropenia overall
15 was about 24 days with a range of eight to 51 days.
16 One of the interesting thing to look at was how did
17 the patient population, back in the 1970s and early
18 '80s compare with the kinds of patients that we're
19 dealing with now? The impression is that the patients
20 that we're treating are much sicker and that we're
21 making them even sicker with the increase in the
22 aggressiveness of chemotherapy.

23 So, I wanted to look at the duration of
24 neutropenia again. In this particular study, duration
25 of neutropenia is about 32 days with a range of 13 to

1 56 days. Another one of the NCI studies. In looking
2 at some more recent studies from the 1993 through
3 1996, the duration of neutropenia has been relatively
4 similar to what was seen in some of the early studies
5 with a mean duration of neutropenia, 14, 19 days, 16
6 days. The duration of neutropenia with PMNs less than
7 100, which again is the highest risk group, of being
8 on the order of seven to 12 days or so. So, the mean,
9 the median, and the ranges of these duration
10 neutropenia has been relatively stable in the
11 published literature to the present time.

12 Now, I just want to shift from the risk
13 factors, being primarily neutropenia, to the kinds of
14 organisms that we're talking about because this has a
15 very important effect in terms of which drug one would
16 select for empirical use in this population. It's no
17 secret to anyone taking care of these patients that
18 candida and aspergillus are really the main culprits
19 that we're most concerned about. But other filament
20 disfungi such as Fusarium and other organisms such as
21 trichosporum are increasing in significance and
22 depending on center. This seems to be a center-to-
23 center problem. There may be other organisms as well.
24 Whereas, in the 1960s and '70s, the predominant
25 candida that was isolated was candida albicans, we're

1 no longer so sure that when a yeast comes back and
2 it's more likely than not to be a non albicans
3 candida, in many instances that we recover.

4 So, what would be the ideal drug that one
5 would choose for empirical antifungal therapy in the
6 persistently neutropenic patient who has not responded
7 to antibacterial drugs? It should be efficacious
8 against the most commonly encountered fungi. It
9 should be a broad spectrum agent. Certainly, this has
10 been the problem with using fluconazole, for example,
11 in many places, either as prophylaxis or certainly as
12 empirical therapy because of its lack of aspergillus
13 coverage.

14 The drug should have low toxicity and as
15 we're hearing from the pharmacy and the hospital
16 administrators now, it should be relatively low cost.
17 After all, large populations of patients are going to
18 receive therapy, many of whom don't need the drug in
19 the first place, again, getting back to the problems
20 with diagnosis. There should be few drug interactions
21 and good pharmacokinetics so that it could be given
22 once-a-day, and certainly not many more times per day
23 because of the cost involved.

24 Now, the biggest problem in terms of
25 empirical therapy and prophylaxis, as I just alluded

1 to, is that the treatment of the two major infections,
2 candidiasis and aspergillosis, probably will involve
3 different drugs until we can have a broad spectrum
4 agent that we are confident will treat both of these
5 infections. For example, in candidiasis, there's many
6 investigators who feel that in certain instances,
7 fluconazole may be more effective than amphotericin.
8 With an increase in the incidence of hepatosplenic
9 candidiasis, for example, there are people who would
10 much rather use fluconazole than amphotericin for the
11 treatment of that. But fluconazole, amphotericin, and
12 itraconazole have all been used for treating
13 candidiasis, all with varying degrees of success.
14 Similarly, in treating aspergillosis, there are fewer
15 options, amphotericin B and itraconazole. So, while
16 there is an overlap, there are certainly some
17 instances where one drug is not as useful as another
18 for treating these infections.

19 Amphotericin, it's been around since the
20 1950s. It has established itself in our minds as the
21 gold standard of therapy. And the most fascinating
22 thing I find from these randomized comparative trials
23 using conventional amphotericin compared to one of the
24 lipid formulations is for the first time, we're
25 starting to see what the actual toxicity of

1 amphotericin B, conventional amphotericin B really is.
2 I've been favorably impressed that it's less toxic
3 than folklore would actually have. The nice thing
4 about amphotericin B is that it's a broad spectrum
5 agent, but the toxicity in terms of systemic reactions
6 with fever and rigors and certainly, the
7 nephrotoxicity, while not as frequent in the
8 randomized studies as I might have expected, it's
9 still formidable. And again, in treating patients who
10 may not need the antifungal therapy at all, I think
11 it's important for us to minimize the toxicity.

12 Now, the lipid formulations that are or
13 have been approved in the United States are Abelcet,
14 ABLC, amBisome and amphocil or Amphotec which -- this
15 slide is out of date -- has been approved in the
16 United States. These formulations now are having the
17 effect of giving us choices in how we're going to
18 deliver amphotericin into patients are bringing up a
19 lot of very interesting points as has been alluded to
20 already this morning.

21 Fluconazole really hasn't been touted as
22 a drug for empirical therapy as much, again, primarily
23 because of its lack of aspergillus activity. And
24 certainly, other species of candida than candida
25 albicans are less susceptible to fluconazole on a

1 clinical basis. Some institutions have had
2 significant problems with candida krusei, for example,
3 which is inherently, apparently clinically resistant
4 to fluconazole. The nice thing about fluconazole is
5 that there's some flexibility about how you can give
6 it. It can be given orally and intravenously and it
7 has few important drug interactions, and relatively
8 low toxicity. So, there are some good points, and
9 there are certainly some bad points about using
10 fluconazole in this population. But overall, because
11 of the problems with aspergillus, it's not used.

12 Now, itraconazole has some problems in
13 this population because of problems with oral
14 absorption, for dependable absorption. But a new IV
15 formulation may be forthcoming and that may put an end
16 to this particular problem and may offer yet another
17 option. It offers an option because it certainly is
18 active against candida and it is a very effective
19 agent against aspergillus. On the downside, there are
20 several important drug interactions that we have to
21 pay attention to that may limit its easy use and
22 require more dose adjustments to the other agents that
23 the patient may be getting.

24 So, what has happened over the last 20
25 years or so to the patient population? I already

1 talked about the duration of neutropenia which seems
2 to be relatively stable over the last 20 years. There
3 certainly is more aggressive cytotoxic chemotherapy
4 being used, increase in the use of bone marrow
5 transplantation for example, and this has the effect
6 of increasing other problems due to cytotoxic
7 chemotherapy such as stomatitis and gastrointestinal
8 mucosal erosion which may put people at increased risk
9 for developing invasive candidiasis.

10 We're seeing the use of more potent, broad
11 spectrum antibacterial agents which have profound
12 effects on normal flora, for example, which may
13 encourage overgrowth of fungi. We're seeing an
14 increase in the incidence of invasive fungal
15 infections in neutropenic patients quite possibly
16 because we're looking for them more carefully. But
17 the diagnosis is still problematic in terms of making
18 an early diagnosis. We're clearly seeing an increase
19 in the variety of fungi recovered from patients. This
20 may be due to an increased appreciation for working up
21 these organisms in a laboratory, but I think also, all
22 told, we are seeing an increase in unusual organisms.

23 Newer things that are going to attract our
24 attention, in addition to the liposomal amphotericin
25 preparations, new azoles such as voriconazole. Lilly

1 & Merck are working on a series of echinocandins,
2 pneumocandins which given their broad spectrum of
3 activity, would be anticipated coming to our attention
4 as potential agents for the empirical therapy in the
5 persistently neutropenic patient. So, the work is not
6 yet done, ones considering the few liposomal
7 preparations for this particular indication.

8 And then there are newer therapies that
9 really will have a significant impact on the incidence
10 and/or treatment of fungal infections in the
11 neutropenic patient. These are some of them. The
12 colony stimulating factors clearly can decrease the
13 duration of neutropenia and whether they have an
14 adjunctive role in augmenting neutrophil function to
15 be kind of adjunctive therapy as an antifungal agent
16 -- that remains to be more definitively studied.

17 It's very interesting that stem cell
18 transfusions which in some circumstances, may end up
19 replacing bone marrow transplant at some point, seemed
20 to decrease the toxicity of the whole treatment
21 course, primarily because of the shorter duration,
22 total duration of neutropenia. We've been very
23 impressed in our institution that the stem cell
24 transplant patients, or stem cell infusion patients,
25 really are having a much better time with respect to

1 the development of fever and the development of fungal
2 infections in our leukemic patients that have been
3 treated with standard chemotherapy. New forms of
4 chemotherapies for a variety of malignancies, again,
5 making patients neutropenic; bone marrow transplants
6 for a variety of solid organ tumors, and a variety of
7 other therapies that enhance one arm of the immune
8 system are also being used. Whether these will have
9 any effect on the increase or decreasing the incidence
10 of fungal infections remains to be seen.

11 A variety of algorithms have been
12 presented about how to deal with the neutropenic
13 patient in terms of prophylaxis and empirical therapy.
14 The important thing in all of these strategies has
15 been the utility or the suggested utility of
16 surveillance cultures. In this era of cost
17 containment however, going whole hog for culturing
18 multiple specimens on a weekly or more frequent basis
19 on patients seems to be a strategy that's not going to
20 meet with approval by the non-medical people who run
21 the hospitals these days. That's a real significant
22 practical downside to a lot of these algorithms.

23 This slide just illustrates that we have
24 a lot of choices to make and will have a lot of
25 choices to make in the future. Amphotericin B

1 conventional, liposomal -- where does itraconazole fit
2 into the equation? Yet, these other new drugs, as we
3 come about. I would just like to echo Tom Walsh's
4 ideas that in giving the drug approval for empirical
5 antifungal therapy, especially this early in the game,
6 really sets the stage for all of the new compounds
7 that we're going to have to deal with over the future.

8 So, to close, I would just summarize and
9 stress once again that fungal infections are really
10 the most important cause of morbidity, mortality in
11 patients rendered neutropenic for the treatment of
12 their malignant disease. That empirical, antifungal
13 therapy is a very important strategy to decrease the
14 negative impact of fungal disease in these patients,
15 again, getting back to the problems with diagnosis and
16 our inability to make timely, early diagnosis so
17 effective, definitive therapy can be used. So, with
18 that, I'll conclude.

19 CHAIRMAN HAMMER: Thank you very much,
20 Alan.

21 That brings us to the sponsor's
22 presentation. The sequence presentation will begin
23 with Marc Gurwith, who is vice president of clinical
24 research.

25 DR. GURWITH: Good morning. I'm Marc

1 Gurwith, vice president of clinical research at
2 Sequus. We're here, as you well know, to discuss
3 Amphotec.

4 I'll go through the names. This drug has
5 several names, past and present. Please indulge me as
6 I'm going to refer to it as Amphotec throughout this
7 presentation. The new common or generic name in the
8 United States is amphotericin B cholesteryl sulfate
9 complex which is somewhat of a mouthful. It has also
10 been known as -- is known in Europe as amphotericin B
11 colloidal dispersion, or ABCD. Most of the medical
12 literature concerning this product refers to it as
13 ABCD or amphotericin B colloidal dispersion. Then the
14 trade name in Europe is ampicill. So, again, at
15 least for brevity, I'll refer to it as Amphotec. As
16 you know, we're here to discuss a supplemental NDA.

17 The proposed indication, as described
18 above -- if you'll excuse the grammatical error of
19 empiric rather than empirical therapy -- is for
20 empiric therapy in febrile neutropenic patients who
21 have failed to respond to antibacterial agents. As
22 you've heard, and I'm sure you already knew,
23 amphotericin B is the standard for this indication and
24 it also has the well known problem, or potential
25 problem, of nephrotoxicity. Amphotec, which is a

1 colloidal dispersion or a complex of amphotericin B
2 and cholesteryl sulfate has been developed
3 specifically to reduce the nephrotoxicity of
4 amphotericin.

5 In support of today's submission, our
6 presentation is four parts. The first is a brief
7 introduction by myself, followed by a summary of
8 preclinical and human pharmacokinetic data by Frank
9 Martin at Sequus. And then a discussion of issues in
10 empiric therapy for antifungal agents, a little more
11 specific to our protocol -- I don't think we'll
12 duplicate what you've heard already -- by Carole
13 Miller from Johns Hopkins. Then I'll conclude by
14 discussing the primary study in the submission and
15 provide some conclusions.

16 Additionally, we have present, Donald
17 Armstrong from Sloan Kettering and Steve Zinner from
18 Brown University who also have helped with the
19 presentation, although the development of Amphotec has
20 preceded their involvement in this program.

21 Here, I'm just trying to briefly summarize
22 the developmental history of Amphotec for its current
23 indication. Phase III studies were initiated in 1992
24 and they were for second line therapy for aspergillus
25 and studies were also done for other fungi. There

1 was, as you've heard, an advisory committee meeting
2 two years ago in April where liposomal or lipid-based
3 antifungals were discussed. Among other issues
4 discussed was the trail design for approval for
5 documented fungal infections.

6 Our NDA for this product was submitted in
7 November of 1995 and this was for second line therapy
8 of aspergillosis. That NDA was approved approximately
9 one year later. However, it wasn't reviewed by this
10 antiviral committee, or this advisory committee, and
11 so I'll just briefly summarize the basis for that
12 approval and some background concerning the current
13 indication.

14 The indication, as you see there, second
15 line therapy; that is, patients who have failed to
16 respond to amphotericin or can't tolerate it because
17 of nephrotoxicity and have invasive aspergillosis.
18 Amphotec has also been approved in Europe for somewhat
19 broader indications, essentially second line therapy
20 for most opportunistic fungal infections.

21 The basis of approval in the United States
22 was really this study which was recently published in
23 the Journal of Clinical Infectious Diseases. This
24 study was well controlled, but it was a retrospective,
25 historically controlled comparison of patients with

1 invasive aspergillosis treated with amphotericin and
2 with Amphotec. The data on this slide summarize the
3 key points from the publication and show, for example,
4 a 49 percent response rate with Amphotec compared to
5 a 23 percent response rate for amphotericin B.
6 There's a similar difference in survival in this
7 study. Then you can see the striking reduction in
8 nephrotoxicity.

9 Now, the FDA review of this study, as
10 described in the package insert, differs somewhat but
11 not substantially. For example, the response rate for
12 Amphotec in the FDA analysis was 46 percent. This
13 data provides proof of the clinical efficacy of
14 Amphotec at least in invasive aspergillosis, but of
15 course, as you've heard already, this is a product
16 that delivers amphotericin B, the parent compound.
17 Not surprisingly, there's evidence of efficacy in
18 other clinical infections.

19 This slide summarizes data that was
20 submitted with the original NDA. These were patients
21 with other opportunistic fungal infections and who,
22 again, could not tolerate amphotericin B, or who had
23 failed to respond to amphotericin B. These were
24 fairly or highly immunocompromised patient population
25 and the response rates you see here are what you'd

1 expect with amphotericin B. These, of course, were
2 from open trials. This data was submitted with the
3 NDA but has not been reviewed in detail by the FDA.

4 Now, to show how Amphotec delivers
5 amphotericin B, maintains its antifungal activity but
6 reduces nephrotoxicity, Dr. Martin from Sequus will
7 review some of the pertinent preclinical and
8 pharmacokinetic data.

9 DR. MARTIN: Thank you, Marc.

10 For those of you that are not familiar
11 with Amphotec -- and it does become somewhat confusing
12 since there are three different lipid-based products
13 -- I'd like to review very briefly some of our
14 findings regarding the physical chemistry of the
15 Amphotec complex which underlies, actually, the
16 scientific rationale behind its development. Then
17 I'll go on to touch some highlights of our pre-
18 clinical and clinical pharmacokinetics which relate to
19 a proposed mechanism of action that we would like to
20 present this morning.

21 Amphotec is a mixture of amphotericin B
22 and sodium cholesteryl sulfate, or cholesterol
23 sulfate. The chemists prefer to call it cholesteryl
24 sulfate. Cholesteryl sulfate is very similar to
25 cholesterol except the 7 hydroxy position is occupied

1 by a sulfate group. Cholesterol sulfate is a natural
2 material. It's found in high concentration in skin,
3 for example, in the liver, and there are intercellular
4 enzyme systems that are able to convert cholesterol
5 sulfate to cholesterol. So, it's a natural metabolite
6 of cholesterol.

7 The complex consists of a 1:1 mixture.
8 That is, for every mole of amphotericin B, there's a
9 mole of cholesteryl sulfate. These two molecules
10 align next to each other, based primarily on
11 hydrophobic interactions. I'd like to stress there is
12 no covalent modification of any kind of the parent
13 molecule. It associates with cholesteryl sulfate
14 because cholesteryl sulfate is a sterol and
15 amphotericin B has affinity for sterols. These
16 complexes then oligomerise and assemble to form a
17 disc-shaped particle.

18 These electron micrographs show the basic
19 shape of these particles. They resemble a compact disc
20 in their shape. In the long axis, they're about 120
21 to 150 nanometers. In the depth, they're only four
22 nanometers thick. So, they are very thin and that is
23 shown here when they're flat against the disc, or the
24 grid on the EM. These particles are quite stable.
25 When they are suspended in water, they form a

1 colloidal dispersion. That is, the particles are so
2 small that they do not separate from the aqueous
3 medium in which they are suspended under the influence
4 of gravity. So, it's a true colloidal dispersion.

5 Now, we chose cholesteryl sulfate
6 prospectively, and we think rationally, based on the
7 relative affinities of amphotericin B for natural
8 steryls. What we found is that the affinity for
9 amphotericin B for cholesteryl sulfate lies
10 intermediate between that of its affinity for
11 cholesterol, that is the component of natural
12 membranes which would be the toxic target for this
13 drug versus ergosterol which, of course, is the major
14 steryl component of fungal cell membranes. Another
15 way of putting that is if the Amphotec disc were
16 incubated with red blood cells, there would be very
17 little net movement of drug from the complex to the
18 cholesterol-containing membrane because the affinity
19 of the drug for cholesterol sulfate is greater than it
20 is for cholesterol. This is evidenced by the fact
21 that Amphotec is not hemolytic in contrast to
22 Fungizone which can cause quite a bit of hemolysis.

23 On the other hand, the opposite is true in
24 the case of fungal cells. Ergosterol has a much
25 higher affinity for amphotericin B than cholesterol

1 sulfate. So, when mixed with fungi in vitro, there is
2 movement of the drug from the amphotec disc into the
3 fungal cell membrane, just driven by chemical
4 equilibria and mass action. So, this was the reason
5 we chose cholesterol sulfate as the carrier lipid for
6 this formulation.

7 Now, also as evidence that the drug does
8 indeed move as active amphotericin B from the Amphotec
9 disc to fungal cells is the susceptibility of these
10 fungi in vitro. Shown here are in vivo susceptibility
11 studies, expresses MIC 90s for the usual suspects in
12 terms of moulds that are clinically important. You
13 can see that the activity of Amphotec is very similar
14 to that of amphotericin B deoxycholate, with the
15 possible exception of fusarium. But in general, the
16 MIC 90s are comparable in the same range in vitro as
17 fungizone.

18 The same is true for yeasts as shown here.
19 Again, the usual group of clinical isolates. These
20 are MIC values which, if anything, favor Amphotec
21 somewhat over amphotericin B deoxycholate. Now, this
22 would not happen if the drug were altered in any way.
23 So, the drug is amphotericin B. It's moving as
24 amphotericin B into the fungal cell membranes and
25 that's how this in vitro susceptibility is expressed.

1 Now, this is all well and good, but in
2 terms of what happens in vivo is quite different.
3 We're now talking about quite a different product,
4 vis-a-vis, fungizone. So, what I'd like to do is
5 contrast what happens when the Amphotec complex enters
6 the blood versus what happens when Fungizone or the
7 deoxycholate micellar product enters the blood. And
8 further, I'd like to segment that into immediate
9 events, those events which occur within a few seconds
10 to minutes after introduction into the bloodstream,
11 versus later events which occur from one hour on. I
12 think you'll find that useful in terms of this
13 discussion. This is a proposed mechanism of action
14 that I'll be giving you. It is by no means
15 definitive, but it is consistent across all our in
16 vitro, in vivo, and clinical data.

17 With respect to Amphotec during this
18 initial period after entering the bloodstream, that is
19 less than one hour, the Amphotec complex is stable in
20 blood. Little drug actually becomes bioavailable
21 because the complex remains intact. It has a higher
22 affinity for amphotericin B than other structures that
23 it might meet in the bloodstream which would be
24 cholesterol containing structures, such as
25 lipoproteins and formed elements. So, the Amphotec

1 complex holds on to the blood. Little drug becomes
2 bioavailable during this period. Little drug
3 distributes to lipoproteins during this period.

4 So, there is very little lipoprotein
5 mediated distribution of amphotericin B to the kidney.
6 It is believed that lipoproteins, and in particular,
7 low density lipoprotein or LDL, is responsible for
8 much of the delivery of amphotericin B to the kidney
9 because it has been shown, quite convincingly, that
10 LDL receptors are expressed in kidney cells. So, the
11 lack of Amphotec's binding to lipoproteins during this
12 period correlates with less kidney uptake and that
13 correlates with less cumulative nephrotoxicity. By
14 one hour, most of the Amphotec complex is cleared from
15 the system, the bloodstream, by elements of the
16 mononuclear phagocyte system, or MPS system. These
17 are principally macrophages residing in liver and to
18 a lesser extent, spleen and bone marrow.

19 Now, to contrast this with what happens
20 after Fungizone administration, as soon as the
21 Fungizone micelle, the amphotericin B deoxycholate
22 micelle hits plasma, the drug and the carrier in this
23 case dissociate. That's because deoxycholate has a
24 fairly high solubility in water, in the millimolar
25 range, and so it has no real allegiance to

1 amphotericin B either. The affinity for amphotericin
2 B is rather low. So, the deoxycholate goes its way
3 and the amphotericin B finds itself on its own. Since
4 it's an insoluble drug basically -- insoluble in water
5 -- it binds very quickly to lipoproteins because
6 lipoproteins are the nearest and most plentiful
7 cholesterol containing structure in the blood.

8 Now, soon after binding to lipoprotein --
9 this is all happening within seconds -- within
10 minutes, the lipoprotein bound drug distributes to
11 tissues. This tissue distribution is somewhat
12 diffuse, but there are several organs that take more
13 drug up than others. The liver, for example, takes up
14 a lot of the drug, but so does kidney. So, it is this
15 pulse of amphotericin B that is being distributed to
16 kidney via lipoproteins that we believe is responsible
17 for the kidney toxicity associated with Fungizone and
18 it certainly correlates with nephrotoxicity we see
19 preclinically. So, it is a pulse of drug entering the
20 kidney via lipoprotein bound amphotericin B. This is
21 all happening within minutes of injection.

22 Now, again, to contrast this with
23 Amphotec. When Amphotec is infused, the complex is
24 stable. It mixes with blood and is circulating in the
25 same compartment as lipoproteins, but there is very

1 little movement of the drug to lipoproteins. Again,
2 for the reasons I've stated already, the affinity is
3 greater for the cholesterol sulfate than it is for
4 cholesterol in the lipoproteins. These particles then
5 are removed from the bloodstream, again, within
6 minutes by the liver, primarily, and to a lesser
7 extent, the spleen. So, in essence, the drug has been
8 distributed to liver without ever having become
9 bioavailable in these first few minutes. That's an
10 important thing to remember because it then does not
11 allow for distribution to the kidney during this
12 period by lipoproteins.

13 Now, this might be all well and good to
14 explain the reduced kidney toxicity, but what about
15 maintenance of antifungal activity? If the drug were
16 to remain sequestered in the liver forever, there
17 wouldn't be any activity. Well, at times greater than
18 one hour after entering the bloodstream, we find that
19 amphotericin B, that is the drug itself, becomes
20 bioavailable as uncomplexed, or free drug, in the same
21 way after Amphotec or amphotericin B deoxycholate.
22 I'll show you some evidence for that in a moment.
23 Moreover, the measured plasma levels of uncomplexed
24 amphotericin B are similar after Amphotec and
25 amphotericin B deoxycholate. When equivalent plasma

1 levels are attained, one would expect similar
2 antifungal activity.

3 We've measured the pharmacokinetics of
4 Amphotec versus amphotericin B in the current study,
5 the study that we're talking about today, 07-26.
6 These are ten patients -- ten from the amphotericin
7 Fungizone arm, ten from the Amphotec arm. Their
8 plasma samples were measured and these are predicted
9 values based on those measurements from a population
10 pharmacokinetics model. You can see here that the two
11 drugs reach a steady state at about after the fourth
12 dose of the drug. The peak levels are climbing up to
13 that point. And that the peak levels and the trough
14 levels are fairly similar for the two drugs injected
15 at this dose.

16 Now, one might ask, "does this drug under
17 the Amphotec arm represent uncomplexed drug? Is it
18 really bioavailable drug?" So, we address this issue
19 by developing an assay and validating an assay that is
20 capable of distinguishing between complexed drug, drug
21 still with the Amphotec complex, versus drug that
22 would be protein bound, or lipoprotein bound. The
23 majority of this area under the curve represents
24 unbound drug. Over 90 percent of what you see here is
25 unbound or uncomplex drug. That is, it's no longer

1 associated with the Amphotec complex. So, in that
2 case, the pharmacokinetics at the doses used in this
3 study, looked fairly comparable.

4 Now, in terms of the efficacy then, in my
5 model here -- if it could be focused a little bit --
6 the tissue distribution -- now this is events later
7 after the injection of amphotericin B and Amphotec.
8 As I've mentioned, the tissue distribution is
9 different. For Amphotec, most is going to the liver.
10 For amphotericin B, the tissue distribution is more
11 diffuse. But after about an hour, the lipoprotein
12 level of the drug declines because of the uptake by
13 the tissues. Now the tissues begin to contribute drug
14 back to the lipoprotein pool. The drug distributes
15 then to other organs and to assay a fungal abscess in
16 the lung via lipoproteins. That is, the lipoproteins
17 now receive drug from the organs. They distribute.
18 They could then distribute their drug to the lung and
19 the drug could then find its way to the abscess. You
20 notice I drew this line. I think it would be uni-
21 directional because once it hits the fungal cell, it
22 would remain there due to the strong binding with
23 ergosterol. There may even be some direct contact
24 between lipoproteins and the fungal cells, although
25 that's less likely.

1 Then the same thing happens basically with
2 Amphotec. The drug comes out primarily of the liver
3 this time, but it is moving around the body in the
4 same fashion as after Fungizone, and at approximately
5 the same plasma levels of free drug. So, it would be
6 expected also to distribute to the lung in exactly the
7 same fashion. It is unmodified amphotericin B and it
8 is being carried in the same fashion by the
9 lipoproteins. We believe this explains the
10 maintenance of the antifungal activity of this
11 product. The mixture of organs that is contributing
12 to the lipoprotein pool is different. When compared
13 at these dose levels, the amount entering the
14 bloodstream is similar.

15 So, in summary, the immediate
16 biodistribution of Amphotec complex to elements of the
17 MPS, we believe is the reason for reduced kidney
18 exposure. In vitro and in animal models that we've
19 looked at, Amphotec has equivalent activity to
20 amphotericin B deoxycholate. In some animals with
21 some endpoints, the equivalency ranges from a 1:1 dose
22 equivalency in some cases, and up to a 1:3 in other
23 cases, and perhaps 1:5 in the worst cases. So, there
24 is some need for higher doses in some animal models,
25 but not in all. In patients in the trial that we're

1 discussing today at the dose levels used, the blood
2 levels of bioavailable amphotericin B after Amphotec
3 were in the therapeutic range and were similar to
4 those after amphotericin B deoxycholate.

5 So, I think the message I'd like to leave
6 you with is that one, that it's amphotericin B. It
7 does have a different tissue distribution and that is
8 the benefit of this drug formula. That is, you avoid
9 this initial kidney exposure. But ultimately, the
10 drug becomes bioavailable and is distributed in the
11 same fashion as Fungizone.

12 Thank you.

13 DR. GURWITH: Thank you, Frank.

14 Now that you've heard about Amphotec
15 delivers amphotericin B, I just want to briefly review
16 its development for febrile neutropenia.

17 A little while after the studies for
18 documented fungal infections were initiated, Sequus
19 began to consider empiric therapy in febrile
20 neutropenia. In late 1993, a protocol was designed.
21 This protocol was developed with collaboration of
22 several investigators and there was even some input
23 from the FDA. The protocol development continued and
24 in early 1994, the study that we'll discuss today,
25 Study 07-26, was initiated.

1 By June 1996, approximately two years
2 later, enrollment was completed and the study was
3 stopped. We did a preliminary analysis, first,
4 primarily for publication. When we saw the results of
5 the outcomes in terms of the differences in safety and
6 the evidence of equivalence for efficacy, Sequus
7 decided to submit a supplemental NDA for this
8 indication. That was submitted in December of 1996,
9 shortly after the Amphotec received its initial
10 approval.

11 As you've already heard, there was a
12 meeting of the Anti-Infective Advisory Committee last
13 March, or actually, just a month ago, where broad
14 spectrum cephalosporin was reviewed for the empiric
15 indication for antibacterial agents. The advisory
16 committee voted to recommend approval of the drug and
17 it was based on demonstration of equivalence in
18 efficacy and in safety with a not approved comparator,
19 but a standard drug, very similar to the situation
20 with amphotericin B. It's of note that neither
21 superiority and safety nor efficacy were required, at
22 least for that vote.

23 Some of the issues -- obviously, not all
24 of them -- some of the medical and statistical issues
25 discussed at that committee and some of their

1 guidelines are relevant to this compound and I'll
2 mention some of them later. But now, Dr. Miller from
3 Johns Hopkins will discuss the particular issues:
4 complexities, concerns, that are peculiar to
5 developing an antifungal for the empiric febrile
6 neutropenia indication.

7 DR. MILLER: Thank you.

8 I'd like to make a change in the schedule.
9 As much as I'd like to be a professor of medicine, I'm
10 an assistant professor of oncology which is a separate
11 department at Johns Hopkins. I'd just like to clear
12 that up.

13 I wanted to bring the clinical perspective
14 from the investigators that helped develop this
15 protocol back in 1994 and also as one of the major
16 contributors of patients to the 07-26 trial, some
17 perspectives on the clinical design as well.

18 As you know, this is an empiric antifungal
19 trial which is a somewhat new avenue for evaluation of
20 drugs. A previous advisory council looked at empiric
21 antibiotics not empiric antifungals. When we started
22 to develop this study -- and the other principal
23 investigators that were mainly involved in the
24 development of the trial were Ralieg Bowden of Fred
25 Hutchison and Dr. Mary White at Memorial Sloan

1 Kettering -- we recognized that there were significant
2 differences between empiric antibiotics and empiric
3 antifungal agents.

4 First, for empiric antifungal agents, you
5 have a much less likelihood that you'll actually get
6 positive cultures at the initiation of your therapy.
7 That's very rare to actually have a positive culture
8 to confirm a diagnosis of "a fungal disease" when you
9 start empiric antifungal therapy. Secondly, at least
10 in the immunocompromised hematologic malignancies
11 patient, the morbidity and mortality related to
12 documented invasive fungal infections remains so high
13 that these are more significant, in many ways clinical
14 problems than many of the bacterial infections.
15 Thirdly, there's a significant difference from the
16 empiric antibacterials is that the standard of care
17 which is empiric amphotericin B is much more toxic
18 than the majority of empiric antibacterial agents.

19 Therefore, one of the questions or goals
20 was to see if you could design an empiric antifungal
21 strategy which delivered amphotericin with decreasing
22 nephrotoxicity which, especially in bone marrow
23 transplantation where we tend to use lots of other
24 nephrotoxins in these patients and the ability to
25 deliver adequate amounts of immunosuppressives

1 including cephalosporin contributes to the overall
2 success of the transplant, we decided to, as I said --
3 the decision was to go ahead and try and evaluate the
4 liposomal, lipid-associated amphotericin B product.

5 I'm not going to re-review the studies
6 that were done in the 1980s to provide the basis for
7 the need for empiric antifungal therapy in febrile
8 neutropenic patients. These were well described by
9 the previous two speakers. But what I'd like to
10 comment on is that the patients that were involved in
11 this study do remain at high risk of fungal
12 infections. Even though we have improved different
13 supportive care since the 1980s. Bone marrow
14 transplant has broadened the use of donors and there's
15 a much higher frequency of both unrelated donors and
16 mis-matched donors. This degree of mis-match from
17 donor to recipient has resulted in increase in --
18 fungal infections and increased immunosuppression.

19 As well in the leukemic population, the
20 intensity of the chemotherapy has significantly
21 increased from the 1980s, in that the standard
22 consolidation therapy in the 1980s was a consolidation
23 with low dose ARA-C plus or minus daunorubicin, other
24 chemotherapeutic agents. Whereas with recent large
25 studies from the ECOG or CALGB, the standard of care

1 is two to four cycles of -- ARA-C consolidation. So,
2 therefore, these patients remain at significant risk
3 of fungal infections.

4 Also, new drugs to prevent or treat graft
5 versus host disease are either under development or
6 have recently been developed. There's also a
7 continued significant use of steroids to prevent or
8 treat graft versus host disease. All of these factors
9 contribute to the maintenance of a high risk of fungal
10 infection in this patient population that was
11 considered for this protocol.

12 Next, despite significant advances in our
13 treatment of fungal infection as clinicians who care
14 for patients who are undergoing leukemia therapy or
15 bone marrow transplant, we recognize that fungal
16 infections are playing a significant cause of
17 morbidity and mortality in these patients. These can
18 be devastating disease once the disease is present.
19 So, as Dr. Walsh and Dr. Sugar discussed, we do have
20 to consider that prophylaxis antifungal therapy is a
21 real treatment option, especially in the bone marrow
22 transplant patients. It's more controversial and less
23 well established in leukemia patients.

24 The most common drug to use for
25 prophylaxis is fluconazole and there is a recent

1 combined CDC, ASBMT, IDSA consensus panel that met in
2 Atlanta to discuss guidelines. Fluconazole was
3 considered to be a reasonable recommendation for
4 standard of care, or could be considered a standard
5 practice as antifungal prophylaxis of bone marrow
6 transplant patients. There is still, however,
7 heterogeneity within different centers about how they
8 use antifungal prophylaxis. However, in general, it's
9 kept uniform within an institution. This study is a
10 double blind, blinded trial so we felt that that's
11 controlled -- which was stratified through
12 randomization by center. Since the use of fungal
13 prophylaxis was generally standard within
14 institutions, that given the fact this is a randomized
15 trial, that that should be dealt with with the
16 randomization. Dr. Gurwith will show the results that
17 that fluconazole prophylaxis was standard in both
18 patient groups.

19 Also, it has to be remembered that
20 fluconazole only can protect against infections with
21 susceptible organisms. That is, candida albicans and
22 some other candida tropicalis. It does not prevent
23 infections with many of the non-albicans, yeast,
24 especially -- torulopsis glabrata and of course,
25 aspergillus is resistant to fluconazole. When you

1 think of patients who have been on fluconazole
2 prophylaxis and consider them for empiric therapy, you
3 do have to remember that these do represent -- these
4 patients who are placed on empiric antifungal
5 therapies do often represent a failure of at least one
6 antifungal prophylaxis.

7 Again, given the data on empiric
8 antifungal therapy, we felt that a placebo trial was
9 no longer possible in this patient population. We
10 also recognized that the fever, while it is how
11 patients get on an empiric antifungal trial, is
12 generally not associated with positive cultures. This
13 is because fungal infections are very difficult to
14 document. Again, we may be suppressing or trying to
15 prevent the emergence of a clinically significant
16 fungal infection with our empiric antifungal therapy.
17 There was also some discussion at the design of the
18 study about the required duration of the therapy for
19 evaluability.

20 Endpoints: survival, of course is an
21 important endpoint; documented fungal infections are
22 being evaluated in this study. Because this is a
23 clinical study looking at a treatment strategy which
24 is an empiric treatment strategy where you expect many
25 of the patients not to actually develop the disease,

1 a clinical indicator which is successful outcome, was
2 also used to analyze the response of these patients.
3 Dr. Gurwith will discuss in greater detail this
4 successful outcome measure. It does combine both
5 clinical efficacy which is completion of the study
6 drug, plus seven days without emergence of a fungal
7 infection. The requirement that the drug not be
8 stopped because of toxicity, and being afebrile on the
9 last treatment day. This was felt that this outcome
10 could be used to evaluate the success of empiric
11 antifungal strategy.

12 Fever, while again, it's important to get
13 the patients onto the trial, we recognize may be the
14 least reliable indicator of response. This was
15 discussed previously as well, in that we know that
16 both drugs, amphotericin and the Amphotec in itself
17 caused fever, especially with the earlier doses.
18 Also, at the time of recovery when these patients were
19 going off study, they were offered many other reasons
20 for fevers including viral infections and/or drug
21 fevers as well.

22 Empiric antifungal therapy is generally
23 started in many clinical situations when there has
24 been no response after three to four days of empiric
25 antibacterial therapy, or when there's recurrent fever

1 after initial response to empiric antibacterial
2 therapy. We, and other investigators in the study,
3 did note that when we took our population that we
4 considered to be at risk, or being potential to be
5 placed on this trial, between 30 and 50 percent of the
6 patients never got to the second fever. That is, that
7 we're getting patients through bone marrow transplant
8 and through leukemia therapy at a greater number
9 without ever applying empiric antifungal therapy.

10 This is partially related to the
11 improvements in some of the standard care, the
12 fluconazole prophylaxis, and due to the fact that some
13 of these patients recovered more quickly than you
14 would expect for them to actually get a second fever
15 or a fungal infection. So, we think that this 30 to
16 50 percent that actually never got on trial may
17 represent the improvements that may be seen with the
18 improvements of prophylactic strategies. However,
19 once patients have gotten on the trial, there's no
20 evidence that these patients are at less risk for
21 fungal infections.

22 Documenting fungal infections was defined
23 as a definite infection if there's a culture of a
24 sterile site, i.e., blood or lung. For sinus
25 infections, a biopsy was used. Clinicians taking care

1 of patients with leukemia or bone marrow transplant
2 recognize that often, we're unable to get tissue
3 documentation of fungal infections due to the
4 patient's clinical status, and also the low yield,
5 even when you go after an infection percutaneously.
6 And so, we have also included in our treatment
7 strategy changes in the antifungal therapy from the
8 investigator, based on presumed or suspected fungal
9 infections.

10 At Hopkins, Janet Kuhlman and Elliott
11 Fishman, as well as others, have published on the CAT
12 scan evidence of fungal disease, correlated it in two
13 studies with autopsy findings. So, at least at our
14 center, we feel very comfortable using CAT scan
15 guidance to at least guide changes in antifungal
16 therapy. In patients who are on an empiric regimen
17 who develop CAT scan changes such as a halo sign or
18 multiple nodular infiltrates, we feel that it's
19 important to treat them as if they actually have a
20 fungal infection. That, in our institution, means
21 increasing the amphotericin dose to 1.25 and adding
22 5FC. So, in this study, those patients were
23 considered a "failure" of the empiric antifungal
24 therapy.

25 The suspected fungal infections, including

1 CAT scan documented, again, were defined as a change
2 that leads to modification away from empiric
3 antifungal therapy to what we call a treatment
4 strategy of antifungal therapy. Antifungal therapy
5 was continued until neutrophil count recovers or until
6 failure occurs. Again, we define failure as either a
7 presumed or documented infection while on the empiric
8 antifungal. Again, if a patient had persistent fevers
9 on amphotericin B with compatible clinical signs and
10 symptoms, again, that could be considered a failure of
11 the empiric antifungal therapy.

12 This study did cover empiric therapy for
13 only 14 days. It was designed based on the feeling
14 that that would cover the majority of the patients and
15 also because clinically relevant fungal infections
16 generally will become manifest within the first two
17 weeks in patients who are neutropenic. Now, we
18 continue the drug for 14 days unless white count
19 recovered before that. In retrospectively analyzing
20 the data when the study was completed, we did show
21 that over 80 percent of the patients did meet the
22 criteria of either completing the study with
23 neutrophil recovery or completing the study due to
24 failure before 14 days. So, this did appear to be an
25 appropriate endpoint.

1 Finally, there's an issue about how does
2 empiric antibacterial therapy and changes in empiric
3 antibacterial therapy affect an antifungal study?
4 Well, it's very clear that empiric antibacterial
5 therapy is standard practice. Empiric antibacterial
6 therapy regimens vary from institution-to-institution,
7 depending on the institution's microbiologic flora and
8 their percent of resistant organisms. Therefore, this
9 study, being with its emphasis on antifungal
10 prevention did not legislate changes in antibacterial
11 regimens. However, again, this is a randomized double
12 blind trial and changes in antibacterial regimens
13 generally are uniform within an institution.
14 Therefore, given the randomization, the changes should
15 fall out with the randomization.

16 Again, it was the opinion of the
17 investigators that changes in -- antibacterial therapy
18 or study would not influence the overall outcome of
19 response to an empiric antifungal strategy and that
20 changes in antibacterial regimens after the initiation
21 of the empiric antifungal agent could be confounded by
22 the response or lack of response, or the toxicity of
23 the empiric antifungal agent. And so that it would be
24 difficult to try and standardize that, after the fact.

25 In summary, the study was a study designed

1 to look at the strategy of empiric antifungal therapy
2 in significantly neutropenic and immunocompromised
3 patients who are at a high risk for fungal infections.
4 The goal of the study was to evaluate safety,
5 especially nephrotoxicity in this patient population,
6 and to look for evidence of equivalence.

7 I thank you.

8 DR. GURWITH: Thank you, Carole.

9 Now that we've heard that actually fungal
10 infections still are important. They still remain
11 common and cause considerable morbidity, even in this
12 era of the '90s with fluconazole and granulocyte
13 factors, let me now review the data from our study in
14 this patient population.

15 Study 07-26 was a double blind, randomized
16 study and enrolled 213 patients. The patient
17 population were patients who failed to respond to
18 broad spectrum antibiotics and were febrile and
19 neutropenic. And by failed to respond, we meant that
20 patients had to have fever at least three days on
21 broad spectrum antibiotics, or if they responded
22 initially to the broad spectrum antibiotics, then if
23 they had a recurrence of fever and that recurrence had
24 to last at least 24 hours.

25 We thought it was important to stratify

1 for risk factors so this study was stratified in
2 advance for age, adults or children and then more
3 importantly, for risk of nephrotoxicity stratified by
4 the use of cyclosporin and tacrolimus. We had four
5 groups, adults, children, with and without
6 cyclosporin, tacrolimus. Adding this second
7 stratification for cyclosporin for the high risk
8 patients did add considerably to the time of
9 enrollment in this study. It took at least another 18
10 months, or almost 18 months, to fully enter the strata
11 number one where adults with concurrent cyclosporin.
12 However, we thought this was important because, again,
13 the reason for developing a lipid based amphotericin
14 was to look at and provide less nephrotoxicity. The
15 cyclosporin group would be the ones at highest risk of
16 nephrotoxicity. Patients received the appropriate
17 dose of the study drug, either amphotericin or
18 Amphotec until they reached an endpoint.

19 As already described by Carole, the
20 endpoints were the end of 14 days when they would come
21 off study, or prior to that, resolution of the
22 neutropenia, recovery of neutrophil counts, a cause of
23 fever being identified, or the patient had to be
24 discontinued for toxicity. So, those were the
25 endpoints. Generally, most patients dropping out for

1 cause of fever identified that was non-fungal, were
2 patients who had bacterial infections identified not
3 during the study, but at baseline where cultures
4 became positive after the patient came on the study.

5 Now, to look at the patient population in
6 more detail, this slide summarizes the usual
7 demographic features. You can see that the two groups
8 are well balanced for age, sex and race, though there
9 is a slight preponderance, or at least a higher
10 proportion of women in the amphotericin B group in
11 comparison to the Amphotec group. We did make an
12 effort to enroll children and approximately 25 percent
13 of the patient population is pediatric, that is under
14 the age of 16. Now, to look at baseline
15 characteristics that relate to risk of fungal
16 infections, you'll see that the population is also
17 well balanced between the two different groups.

18 This is a high risk patient population.
19 Almost 70 percent of the population overall were bone
20 marrow transplant recipients. About 43 percent of the
21 population overall were the high risk patients,
22 allogeneic marrow transplants. These patients are
23 obviously at more risk of nephrotoxicity, but also
24 fungal infection. Defining severe neutropenia as ANC
25 count of less than 100, almost 90 percent of this

1 population had severe neutropenia at baseline.

2 During the review last month of cefepime,
3 some of these things became an issue, how much of a
4 high risk population were included? If I remember the
5 figures correctly, only 15 percent of the population
6 in the review of the antibacterial drugs were bone
7 marrow transplant recipients. So, this shows you that
8 this is, again, a high risk population both for
9 nephrotoxicity and for fungal infection.

10 As you've heard, prophylactic fluconazole
11 is common, or is becoming standard in this patient
12 population. About 80 percent of both treatment groups
13 received prophylactic fluconazole. But please
14 remember that the study design required that the
15 prophylactic fluconazole, be discontinued at the time
16 of study entry. If you look at duration of prior
17 broad spectrum antibiotics, patients had to have broad
18 spectrum antibiotics to enter the study and the
19 populations are, again, well balanced. About a third
20 in each group had received these antibiotics for a
21 week or less, and two-thirds had received them for
22 more than a week.

23 Then finally, looking at fungal
24 colonization at baseline based on the results of
25 surveillance cultures, the Amphotec population looks

1 like it was somewhat more colonized by fungi. These
2 were usually yeast, candida or other yeast.

3 To evaluate the clinical impact of
4 Amphotec, we looked at a number of safety and efficacy
5 variables, though the primary variable was safety.
6 The primary efficacy variable was a composite endpoint
7 or variable that was modeled on similar variables from
8 other studies. It was modeled a lot, maybe even close
9 to plagiarized, from the MSG NIH study but it is,
10 obviously, not identical to their endpoints. It also
11 resembles composite endpoints used in other EORTC
12 studies, both ongoing or planned.

13 The endpoint required that the patient
14 survive the study, survive at least seven days beyond
15 the end of the study; develop no new infection on
16 study or within seven days following the study, though
17 fungal functions either documented or suspected that
18 were present at the time of study entry are not
19 included in this. Then the patient could not be
20 terminated due to toxicity. Finally, the patient had
21 to be afebrile at the end of the study and that was
22 defined as a temperature of 38 degrees, or less than
23 38 degrees on the last dosing day. But we excluded
24 study drug related fevers or transfusion related
25 fevers.

1 As you've heard, empiric therapy is a
2 treatment strategy and so, we feel that composite
3 endpoint like this which evaluates the clinical
4 features desirable in that treatment schedule is
5 pertinent and clinically valuable, though again, it's
6 not the only efficacy variable we looked at. In order
7 to establish equivalence for this and other efficacy
8 endpoints, we used 95 percent confidence intervals
9 around the difference between the two treatment
10 groups. In the next series of slides, we show the
11 treatment differences and the 95 percent confidence
12 interval for the difference with the lower or upper
13 bound that's pertinent outlined in yellow.

14 So, when we look at this data, Amphotec
15 and amphotericin B appeared to be equivalent in terms
16 of the successful outcome variable. In fact, the
17 point estimates for this variable slightly favor
18 Amphotec. If you look at the evaluable patient
19 population, 50 percent of the patients had a
20 successful outcome in comparison to 43 percent, and
21 very similar numbers for the intent to treat
22 population. And then the lower bound, which is the
23 pertinent bound in a variable that is a desirable
24 variable such as successful outcome, the lower bound
25 is approximately seven percent for both groups and

1 well within the 20 percent maximum tolerated
2 difference that was one of the proposed guidelines for
3 the anti-infective committee, or published proposed
4 guidelines for anti-infectives in febrile neutropenia.
5 The 20 percent is based on response rates in the
6 magnitude that we see here around 40, 50 percent --
7 even up to 70 or 80 percent.

8 The definition of successful outcome
9 excluded fevers related to study drug or transfusion
10 and so makes some assumptions. So, we looked at a
11 modified successful outcome variable which didn't
12 require any assumptions. This successful outcome
13 variable is identical to the previous one except that
14 the patient was required to be afebrile at the end of
15 study, regardless of the presumed cause of fever. And
16 so, when we look at the data using this modified
17 definition of successful outcome, we, again, see that
18 the two drugs appear equivalent. The successful
19 outcome rates are lower, 38 percent for the evaluable
20 patients and 37 percent for amphotericin B. The lower
21 bound of the confidence interval is around 12 to 13
22 percent, depending on the group. But again, for
23 response rates of this magnitude, this is well within
24 the 20 percent maximum tolerated difference.

25 Now, obviously, as you've certainly heard

1 from Dr. Walsh, fungal infection is an important
2 endpoint for this drug, or in this treatment strategy
3 and so, we did look, obviously, at fungal infections.
4 We defined fungal infection occurring on study -- that
5 is, an emerging or new fungal infection, as a patient
6 who had a compatible, clinical syndrome. And then a
7 documented fungal infection would be one where there
8 was microbiologic proof of infection such as biopsy,
9 positive cultures from biopsy or histologic proof from
10 a biopsy, or cultures from normally sterile sites.
11 And then suspected or presumed fungal infection were
12 patients with a clinically compatible syndrome, but
13 without the microbiologic documentation.

14 As you've heard from several speakers,
15 it's easy to suspect fungal infection in these
16 patients, very hard to prove it. But nevertheless,
17 these suspected or presumed fungal infections have a
18 major clinical impact. Once they're considered, the
19 clinicians generally make a change in the antibiotic.
20 They escalate the dose of amphotericin to a treatment
21 dose. Or they may change the antifungal, or they may
22 add an additional antifungal. So that, we felt that
23 suspected infection, although not as striking as
24 documented fungal infection, still is a valid thing to
25 look at. Again, when we look at fungal infections, we

1 see that the two treatment groups remain comparable or
2 equivalent.

3 For the intent to treat population -- and
4 the results are really quite similar in the evaluable
5 population -- the rate of documented fungal infection
6 was almost exactly four percent for both treatment
7 groups, four in each group. In the upper bound is now
8 for undesirable outcome -- the upper bound is the
9 relevant boundary. The upper bound is below the
10 maximum tolerated difference of ten percent. It's
11 approximately eight percent. The maximum tolerated
12 difference of ten percent comes, again, from these
13 same suggested guidelines or proposed guidelines which
14 would say that for an endpoint with response rates of
15 90 to 100 percent, or zero to ten percent, a maximum
16 tolerated difference of ten percent would be
17 appropriate.

18 If you look at documented plus suspected
19 fungal infection, of course the rate is higher. But
20 the two groups again look equivalent. The point
21 estimate is slightly better for Amphotec, 14 percent
22 versus 16 percent. The upper bound is seven-and-a-
23 half percent. Again, below the ten or 15 percent that
24 would be appropriate for an outcome rate of this
25 magnitude in the comparator drug. The other thing to

1 note is that the four percent rate for documented
2 fungal infection is exactly in the range, two to six
3 percent, that were reported in the original EORTC and
4 Pizzo studies in the amphotericin B group. So, the
5 placebo group or the untreated group in those two
6 studies had a much higher rate, but the amphotericin
7 group was in this range. So, again, this suggests
8 that we're still in an era where we have similar rates
9 of fungal infections despite this empiric treatment
10 strategy.

11 I should note that our original definition
12 of successful outcome included fungal infections only
13 up to the end of treatment. After the study was
14 completed at the suggestion of our investigators and
15 of the FDA, we expanded the definition of fungal
16 infection to include fungal infections that went
17 beyond the end of treatment, and occurred in the seven
18 day follow-up period. When the patients were looked
19 at in retrospect from the seven day period, some of
20 those patients that originally were considered to have
21 suspected fungal infections were found not to have a
22 fungal infection. An alternative diagnosis was
23 discovered, and so those patients were removed from
24 the category of suspected fungal infections. There's
25 12 such patients so those were 12 patients terminated

1 originally from the study because the investigator
2 thought he had a fungal infection. Those 12 are six
3 in each group. If we add them back to the study
4 group, we see similar rates of fungal infection with
5 little difference between the two groups, and similar
6 rates of successful outcome. Or at least the
7 successful outcome rate decreases somewhat, but the
8 difference between the two groups is small and the
9 confidence interval is also similar.

10 Obviously, another variable to look at in
11 this patient population is defervescence. In this
12 study, we define defervescence as being the patient
13 had to be afebrile for 48 hours. In this definition,
14 we did not make any assumptions about the cause of
15 fever. So, the patient had to be afebrile for 48
16 hours regardless of the cause of fever.

17 Although defervescence or fever, again, as
18 you've heard, is the reason the patients are entered
19 into the study, as you've heard from Carole, it's not
20 necessarily the best indicator of efficacy or outcome
21 in this patient population because it's only a proxy
22 for the fungal infection. A number of the patients
23 who have the fever have other causes of the fever. Or
24 even if the original fever was due to fungal
25 infection, they remain neutropenic and other bacterial

1 non-fungal causes such as viral or even non-infectious
2 causes can occur as well. Nevertheless, when we look
3 at defervescence, the two groups, again, appear
4 equivalent. The point estimates here slightly favor
5 amphotericin B for the evaluable patient population.
6 Fifty-eight percent had defervescence compared to 54
7 percent for Amphotec. The confidence interval for the
8 difference is 18 percent. Again, within the 20
9 percent maximally tolerated difference for an endpoint
10 in this range.

11 Survival, obviously is another important
12 variable. It was part of the composite endpoint of
13 successful outcome but that looked at survival only at
14 seven days. This slide shows a Kaplan-Meier estimates
15 of survival based on the 28 day post-treatment period.
16 So, whether the patients survived up to 28 days
17 following the end of treatment. As you can see, the
18 two groups appear very similar in these Kaplan-Meier
19 estimates. There were only two infections in this
20 study that were thought to be due to fungal infection,
21 one in each treatment group.

22 So, before discussing safety, I just want
23 to try to summarize the efficacy variables because
24 there are a number of them. As Dr. Feigal mentioned,
25 we were looking at a hierarchy of efficacy variables.

1 On this slide, we've summarized these
2 different efficacy variables and the point estimates
3 for the difference is signified by the green circles.
4 So, this would be the point estimate for the
5 difference between the two groups for documented
6 infection and it is right on zero because it was four
7 percent for both groups. As you can see, these point
8 estimates for the differences are low and close to
9 zero for all these points. Then the yellow square for
10 each group, for each line, is the upper or lower bound
11 of the 95 percent confidence interval. Again, the
12 appropriate boundary and you can see these boundaries
13 are within the appropriate 10 to 20 percent maximally
14 tolerated differences.

15 So, to summarize efficacy, this study
16 demonstrated efficacy equivalent to amphotericin B for
17 Amphotec for multiple endpoints: successful outcome,
18 fungal infection, defervescence and survival.
19 Antifungal efficacy has already been shown in clinical
20 trials with documented fungal infection. Then we've
21 shown you some preclinical and pharmacokinetic data
22 that suggests that amphotericin B and Amphotec should
23 have comparable efficacy since we're delivering
24 amphotericin B -- since basically, the Amphotec
25 complex is delivering amphotericin B.

1 We feel these results are reassuring in
2 terms of efficacy and now we'd like to look at safety
3 since, again, that was the reason for developing
4 Amphotec, to reduce nephrotoxicity. In contrast to
5 efficacy where we've had to have a more problematic
6 look at trying to prove equivalence which requires
7 using 95 percent confidence intervals and requires
8 making comparison of those confidence intervals with
9 not as well accepted guidelines, with safety we're
10 trying to show differences than equivalence. We use
11 just the conventional statistical measures of
12 different testing. So, we'll look at p-values and use
13 the conventional 0.05 level of significance.

14 As you've heard -- at least we all are
15 aware of the nephrotoxic potential in amphotericin,
16 but we may not be as clear or as obvious as maybe
17 we'll see from this study. Let me back up. In order
18 to look at renal toxicity, we defined a variable
19 toxicity which was simply a doubling of the serum
20 creatinine from baseline, or an increase in serum
21 creatinine of one milligram, or a decrease of 50
22 percent of the creatinine clearance.

23 This data shows you how significant or how
24 great the potential for nephrotoxicity is, at least in
25 this febrile neutropenic patient population. Overall,

1 slightly more than 50 percent of the amphotericin B
2 patients develop nephrotoxicity, compared to 20
3 percent in the Amphotec population. This is a
4 statistically significant difference. If you look at
5 median time to nephrotoxicity, you see a delay in the
6 development of nephrotoxicity in the Amphotec group.
7 This is, again, statistically significant. Again, as
8 several of the speakers already have told you or
9 suggested, in this febrile neutropenic patient
10 population receiving empiric therapy, the
11 nephrotoxicity may be particularly undesirable since
12 the receiving drug, amphotericin, where only a
13 minority of the patients will benefit. Many of these
14 patients do not have fungal infection. They have
15 another reason for their fever. So, giving them a
16 nephrotoxic drug that they don't benefit from is not
17 desirable, especially when many of these patients will
18 receive concurrent nephrotoxic agents, or other
19 nephrotoxic agents.

20 In this study, we also looked at children
21 and might have expected to see less nephrotoxicity in
22 the pediatric group because of greater renal reserve,
23 or at least proposed greater renal reserve in
24 children. But as you can see on this slide, even the
25 small group, the rate of nephrotoxicity for

1 amphotericin is striking. It's still a little over 50
2 percent compared to only 12 or three patients in the
3 Amphotec group. Again, a statistically significant
4 difference and the time to renal toxicity is, again,
5 even for the pediatric group, different and
6 statistically different. Perhaps the pediatric
7 patients with greater renal reserve do show somewhat
8 of a delay in developing nephrotoxicity in comparison
9 to the adults.

10 Now, I'm sure you all know that
11 cyclosporin is a very potent nephrotoxin and of
12 course, is used in the bone marrow transplant
13 recipients. And so, it, along with amphotericin, is
14 a significant risk factor for nephrotoxicity. This
15 slide really shows how profound that risk is. Sixty-
16 eight percent -- almost 70 percent -- of the
17 amphotericin B population receiving cyclosporin or
18 tacrolimus develop nephrotoxicity. If you look at the
19 Kaplan-Meier estimates, the rate approaches 90 percent
20 by Day 14. This compares to 31 percent in the
21 Amphotec population. Again, both the time to toxicity
22 and the rate of toxicity is statistically significant.
23 If you look at this slide which is Kaplan-Meier
24 estimates of the time to toxicity, you see how quickly
25 nephrotoxicity develops in the amphotericin B group,

1 by three or four days. And that you see a difference
2 at that time, three to four days, and that remains
3 present for the rest of the study.

4 Now, if you look at the patients at low
5 risk, non-cyclosporin patients, we see a similar
6 striking difference between amphotericin B and
7 Amphotec. The rate in the amphotericin B group is 35
8 percent in this lower risk patient population compared
9 to eight percent -- more than a four-fold reduction in
10 nephrotoxicity. And again, based on Kaplan-Meier
11 estimates, the time to nephrotoxicity is significantly
12 delayed in the Amphotec group. If we look at Kaplan-
13 Meier estimates of time to toxicity on these curves,
14 you again, see a separation between the two groups and
15 that surprisingly early development of nephrotoxicity,
16 even in the low risk group, with amphotericin.

17 Now, these patients, besides getting
18 cyclosporin, amphotericin, receive aminoglycoside
19 antibiotics which are considered another risk. So, in
20 this slide, we look at how much or how little the
21 aminoglycosides contributed to nephrotoxicity. Now,
22 the groups were not stratified by aminoglycoside use.
23 They were stratified for the cyclosporin use. So,
24 this is a retrospective analysis. But if you look at
25 the top line, this is patients who received

1 cyclosporin and they divide into those that received
2 aminoglycosides as well, for those that didn't. And
3 as you can see, surprisingly, for neither Amphotec nor
4 amphotericin B do we see much of an increase, or any
5 increase in the rate of nephrotoxicity for the
6 aminoglycosides. Then if we look at the bottom line,
7 we're looking at patients who did not receive
8 cyclosporin and whether they received aminoglycosides
9 or received neither nephrotoxic drug. And again, we
10 don't really see much of a added difference from the
11 aminoglycosides. This at least was surprising to me.
12 It may be a result of the fact that the
13 aminoglycosides were not used for that long a period
14 in this patient population.

15 Another consequence of renal injury from
16 amphotericin B is potassium depletion. In this slide,
17 it looks at the change from baseline of serum
18 potassium. You can see that, first of all, the two
19 study populations are well balanced at baseline in
20 terms of serum potassium. The mean serum potassium
21 was 3.9 at baseline for Amphotec and 4 for the
22 amphotericin B group. In both patient populations,
23 there is a decline in serum potassium either at Day 7
24 or at the end of treatment, but a statistically
25 significantly greater decline in the amphotericin B

1 group. As far as I know, this is the first time this
2 particular finding has been demonstrated with a lipid-
3 based amphotericin.

4 These are differences that relate to the
5 serum potassium or the rate of decline in serum
6 potassium. When we showed this to several people,
7 they asked about the clinical significance of this.
8 So, we decided to do an analysis, trying to define a
9 level of hypokalemia that might be clinically
10 significant. To be included in this analysis of
11 hypokalemia, the patient had to have a serum potassium
12 below a certain level on at least one day during the
13 study. So, in this analysis -- admittedly, it's a
14 post hoc analysis, but we tried to define a level of
15 serum potassium that would be considered clinically
16 important. The top line looks at patients who had a
17 serum potassium of less than three on at least one day
18 during the study. As you can see, there is a
19 difference. Twenty-three percent of the amphotericin
20 B group reached that level of hypokalemia compared to
21 seven in the Amphotec group. This is a statistically
22 significant difference. If you look at a more
23 significant level, or a more profound level of
24 hypokalemia, you see a difference as well, five versus
25 zero. But the difference is not statistically

1 significant.

2 We also looked at serum magnesium in terms
3 of change from baseline in serum magnesium. There, we
4 saw a decline in both groups, a small decline in both
5 groups of serum magnesium. Again, a greater decline
6 in the amphotericin B group, but not a statistically
7 significant difference.

8 So, to summarize the findings with regard
9 to renal toxicity, in this febrile neutropenic patient
10 population, Amphotec was shown to have greater renal
11 safety than amphotericin B. You see this overall.
12 You see it in adults, children, in low risk patients,
13 and even in patients with high risk due to
14 nephrotoxicity from cyclosporin. The difference
15 between the two drugs is highly statistically
16 significant. We also see evidence of less potassium
17 depletion.

18 Now, to look at the other measures of
19 safety, this is the mortality in the study group.
20 Again, just looking at the deaths within 28 days of
21 the end of the study, again, the groups look
22 equivalent. There were 16 deaths, or approximately 15
23 percent of the Amphotec group or 13 percent in the
24 amphotericin B group. As I mentioned before, there
25 were only two deaths that were considered to be

1 related to fungal infection, one in each study group.
2 Then there was one death in this 28 day period that
3 was considered possibly related to study drug. That
4 was an amphotericin B patient who developed
5 hypokalemia and had a cardiac arrest. The
6 investigator judged the cardiac arrest to be related
7 to an arrhythmia, secondary to hypokalemia.

8 Now, if we look at patients who
9 discontinued study early due to death or adverse
10 events, we can see a similarity or comparability
11 between the two study groups. There were only two
12 deaths that occurred on study while the patient was
13 receiving study drug. Both of these were in the
14 amphotericin B group. One was the patient I just
15 described with hypokalemia. Another was a patient who
16 died of hepatic toxicity or hepatic failure. This was
17 not considered related to study drug.

18 Then if you look at the adverse events
19 leading to discontinuation of study drug, you see,
20 again, comparability. Seventeen percent of the
21 Amphotec group and 19 percent of the amphotericin B
22 group discontinued early due to an adverse event.
23 However, the reasons for discontinuing are a little
24 different. The amphotericin B group discontinued
25 predominantly due to nephrotoxicity, one versus 12,

1 and the Amphotec group discontinued predominantly due
2 to infusion related adverse events, chills, fever,
3 hypoxia, hypotension, or other reasons. Our analysis
4 of this data, as you'll see, is slightly different
5 from the FDA's analysis. Some of the differences
6 relate to what we put into other and their more
7 detailed analysis of those groups.

8 Now, to look at the adverse event in terms
9 of conventional adverse event -- to look at the safety
10 in terms of conventional adverse event profiles, on
11 this slide we summarize adverse events that were
12 considered possibly or probably related to study drug
13 and it occurred in at least ten percent of one of the
14 two study groups. You can see there's two that are
15 statistically different. Chills occurred commonly in
16 both groups, 65 percent in the amphotericin group and
17 80 percent in the Amphotec group. This is a
18 statistically significant difference. Then adverse
19 events related to renal function occurred
20 significantly more common in the amphotericin B group,
21 40 percent versus 24 percent. The other events
22 appeared similar.

23 We're well aware of the propensity for
24 amphotericin to cause chills and fevers, acute
25 infusion related events, and it's generally considered

1 that these respond to premedications and tend to
2 decrease anyway over time. This slide compares the
3 two groups and shows that for both Amphotec and
4 amphotericin B, we see this decline. With dose number
5 one or Day 1, we see a rate of 64 percent for the
6 Amphotec group and 52 percent for the amphotericin B
7 group. Then in both groups, this declines
8 progressively with each dose or each dosing day. By
9 Day 7, the rate is approximately 20 percent in both
10 study groups.

11 Other adverse events that were reported at
12 least ten percent were these. The only one that's
13 statistically significant of the rest of these adverse
14 events or hypoxia, or adverse events that were coded
15 by COSTART to hypoxia, 12 percent versus three percent
16 for amphotericin B. This is a statistically
17 significant difference. The rate of hypomagnesemia
18 was double in the amphotericin B population, but this
19 is not a statistically significant difference.

20 Now, to look in more detail at these
21 hypoxia related events, we did this analysis. There
22 were 13 in the Amphotec group, three in the
23 amphotericin B group. These seemed usually, if not
24 always, associated with chills and fever. Four of
25 these were assessed as severe. They all resolved

1 without sequelae. Most of the patients, 63 percent,
2 had easily identified pre-disposing factors:
3 pulmonary infiltrates, congestive failure, fluid
4 overload that might help contribute to the hypoxia.
5 The treatment was generally supplemental oxygen. So,
6 these events looked to be acute infusion related,
7 reversible episodes of desaturate, temporary
8 desaturation. And they're probably related to
9 vasodilation occurring during the chills and fever.
10 They didn't seem to be associated with pulmonary
11 injury. They were reversible and there appeared to be
12 no new infiltrates or permanent changes associated
13 with these episodes.

14 So, to summarize the other safety
15 features, we found no difference between Amphotec and
16 amphotericin B in mortality or in rates of adverse
17 events. The adverse events were comparable with the
18 exception that the rates were comparable but the
19 Amphotec group had more infusion related events and
20 the amphotericin B group had more renal events.

21 So, to put this in perspective in terms of
22 our supplemental NDA, I just want to summarize these
23 key points. First of all, Amphotec delivers
24 amphotericin B . It's a novel lipid complex and as
25 Frank Martin has shown you, it preserves antifungal

1 activity but substantially reduces nephrotoxicity.
2 Previous clinical studies showed its efficacy in
3 patients with aspergillosis and other fungal
4 infections, and this is confirmed in preclinical
5 studies.

6 Then when we look at Study 07-26, this
7 shows you that Amphotec has comparable efficacy in
8 this febrile neutropenic patient population. It has
9 substantially less nephrotoxicity in these patients.
10 Then the benefits of the reduced nephrotoxicity are
11 even more profound in the high risk subgroups and in
12 children. Then finally, Amphotec and amphotericin B
13 looked otherwise similar in terms of safety variables,
14 with the possible exception of these acute reactions.
15 Though these generally are easily managed with
16 premedications or other measures.

17 So, to conclude and summarize in terms of
18 this NDA, if we look at everything that's been done in
19 the development of Amphotec starting with preclinical
20 studies and phase II and phase III clinical trials,
21 all the data provides evidence that Amphotec has
22 similar antifungal efficacy to amphotericin, but has
23 less nephrotoxicity. You can see comparable in vitro
24 activity. You see comparable activity or efficacy in
25 animal models of fungal infection. And in clinical

1 studies of patients with documented fungal infections,
2 you again see evidence of comparable or equivalent
3 antifungal activity. Then in these febrile
4 neutropenic patients, you see, again, evidence of
5 comparable activity based on multiple endpoints.

6 Finally, you can see clearly in this
7 neutropenic patient population that this antifungal
8 activity is provided with much less nephrotoxicity,
9 which is important in this patient population. Based
10 on that, we suggest that Amphotec provides a less
11 nephrotoxic alternative to amphotericin B in this
12 patient population and propose the indication that I
13 showed you originally.

14 Thank you.

15 CHAIRMAN HAMMER: Thank you.

16 We're going to reserve some time for
17 questions after the break.

18 Perhaps it would help the panel if I could
19 just ask one clarification. This study, as I read it
20 from your briefing packet, was originally designed as
21 a safety study primarily powered for nephrotoxicity.
22 Defervescence was the only primary objective as an
23 efficacy endpoint. There were some secondary
24 objectives such as documented fungal infection. Could
25 you just please clarify for us how your efficacy

1 analysis and your combined endpoint evolved in the
2 course of this trial?

3 DR. GURWITH: Sure.

4 CHAIRMAN HAMMER: One that occurred in
5 relation to the results in the unblinding?

6 DR. GURWITH: Right. As you said,
7 originally, this was an early study looking at
8 Amphotec in febrile neutropenia and the primary
9 endpoint was safety. That was what the power was
10 based on. The only variable, originally, as a primary
11 variable was defervescence. Near the end of the
12 study, as enrollment was ceasing but before the blind
13 was broken, we met with our investigators. And again,
14 primarily, for the thinking ahead for the publication
15 and the presentation of these results and developed an
16 analysis plan.

17 As part of the development of that
18 analysis plan, we looked at what was now available in
19 terms of what we knew -- we looked, actually, at the
20 brief outline of the MSG study and looked at their
21 definition of successful outcome. We thought we
22 should have a clinical definition of a composite
23 endpoint that looked at the treatment strategy. So
24 this was developed before the blind was broken, but
25 after study was almost complete. In addition, the

1 study included a planned interim analysis primarily to
2 look at safety and those hadn't shown any differences.
3 But those were prior to that successful outcome
4 variable being defined.

5 CHAIRMAN HAMMER: Thank you.

6 We're going to take a 15 minute break and
7 then return. Thanks.

8 (Whereupon, off the record at 10:58 a.m.,
9 until 11:17 a.m.)

10 CHAIRMAN HAMMER: Please take your seats.

11 We're going to defer Committee questions
12 to the sponsor until after the FDA presentation which
13 will be started by Dr. Teresa Wu.

14 DR. WU: My name is Teresa Wu. I am the
15 clinical reviewer for this application.

16 (Slide.)

17 This application which we are discussing
18 today has been reviewed by various reviewers. This
19 slide lists names of those who are not making
20 presentation today. This presentation will be shared
21 by myself and Dr. Shen. The order of topics is listed
22 on this slide. I shall be covering for the regulatory
23 overview, design and the sequence of results. After
24 Dr. Shen's presentation on statistical evaluation of
25 equivalence, I shall continue to present subgroup

1 analyses, safety, and summary.

2 In 1994 and 1995 respectively, two public
3 meetings were held in response to a number of
4 liposomal antifungal drugs which entering into
5 clinical studies approximately around the same time.
6 Discussions at both meetings were primarily in the
7 context of amphotericin -- of liposomal amphotericin
8 B. In the 1994 meeting, design issues were the
9 primary objective. The consensus from the panel on
10 the design for empiric antifungal study was that an
11 equivalence chart design should be used, given that
12 Fungizone has been accepted as a standard care in
13 neutropenic febrile patients despite that this
14 indication has not been an approved indication for
15 Fungizone. But there was no disagreement among
16 panelists that Fungizone should be compared.

17 In the 1995 meeting, the same Committee as
18 today's, endorsed FDA's proposal for a regulatory
19 approval for such indication. The statement states
20 like this: "For this indication, at least a one
21 treatment study of any fungal infection which can
22 demonstrate antifungal efficacy, plus at least one
23 adequate, well controlled empiric trial will be the
24 requirement."

25 In the case of Amphotec, the treatment

1 study that can be used as long as the two requirements
2 was contained in its original NDA, which marketing
3 approval for second line treatment of aspergillosis
4 was granted in late 1996. Basis of approval was from
5 five open label studies including emergency use of
6 Amphotec which consists of 80 evaluable patients
7 according to FDA's data.

8 I would like to make a point. In contrast
9 to the data which has just been published in recent
10 Clinical Infectious Disease, the database consists of
11 slightly different patients. But overall, among 80
12 patients in FDA's database, the response rate is very
13 close to that of the publication. We had the response
14 rate of 46 comparing to the 49 reported in that paper.

15 I would like also to add another comment.
16 That is, we are reluctant to make a direct comparison
17 to historical control data. It is very problematic to
18 use historical control data, let alone this is a
19 second line indication patient population we are
20 dealing with. That is, in the historical control
21 data, there was no way one could identify amphotericin
22 B failure patients. If they were a failure, they
23 would not be staying on amphotericin B. Second of
24 all, the survival analysis is equally problematic
25 because in the Amphotec group, a patient had to

1 survive that long in order to receive Amphotec while
2 amphotericin B patients were not in the same baseline.
3 So, we would not make any direct comparison with
4 historical data as the paper did.

5 The empiric study for this indication is
6 the one that is going to be discussed today. It was
7 a double blind, randomized pilot study with a total
8 enrollment of 213.

9 Now, next, I'm going to discuss on the
10 design issue. There are several selected design
11 issues which will be of interest in today's
12 discussion. First is the sample size. This pilot
13 study was originally designed to compare the
14 nephrotoxicity of Amphotec versus Fungizone. The
15 sample size was powered to detect a decrease of 35
16 percent in renal toxicity in the Amphotec group,
17 assuming the rate of renal toxicity was 50 percent in
18 the Fungizone group.

19 The definition of nephrotoxicity was given
20 in Sequus' presentation. Based on their original
21 estimate, the goal was to enroll 60 evaluable patients
22 in each group. However, the study continued to enroll
23 and at the completion, 196 evaluable patients were
24 enrolled out of this total of 213.

25 Being a pilot study, efficacy endpoints,

1 which were described in Sequus' presentation, were not
2 used in the sample size calculation. Of all endpoints
3 presented by Sequus, including primary and secondary,
4 the original protocol included only defervescence as
5 a secondary objective.

6 Let's also take a look at the nature of
7 the study population. In febrile neutropenic patients
8 who have been treated with a broad spectrum antibiotic
9 for an average of longer than seven days, the actual
10 incidence of a fungal infection in this population is
11 largely unknown. The only figure we could find was in
12 1982, a paper published by Pizzo and his coworker, in
13 that an incident of 33 percent was cited. Recognizing
14 the recent development of new modalities including
15 fluconazole prophylaxis and a GCSF use, the incidence
16 of fungal infection is likely to be even lower than 33
17 percent. As you have heard from previous
18 presentation, in Sequus' study, 75 percent of patients
19 had prior fluconazole prophylaxis and 40 percent had
20 a concurrent use of GCSF.

21 There's another aspect unique to this
22 population. That is, once patients start empiric
23 antifungal therapy, concurrent bacterial viral
24 infections are very common. In the presence of the
25 infection other than fungal etiology, assessment of

1 empiric antifungal infection becomes more complicated.

2 Let's now look at the design of the Sequus
3 study so we can get back to what is our concern in
4 terms of the patient population enrolled in this
5 trial. We look at the study and we make some sense
6 that how the design might impact on the instance of
7 fungal infection.

8 These are the reasons for study
9 discontinuation. That means the study duration was
10 determined by whether a patient's neutrophil had
11 recovered. If not, whether a maximum of 14 days were
12 reached. To fulfill either one of these two, this was
13 considered as study completion. Other reasons such as
14 cause of fever identified. This cause of fever could
15 be due to documented or suspected fungal infection, or
16 bacterial infection, or toxicity, or adverse event
17 including the most serious one being death. All these
18 three could be reasons for early discontinuation.

19 Let's now look at the distribution of
20 population according to various reasons for treatment
21 discontinuation, whether this is completed or early
22 discontinued. These two charts are arranged clockwise
23 in decreasing number of subjects. The blue color
24 represents neutrophil recovered; green represents 14
25 days has been reached; red color represents adverse

1 events; white color or light grey color represents
2 cause of fever being identified during study; grey
3 color represents infection at enrollment; yellow color
4 represents death; the last one, which is teal color,
5 represents other reasons, for instance, administrative
6 reasons.

7 There are two messages I wish to convey by
8 using this slide. Number one is the similarity
9 between these two treatment groups in terms of the
10 distribution of patients according to reasons of
11 discontinuation. However, I would like to point out,
12 there is a large proportion of patients who
13 discontinued the study treatment early. There was
14 roughly about 40 percent of patients in this group.
15 Obviously, the highest percentage is due to adverse
16 event which is illustrated in the red color. But I'd
17 like to bring your attention to this portion. This is
18 the portion where a patient discontinued because they
19 had either diagnosed or undiagnosed infection being
20 identified. This information will lead to my next
21 slide.

22 We know already in this patient population
23 the incidence of fungal infection was very low to
24 begin with. The design have further reduced the
25 instance of fungal infection because some patients who

1 had either suspecting infection and left the study
2 prematurely. This low instance you will have seen
3 from Sequus' presentation. We will come back to
4 interpret their result later.

5 Let's now turn our attention to another
6 design issue, that is the so-called suspected fungal
7 infection. In neutropenic patients, microbiological
8 evidence of the infection requires invasive procedure
9 and are generally avoided by clinicians. A suspected
10 fungal infection then becomes a purely clinical
11 diagnosis which is subjective to a wide variation
12 interpretation. There was no definition provided in
13 the protocol that would provide a minimum level of
14 uniformity of data. Rather, investigators were asked
15 after the study was completed, using a set of
16 criteria, to evaluate all patients with respect to the
17 original diagnosis of suspected fungal infection.

18 In the meantime, during this chart review
19 process, more patients were identified -- assessment
20 of radiographs, clinical findings was not conducted by
21 an independent reviewer. Not surprisingly, 50 percent
22 of original suspected cases diagnosed during study
23 were discounted later. The numbers showing in Sequus'
24 presentation was based on reevaluation the database of
25 suspected fungal infection was different from that

1 presented in original NDA. The difficulty with the
2 diagnosis of suspected fungal infection provides with
3 us, less than desirable comfort level to include the
4 number in our efficacy measurement.

5 While we agree with Sequus' presentation,
6 defervescence is such a non-specific and insensitive
7 measurement in empiric antifungal trial.
8 Nevertheless, in their successful outcome analysis, it
9 placed an equal but not less important role in the
10 combined endpoint analysis. Thus, another endpoint,
11 that is, documented fungal infection.

12 Temperature records become important. As
13 we noticed upon review of this NDA, temperature
14 records were collected without paying attention to a
15 possible association with a drug or blood transfusion.
16 However, records did allow the applicant
17 retrospectively assign an association according to the
18 time of transfusion. Since in the case report forms
19 not all fever data were documented -- only the highest
20 temperature in the eight hour period was captured --
21 therefore, after adjustment, the data may indicate
22 that the patient was afebrile while, in fact, other
23 fever data were never captured in the case report
24 form.

25 The case report form only contained

1 follow-up information on limited patients. Those
2 patients, first of all, had to receive at least seven
3 doses of treatment drug or they dropped out due to
4 adverse event. Other than this, patients were not
5 followed. Included in the follow-up records were
6 cultures, radiographs, and laboratory data. Notably
7 missing was temperature data. In other words, no
8 subject in this study, whether they had follow-up or
9 not follow-up, they had no temperature data documented
10 in the case report form after treatment discontinued.
11 As a result, time to defervescence or duration to
12 defervescence in relation to neutropenia can not be
13 accurately evaluated. Although data were not
14 presented today by Sequus, the data were included in
15 their background information.

16 Let's comment on successful outcome. This
17 successful outcome analysis is a combined endpoint
18 approach. The decision to use this approach as a
19 primary efficacy parameter was not made a priori, but
20 after study completion. It is comforting to know that
21 the applicant has assured us this decision was made
22 before blinding. But I should also mention that the
23 study had a planned interim analysis performed in
24 January 1996 when a total of 52 patients were included
25 in the interim analysis. As stated in the NDA, the

1 purpose of this interim analysis was to provide a
2 preliminary information for conducting a subsequent
3 empiric trial which was originally planned for the
4 pilot study.

5 The combined endpoint approach, in and of
6 itself, is problematic because this is a net result of
7 a combination of both efficacy and toxicity. When
8 these two events, which may not point to the same
9 direction combined in a combined analysis, this
10 becomes very problematic when this is used as primary
11 efficacy endpoint. The appropriateness of such
12 approach is of concern and therefore, we have included
13 this topic in the questions for Committee's
14 discussion.

15 Now, let's turn to Sequus' results.
16 First, is the incidence of a documented fungal
17 infection. We chose not to use the intent to treat
18 data since one patient in each arm had a documented
19 fungal infection at enrollment. Therefore, these two
20 patients should not be considered as eligible for
21 empiric study efficacy assessment. Therefore, we used
22 evaluable patient population.

23 As I presented before when we talked about
24 the study design -- that is, the study design
25 presented by Sequus might have reduced the incidence

1 of fungal infection. Therefore, we are uncertain
2 whether the low incidence was a result of a study
3 design or a true treatment effect. Given the upper
4 bound of a confidence interval of 8.3 percent, it
5 implies that in the worst case, the Amphotec group
6 could have as many as three times more patients
7 develop a documented fungal infection compared to
8 Fungizone. Under this circumstance, it is very
9 difficult for us to consider these two treatments were
10 truly equivalent.

11 Now, let's take a look at Sequus' result
12 of defervescence. This result will be explained and
13 explored by Dr. Shen in his presentation. However, as
14 a background for his discussion, I'd like to revisit
15 the long list of very familiar differential diagnosis
16 listed for either persistent or recurring fever. In
17 general, the list can be broken down into two groups:
18 a group due to fungal infection and a group due to
19 non-fungal infection, or non-infectious cause which
20 include, but are not limited to, the following:
21 resistant bacterial infection, viral infection,
22 parasitic infection, drug transfusion reaction, and
23 tumor itself or during lysis.

24 We, therefore, considered the population
25 in an empiric trial is a so-called mixed patient

1 population. Dr. Shen will then elaborate on how the
2 result of equivalence with respect to defervescence
3 influenced by the dilution effect of a population
4 without fungal infection.

5 DR. SHEN: As Dr. Wu has indicated, the
6 variation of equivalence of Amphotec and Fungizone is
7 complicated by the nature of the population study.
8 There are two -- issues I wish to discuss. The first
9 is the statistical procedure which is followed to
10 evaluate equivalence. The second is that we wish to
11 make an inference regarding the treatment effect for
12 the fungal infected population, but all we see are the
13 results for all patients treated including fungal
14 infected and the non-fungal infected patients. The
15 concern is that the two treatment difference could be
16 diluted by the non-fungal infected patients.

17 Statistical equivalence is not based upon
18 the simple observed difference but it is based upon
19 the confidence interval for the difference. Let's
20 walk through the calculation and the interpretation of
21 a confidence interval. As an example, assume that we
22 have two treatments which have 100 subjects per arm.
23 The observed success rate is 40 percent for the
24 experimental arm and 50 percent for the control arm.
25 This leads to an observed difference of negative ten

1 percent. But this is the simple estimate. The true
2 difference for the two treatments may not be negative
3 ten percent. The confidence interval reflects the
4 uncertainty due to the sampling of subjects.

5 For present example, the 95 percent
6 confidence interval is negative 25 percent to a
7 positive five percent. This means that we can be 95
8 percent confident that the experimental arm could be
9 as much as 25 percent better than the control arm, or
10 could be as much as five percent worse. The variation
11 of statistical equivalence is based upon whether these
12 bounds exceed amount agreed upon -- events.

13 This slide contains the result prepared by
14 the applicant for the defervescence as presented in
15 their background package for the intent to treat
16 population. You can see that the lower bound of the
17 confidence interval is negative 16.8 percent and the
18 upper bound is ten percent. However, the confidence
19 interval is for the difference for total population as
20 discussed by the applicants in their background
21 material. The fungal infected population may be only
22 10 to 20 percent of the total population.

23 Since we can not identify fungal infected
24 subjects, we are forced to use confidence interval for
25 the total population as presented by the applicant to

1 make inferences to the fungal infected population.
2 This may lead to a dilution of difference between the
3 treatment by the non-fungal infected population.
4 Because of this, the equivalence in the total starting
5 population may not accurately reflect what is
6 happening in the fungal infected population.

7 As an example of the dilution of treatment
8 effect, assume that the rate of defervescence will be
9 the same for subjects without a fungal infection.
10 Further assume that in patients with fungal
11 infections, the experimental treatment is 20 percent
12 less effective than the control treatment. In this
13 situation, as the propulsion of fungal infected
14 patients decreases, the expected difference in the
15 overall population decreases. Where 100 percent of
16 patients are fungal infected, the expected overall
17 difference is the assumed at -- percent. But if only
18 25 percent of subjects are fungal infected, the
19 expected overall difference is five percent. The
20 confidence interval will behave in a similar fashion.
21 That is, the center of the confidence interval will be
22 closer to zero when the underlying population has
23 fewer fungal infected patients.

24 In conclusion, the applicant's analysis
25 for defervescence was conducted for the total

1 population. The resulting confidence interval is
2 fairly wide and the low bound of the most favorable
3 confidence interval is 16.8 percent. Such a low bound
4 won't be open to considerable discussion even if the
5 entire population are fungal infected. Furthermore,
6 this fairly wide confidence interval is the result of
7 analysis based upon a mixed population. The
8 relatively wide confidence interval and the mixed
9 population suggests that there's still considerable
10 uncertainty regarding the equivalence of Amphotec and
11 Fungizone with respect to defervescence in the fungal
12 infected subjects.

13 Dr. Wu will now continue with her
14 presentation.

15 DR. WU: In Dr. Shen's discussion, he
16 highlighted the difficulty with inferring results of
17 statistical equivalence based on a mixed population as
18 a whole to fungal infected patients. We, therefore,
19 conducted several subgroup analyses on defervescence
20 in patients who were more likely to be fungal
21 infected.

22 We recognized the limitation of the sample
23 size and we also recognized that there are many
24 reasons, unbeknownst to all of us, which can make
25 fever go away. So, our intention of performing

1 subgroup analysis was not to draw any conclusions. We
2 would like to see whether we were able to find some
3 internal consistency in support of Sequus equivalence
4 results. Moreover, we would like to know whether or
5 not more information can be learned from this pilot
6 study that will serve as a guide for designing future
7 trials.

8 In FDA's subgroup analysis, at two
9 consecutive days of less than 38 degrees was defined
10 as defervescence. This is an operational definition,
11 inconsistent with Sequus. However, I shall point out
12 that evidence in support of its clinical relevance of
13 such two day defervescence can not be found in the
14 literature.

15 Two subgroup analyses which -- to do are
16 the proportion of defervescence in patients with and
17 without neutrophil recovery; and the patients with and
18 without antibiotic modification. We further expand
19 analysis of the defervescence in the absence of
20 antibiotic modification by including those who had
21 antibiotic modified, methodologies of which will be
22 presented later. Finally, for the sake of
23 completeness, we also performed a successful outcome
24 analysis. We used similar, but not identical to the
25 scheme presented by Sequus.

1 This is a subgroup analysis in patients
2 with or without neutrophil recovery. As expected for
3 both treatment groups, there is a higher proportion of
4 defervescence at the end of the study treatment in
5 patients whose neutrophil counts were recovered than
6 those who did not. The top group though is what we
7 are interested in because a patient who did not have
8 a neutrophil recovery at the end of the study were the
9 ones most likely to develop fungal infection.
10 Although we can not make any conclusion based on the
11 results due to the small size, as you can see, the
12 direction of lower bound of a confidence interval
13 moved more to the negative side against Amphotec.
14 This is somewhat disturbing.

15 There were approximately 50 percent of
16 patients in both groups that had antibiotic regimen
17 modified at some point of the study. It could be as
18 early as at entry time and then almost anytime
19 throughout the study. During the study, typically,
20 the change of antibiotics occurred in patients with
21 either a persistent fever or on or soon after an
22 event, a new fever occurred. The duration of initial
23 defervescence which occurred before the new fever
24 sometimes defervescence ranged from two to eight days.
25 The types of modification commonly included

1 ceftazidime between replaced by a combination of
2 gentamicin plus piperacillin, or aztreonam. The
3 common added new antibiotics were vancomycin, flagyl,
4 or acyclovir.

5 This subgroup analysis is very similar to
6 the one we performed for the neutrophil recovery.
7 These results show that patients without modification
8 appeared to have a slightly higher of defervescence
9 rate than that group with modification. Then the
10 group with modification is the one we are interested
11 in because we speculate that patients who need an
12 antibiotic modified were more sick than those without.
13 Therefore, as a speculation, there might be more with
14 a higher likelihood of developing fungal infection.

15 Although the results between this group
16 did not show very much difference and the direction of
17 the confidence interval between these two groups are
18 very similar, but next, we'd like to explore a little
19 bit further in the patients who had antibiotic
20 modified. That is, we would like to see what happened
21 to their initial fever which happened before
22 antibiotic modification took place. Because we
23 speculate that the actual difference between these
24 groups, in a group with modification, might have been
25 masked by such modification. Therefore, we would like

1 to uncover the difference.

2 So, we further expanded the analysis to
3 include the two types of patient in this analysis.
4 One who never had an antibiotic modified during the
5 study, and the one that had antibiotic modified. For
6 those who had antibiotic modified, we assessed
7 defervescence prior to the day of modification. In
8 order to accomplish this, two restrictions were
9 needed. One is, a patient had to have received at
10 least three doses of study drug, and the patients were
11 not evaluable if the modification occurred on Day 0,
12 Day 1 or Day 2.

13 As a result of the two restrictions, the
14 number of patients invariably dropped in both groups.
15 A proportion of patients would defervesce in the
16 absence of antibiotic modification is higher in the
17 Fungizone group. The direction of confidence interval
18 is further shifted to the left against Amphotec. This
19 is a result not consistent with the Sequus conclusion
20 of equivalence.

21 Given the small sample size in the
22 subgroups, no conclusion can be drawn from this
23 observed difference. However, a result like this,
24 based on a pilot study, may suggest to us that maybe
25 by increasing the sample size, such issue will be

1 clarified. Or one would like to think whether or not
2 the timing or rationale for antibiotic modification
3 should be seriously considered in a future trial.

4 For the sake of completeness, we did a
5 successful outcome analysis. Because our previous
6 concern about the reliability of so-called suspected
7 fungal infection, we chose in our analysis not to
8 include them, but only include documented fungal
9 infection. And just to remind you, the analysis was
10 based on defervescence without antibiotic
11 modification.

12 As expected, similar results at
13 defervescence analysis can be seen in the outcome
14 analysis. The observed success rate is lower in
15 Amphotec group than in Fungizone group. Once again,
16 we see the shift of lower bound of a confidence
17 interval more to the left against the Amphotec. This
18 is somewhat disturbing results and we don't think it
19 is quite consistent with Sequus.

20 Last, I would like to comment on the
21 safety. We concur with the Sequus conclusion of a
22 better nephrotoxicity of Amphotec, but we used a
23 different approach. Instead of looking at the
24 percentage of patients who developed nephrotoxicity,
25 we compared the mean of individuals' serum creatinine,

1 net change from their own baseline, over time, during
2 study treatment.

3 The top graph represents Fungizone. The
4 green line represents Amphotec. Each number at each
5 point represents a number of data available at that
6 time point. The baseline value for both the treatment
7 arms were quite similar, 0.84 serum creatinine level
8 for AmphoB group and 0.83 for Amphotec group. As you
9 can see, over time, the difference at time point, Day
10 3, Day 7, and Day 11, is roughly about .04 mg per ml.
11 The difference at these three points are statistically
12 significant.

13 Next, I would like to comment on the
14 adverse event resulting from drug associated toxicity.
15 This adverse event lead to the study discontinuation.
16 The total numbers of adverse events considered to be
17 associated with the study drug -- this is by
18 investigator -- in both groups are similar. But more
19 patients in the Amphotec group discontinued due to
20 infusion associated toxicity as compared to the
21 Fungizone group. Infusion associated toxicity
22 included the fever, chills, hypotension and the
23 hypoxia. The types of infusing associated toxicity,
24 most of them were listed as serious. Nine out of 12
25 cases listed as serious.

1 As to the serum creatinine as a reason for
2 study discontinuation, it's more prominent in the
3 AmphoB group, in the Fungizone group. The level of
4 serum creatinine that led to treatment discontinuation in
5 Fungizone groups were mostly in the range of
6 creatinine level of 2.8 mg per -- or above.

7 So, in summary, this study was originally
8 a pilot study designed to assess nephrotoxicity. With
9 respect to efficacy assessment, we think the design
10 may have reduced the likelihood of including patients
11 who were more likely to develop fungal infection. The
12 lack of a robustness of a study design makes the
13 interpretation of subgroup analyses uncertain.

14 With respect to safety assessment, we
15 think the results support the conclusion that Amphotec
16 was less nephrotoxic in this patient population for
17 this 14 day treatment duration. However, infusion
18 associated toxicity was more frequent in the Amphotec
19 group. Hypoxia, hypotension, fever, chills are worth
20 noting.

21 For the Committee, we have two questions.
22 The first question is to ask you to assess the
23 adequacy of the study trial. The second question is
24 to specifically ask the Committee to consider what
25 kind of a parameter would be important in the

1 successful outcome analysis.

2 That finishes FDA's presentation.

3 CHAIRMAN HAMMER: Thank you very much.

4 It's noon time and in order to stay on
5 schedule, what I'd like to suggest is that we break
6 for lunch, return promptly at 1:00. We'll begin with
7 a question period for both the sponsor and the FDA by
8 members of the Committee.

9 Thank you. We're adjourned until 1:00.

10 (Whereupon, the meeting was recessed at
11 12:00 noon, to reconvene at 1:00 p.m., this same day.)

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1 So, I'd like to start on my right. Dr.
2 Kan, do you have any questions for either the sponsor
3 or the FDA?

4 DR. KAN: My question would be directed to
5 some of the adverse events seen and specifically, what
6 is the nature of the hypoxia that was seen for the
7 Amphotec patients?

8 DR. GURWITH: Well, I attempted to show
9 you originally and rather than repeating that slide,
10 I'll just quickly summarize what that showed. Then
11 I'll ask Dr. Miller, who reviewed these cases in some
12 detail and actually took care of some of the patients,
13 to elaborate on it.

14 Basically, from the review, it appeared as
15 if the hypoxia was reversible, acute -- related to
16 reversible, acute infusion related reactions
17 associated with chills, vasodilation and temporary
18 oxygen desaturation, not permanent pulmonary injury.
19 We looked to see if GCSF might be related and only one
20 out of all the patients had received any concurrent
21 GCSF. But why don't I have Dr. Miller address this.

22 DR. MILLER: Thank you.

23 Can I have the first overhead?

24 I've summarized on two sheets, the 16
25 patients who were called adverse event equalling

1 hypoxia.

2 The first one, please?

3 CHAIRMAN HAMMER: We appreciate the data.
4 Just please keep the answers brief so we can get
5 through the entire Committee.

6 DR. MILLER: Okay, sorry.

7 Just showing the patients, all the
8 patients had either all or autologous bone marrow
9 transplant. The worst desaturation was to 60 percent,
10 but it resolved within 30 minutes. Some patients, the
11 O₂ sats only fell as low as 94 percent. Since this
12 was an adverse event that was defined by the
13 investigators, they considered that hypoxia which is
14 not very clinically significant.

15 As you can see, five patients on Amphotec
16 stopped because of these hypoxic reactions, but the
17 rest of the patients, eight of the patients, continued
18 on the study drug despite having an episode of
19 hypoxia. They were very much associated with rigors
20 and again, clinically, it's very difficult to assess
21 O₂ saturations. They're not very accurate when you're
22 having a rigor. So, I don't know. These were mainly
23 done during the rigor. So, I think that while they
24 were significant and they were adverse events, they
25 all were reversible and I think were managed by

1 continuing on with adding pre-medications, resolving
2 the rigor, and patients could continue on the study.

3 Could I have the second overhead which
4 just shows the amphotericin patients?

5 Again, three patients, Day 1, Day 2 and
6 Day 6. All associated with rigors. All required
7 oxygen. One of the patients -- this drug was
8 discontinued due to toxicity, Day 2; one completed
9 study; and one had an increased creatinine.

10 Just from adverse events, I'd like to just
11 show in another way the chills and fevers by day of
12 dosing.

13 Can you put the next overhead on?

14 Just showing that yes, there was a
15 significant incidence of chills or fever both with
16 Amphotec and amphotericin B. But as you repetitive
17 dose, it significantly decreased from Day 1 to Day 7
18 and the amphotericin B and Amphotec were very similar
19 after the first three days. So, these are reversible
20 acute events related to study drug infusion.

21 Does that answer the question?

22 DR. KAN: Yes, thank you.

23 DR. MASUR: Scott, could I ask just a
24 follow-up question on that topic?

25 CHAIRMAN HAMMER: Sure, Henry.

1 DR. MASUR: You know, there is some
2 precedent in the literature for lipid preparations
3 causing deterioration of pulmonary function. Do you
4 have any data as to whether the infusion of this drug
5 causes hypoxemia? In other words, you're maintaining
6 this is due to rigors, but do you have any data as to
7 what infusion does to pulmonary function?

8 DR. GURWITH: I don't think we have any
9 direct data looking at pulmonary function before and
10 after infusion.

11 And I don't think we have any preclinical
12 data, do we?

13 Nothing in the preclinical toxicology --
14 taking care of patients. Receiving this drug suggests
15 that -- gives us much reason to think that that would
16 be the case, that there was an independent hypoxemia.

17 DR. MASUR: Well, though, there is a case
18 report in the Annals of Internal Medicine using a
19 different preparation in which a different lipoidal
20 amphotericin associated with respiratory failure.

21 DR. GURWITH: Right.

22 DR. MASUR: Do you have some reason to
23 think that that would be different with this
24 preparation?

25 DR. GURWITH: Well, specifically, I

1 believe that patient -- the case report you're talking
2 about, I believe there were actually pulmonary
3 infiltrates associated with that. It's a different
4 lipid-based agent. I think that's the drug that's
5 predominantly concentrated in the lung in contrast to
6 our drug.

7 DR MARTIN: I just had one comment on the
8 physical chemistry of the system. The formulation
9 which you're referring to had a mean particle size in
10 the micron range. It was about two microns, three
11 microns as a mean size. Therefore, if one of two of
12 those particles were to aggregate they could, indeed,
13 cause a clogging of the capillaries in the lung.

14 This product we're talking about here has
15 a mean diameter of 100 nanometers. That's 1/100th or
16 1/50th the size of a red blood cell. So, as a primary
17 particle, it's not very likely that it could cause an
18 occlusion, even if it aggregated with several of its
19 neighbors. It's just simply too small.

20 CHAIRMAN HAMMER: Dr. El-Sadr has one
21 quick follow-up question.

22 DR. EL-SADR: Obviously, you're giving
23 more sort of total amphotericin with this agent -- I
24 mean, if you give the placebo, I guess the vehicle by
25 itself, do you get the same rates of -- do you get any

1 fevers, or rigors?

2 DR. GURWITH: Again, the formulation is
3 such I don't believe we could actually produce it --

4 DR. EL-SADR: You can't do it.

5 DR. GURWITH: -- as a vehicle.

6 Again, maybe Frank will answer.

7 DR. MARTIN: Sorry.

8 It's impossible to create this disc
9 without the drug. The drug is a very membrane-active
10 drug. It binds to sterols and this is a very unique
11 formulation that relies on the drug to form the disc.
12 You can make liposomes, closed spheres, of cholesterol
13 sulphate out of cholesterol sulphate alone, but it
14 wouldn't resemble this product. So, it wouldn't be
15 very meaningful.

16 CHAIRMAN HAMMER: Thank you.

17 Dr. Kan?

18 DR. KAN: Getting back to some of the
19 preclinical studies, were tagged drug ever used for
20 animal models to look at the distribution early-on?

21 DR. GURWITH: I believe the answer to that
22 is --

23 DR. KAN: To assess whether there was
24 lung--

25 DR. GURWITH: -- no. We haven't done any

1 tag study.

2 DR. KAN: Thanks.

3 CHAIRMAN HAMMER: All right, thank you.

4 Dr. Wong?

5 DR. WONG: Yes. I'd like to get to the
6 issue of antifungal efficacy. It concerns me that,
7 you know, along with the FDA reviewers that most of
8 the efficacy results that you showed were indirect.
9 Since candida infection is the most common fungal
10 infection that would be expected to be seen in
11 neutropenic patients treated empirically, do you have
12 direct data that this drug is an effective agent
13 against candida infections?

14 DR. GURWITH: Direct data -- well, the
15 data we demonstrated, that I showed originally from
16 the original NDA showing response rates in candida, we
17 also have a --

18 DR. WONG: I'm sorry. That was kind of a
19 summary slide showing some percentages, but I guess we
20 didn't have access -- or I don't have access to any of
21 the --

22 DR. GURWITH: Right.

23 DR. WONG: -- experimental details or
24 such.

25 DR. GURWITH: Certainly. The patients

1 described there were patients who were in the safety
2 database of 572 patients that Dr. Wu referred to.
3 These were all patients who received Amphotec in open
4 label trials and were mostly, if not almost all of
5 them, had failed to respond to amphotericin B or were
6 intolerant of it. Some of them had aspergillus, but
7 then a large number had candida. So, the response
8 rates taken from that that you saw in that slide are
9 from those patients.

10 We've also sub-setted those patients for
11 publication by candidemia and you see similar rates of
12 response in the candidemia patients. And we do have
13 preclinical evidence of the infection in animal models
14 against candida.

15 DR. WONG: Could I just follow up briefly?

16 There were a few patients in the study
17 we're discussing today that did turn out to have
18 documented fungal infections.

19 DR. GURWITH: Right.

20 DR. WONG: They were balanced in the two
21 groups.

22 DR. GURWITH: Right.

23 DR. WONG: But what we don't know is, what
24 was the ultimate outcome in those cases?

25 DR. GURWITH: Larry, could we put up the

1 slides for the patients with documented fungal
2 infections?

3 First of all, to just go through, those
4 are eight patients. I think to correct something that
5 was said, even the two patients in the intent to treat
6 population were infections that developed on study.
7 These were not present at baseline.

8 So, just to go through them, there were
9 four patients in the amphotericin B group. One
10 patient developed skin lesions on Day 4 and the
11 cultures were biopsied no growth and the patient --
12 actually, I don't have the follow-up on that patient.
13 The second patient was, again, an amphotericin B
14 patient, had candida esophagitis, died and was found
15 to have candida ulcerations at post-mortem. A third
16 patient, again amphotericin patient, had a pulmonary
17 infection suggested by CT and X-ray, and then died 32
18 days later. Then a fourth patient developed a blister
19 at the side of his Hickman catheter and the skin
20 biopsy was positive for aspergillus. So, those are
21 the four documented amphotericin patients.

22 For the Amphotec patients, one patient
23 grew aspergillus from a biopsy, sinus biopsy, and then
24 the patient died. This was seven days after the end
25 of the study. The patient died 19 days after the end

1 of the study.

2 DR. WONG: That's one.

3 DR. GURWITH: A second had positive blood
4 cultures for candida glabrata four days after the
5 study was completed. He didn't die. One patient had
6 a positive blood culture for candida parapsilosis one
7 day after. Then the fourth patient had negative blood
8 cultures but had a catheter tip also grew candida one
9 day post-treatment. That patient survived. So, those
10 are the eight documented fungal infections.

11 Just briefly, the 11 Amphotec and the 13
12 amphotericin B suspected fungal infections were all
13 pulmonary syndromes.

14 CHAIRMAN HAMMER: I might just ask Dr. Wu,
15 which two patients were excluded, as there seems to be
16 controversy about one patient in each arm being
17 excluded by the FDA and being included by the sponsor?

18 DR. WU: I recall one patient candida
19 glabrata in the blood. The culture was taken on the
20 day of admission but it turned out to be positive
21 three or four days later. I can not recall what is
22 another one on the other arm. But both of these,
23 their culture was taken on the day of admission.

24 DR. GURWITH: That's correct. There were
25 several patients whose cultures were positive on the

1 day of admission but they were dropped from the study.
2 They aren't included in the eight patients we
3 described as having documented emerging fungal
4 infections. But there were, I know, at least two
5 patients who had positive cultures day of admission
6 and those didn't become positive until a day or two
7 later.

8 CHAIRMAN HAMMER: Dr. Sugar?

9 DR. SUGAR: I have two questions. The
10 first is, given the way clinicians usually manage
11 amphotericin, the drug is continued until we get a
12 creatinine 2.5 to 3, and then we start worrying about
13 dose modifications and the like.

14 Do you have any data to speak to those
15 numbers and how both of those groups approached that?

16 DR. GURWITH: I don't think much more than
17 the analysis you saw from the FDA. We have similar
18 analyses of mean serum creatinines by study day. The
19 patients were supposed to discontinue due to grade
20 four nephrotoxicity, or had the drug held for grade
21 three. And so, in a sense, that would have been the
22 protocol required response to the increase in serum
23 creatinine.

24 DR. SUGAR: Okay.

25 Dr. Wu, you had a graph where you showed

1 increases over the baseline. But if everyone started
2 with normal creatinines, you barely got up to two, I
3 think.

4 DR. WU: Well, in this trial, the trial
5 duration was relatively short. In the Amphotec
6 patients, very, very few people reached that high
7 level of so-called 2.5. Is that what you were
8 interested? So, we could not do that comparison.
9 Once the patient reached a serum creatinine of 2.5,
10 what will be the fate in patients on both treatment
11 arms? We don't have enough data to do that type of
12 analysis.

13 However, this type of comparison can be
14 obtained from their original NDA. That is, those
15 patients were either AmphoB intolerant or AmphoB
16 failure. So, I think we had a number of people in
17 that database who had serum creatinine that reached
18 2.5. Then we followed their mean serum change to
19 baseline. At this time, the baseline is 2.5. We
20 compared this data versus historical control data,
21 used the same baseline -- that is, 2.5 serum
22 creatinine. We used the same methodology. We
23 discovered that there is evidence to indicate this
24 drug is less nephrotoxic.

25 DR. SUGAR: Okay. I think from a clinical

1 perspective, that's important.

2 The second is, it seems like four mgs per
3 kilo is equivalent, at least in this study, to .8 mgs
4 per kilo of Fungizone. It seems like if a patient
5 develops a documented fungal infection after receiving
6 this empirical therapy, that there won't be any room
7 to maneuver to a higher dose? What are the plans for
8 that and what is the toxicity as the dose is
9 escalated?

10 DR. GURWITH: You're talking about
11 increasing the dose of Amphotec or --

12 DR. SUGAR: Amphotec. Amphotec.

13 DR. GURWITH: First of all, in our label,
14 you can increase the dose up to six milligrams. That
15 was based on efficacy considerations. We have a
16 published maximum tolerated dose and there, the
17 maximum tolerated dose was 7½ mgs per kilo per day.
18 There, actually, the dose limiting toxicity was acute
19 reactions, not irreversible organ damage. So,
20 possibly, you could even go higher. But we really
21 find that doses of four to six are adequate.

22 DR. SUGAR: Do you have any data to show
23 about the toxicity at six?

24 DR. GURWITH: In the original NDA
25 retrospective analysis, we compared adverse event

1 rates for four milligrams and six milligrams. Now the
2 groups aren't randomized that way except in one study,
3 and there appeared to be a small increase in the
4 number of adverse events at six. But terminations due
5 to toxicity weren't different in the two dose groups.

6 CHAIRMAN HAMMER: Thank you.

7 Dr. Elashoff?

8 DR. ELASHOFF: Yes. In the baseline
9 characteristic slide 36, it shows that fungal
10 colonization at baseline was almost twice as frequent
11 in the Amphotec group as in the amphotericin B group,
12 and definitely, statistically significant. Exactly
13 what is that variable? What does that mean?

14 DR. GURWITH: This was not a predetermined
15 variable. Actually, it was a request by the reviewer
16 just to look at that data, and it's a good suggestion.
17 So, what it is is, we looked at surveillance fungal
18 cultures that were obtained on the day before or the
19 day the patients were started on study. By
20 surveillance cultures, the usual throat, rectal,
21 urine, cultures of non-sterile sites. So, there's
22 other data suggesting that at least with candida
23 fungal colonization, especially the heavily colonized
24 patients, are more likely to get fungemia or invasive
25 fungal infection. So, it suggests that the Amphotec

1 group was maybe more predisposed to develop fungal
2 infection due to the greater colonization, but this
3 was not rigorously collected in the sense that we
4 didn't specify they had to have so many cultures
5 before entering the study.

6 DR. ELASHOFF: The second question is sort
7 of related. It sounded like you dropped from the
8 study, patients who had a documented fungal infection
9 at baseline. But I thought that since we were
10 entering patients who had a fever, the implication was
11 that they would have -- if they did have one -- a
12 fungal infection at baseline and those were the very
13 people that this treatment was intended to work for.
14 So, why were they dropped out of the study?

15 DR. GURWITH: Let me ask Dr. Miller to
16 answer. But briefly, the patients to be entered in
17 this trial had to have suspected fungal infection or
18 really, failure to respond to broad spectrum
19 antibacterials. If a patient is known to have a
20 fungal infection when you start them, you'd probably
21 use a different dose of amphotericin at least. It's
22 really a different patient population.

23 So, it's really no longer empiric therapy.
24 At least the empiric therapy was considered an
25 innovation or a step beyond what people used to do

1 which was treat only when there was documentation of
2 fungal or bacterial infection.

3 Maybe Carol could enlarge on that.

4 DR. MILLER: Again, the definition of
5 empiric means lack of documented therapy. It's
6 different in many antibacterial studies. It is felt
7 clinically that if a patient has a positive blood
8 culture -- and I think one of the people who dropped
9 out had positive blood cultures taken at the time of
10 their fever. Those patients, you would not want to
11 treat them with .8 of Ampho or you'd want to go --
12 clinically and depending on the species, some of them
13 have parapsilosis -- at least one had parapsilosis --
14 you'd want to go to full treatment doses of
15 amphotericin.

16 So, when you think of empiric therapy,
17 it's considered a failure when a patient has a
18 suspected or documented fungal infection requiring
19 change from empiric dosing to treatment dosing of
20 antifungal agents.

21 CHAIRMAN HAMMER: I'm sorry to interrupt,
22 but .8 mgs per kg of amphotericin is not a sub-
23 therapeutic dose for certain candida species. I mean,
24 often those are treated in the range of .5 to .8 mgs
25 per kg.

1 DR. MILLER: Right. I mean, in patients
2 who are severely neutropenic, as soon as we get a
3 culture, we may not know the specification. If you
4 get a germ tube negative yeast, which is what you get
5 at one day, we have a significant candida krusei
6 problem. I mean, not problem, but a significant
7 candida krusei population.

8 Therefore, if we have a germ tube negative
9 yeast, we will assume that it's candida krusei until
10 the culture today and we go to 1.25 of Ampho. And so,
11 we need to change. We would not continue somebody
12 with no white cells on a possibility of .8 of
13 amphotericin until we get the culture results. But I
14 agree that if you know what they have, certainly, you
15 can treat some of those with lower doses.

16 DR. ELASHOFF: Just a clarification of
17 that. The results of these cultures were known before
18 they started therapy?

19 DR. MILLER: No, it was drawn at the time
20 when the patient has their fever that would be --

21 DR. ELASHOFF: So, it's still empiric
22 therapy if it isn't known at that time?

23 DR. MILLER: But then at that point, two
24 days into the study, you have to stop the drug and go
25 to full dose amphotericin. That was not a failure of

1 the empiric therapy because the fungal infection was
2 present at the diagnosis. That's why they did an
3 intention to treat analysis as compared to an
4 evaluable patient analysis to make sure all those
5 patients were included.

6 DR. WONG: Can I just follow up?

7 But it's precisely for that reason then
8 that, it seems to me, we can't conclude whether or not
9 the Amphotec is an effective drug. The people for
10 whom the empirical therapy is really designed is that
11 minority of the total who really have the infection.
12 If there's a sub-set that subsequently prove really to
13 have the infection, it's in those patients that you
14 want to know "did it work or did it not?" If they're
15 excluded from subsequent treatment, then we're just
16 left with never knowing.

17 Is that unfair?

18 DR. GURWITH: When we treat empirically --
19 again, we're treating presumptive fungal -- we already
20 have evidence of efficacy in patients who have
21 documented fungal infection. So, that's one thing.
22 These patients have documented fungal infections at
23 the time they've started on study. Like a lot of
24 bacterial infections, or even more-so, it takes a few
25 days for that documentation to come clear, but they

1 had that infection at the time.

2 In terms of dealing though with fungal
3 infections -- you know, the evidence and small numbers
4 of fungal infections -- at least my view of what we're
5 doing when we treat empiric -- we have a patient with
6 fever, low white count and hasn't responded to
7 antibacterials. What people think they're doing is
8 treating a subclinical infection before it becomes
9 manifest because it's hard -- you know, these are the
10 exceptions when the fungal infection becomes well
11 documented. And so, when it does become well
12 documented on treatment, that's a failure.

13 But all those patients who were febrile at
14 the start of therapy represent a mixture of patients
15 who had subclinical fungal infections which didn't
16 become manifest in those that maybe had other causes
17 of fever.

18 And again, maybe Dr. Armstrong, who's
19 present here from Memorial Sloan Kettering, whose done
20 a lot in the difficult and frustrating field of making
21 fungal diagnoses, maybe could add to this comment.

22 DR. ARMSTRONG: First, in response to
23 Brian Wong's question, I think that Connie tried to
24 make it clear that once yo know what the infection is,
25 that the treatment might be altered either by going

1 back to higher doses of amphotericin B, or by pulling
2 catheters, or by doing other things. If it's
3 parapsillosis, you'll pull a catheter. There are
4 other things that you do which would take the patient
5 out of the study of the empirical therapy.

6 I hope that's clear, Brian.

7 CHAIRMAN HAMMER: Thank you.

8 DR. ARMSTRONG: That gesture means it's
9 not clear?

10 DR. WONG: I guess it's clear the way the
11 study was designed, but I guess in my mind, it's not
12 clear that we can draw conclusions about efficacy of
13 the drug with that design. I mean, it seems we're --

14 DR. ARMSTRONG: The -- of the drug for the
15 isolated fungus.

16 DR. WONG: Correct.

17 DR. ARMSTRONG: Correct. That would be
18 another question that you'd be asking.

19 DR. WONG: I mean, if empirical therapy is
20 presumptive therapy for many patients, some of whom
21 have fungal infections and many of whom do not, it's
22 really the small group that really has fungal
23 infections that we care about. If we have some of
24 those patients who subsequently prove to have fungal
25 disease, it seems to me that efficacy can be assessed

1 by analyzing those and only those, and not by
2 analyzing, you know, numbers of fevers at the end in
3 the people who never had fungal disease to begin with.

4 DR. ARMSTRONG: That's another study and
5 another question.

6 DR. WONG: Okay.

7 CHAIRMAN HAMMER: I think this gets a
8 little back to the fact that this was designed as a
9 toxicity study essentially, not originally designed as
10 you might design an efficacy study prospectively in
11 March or April of 1997. I think we have to deal
12 with --

13 DR. WONG: Right. But the question --

14 CHAIRMAN HAMMER: I think the point is
15 well taken.

16 DR. WONG: -- that's being put to us now--

17 CHAIRMAN HAMMER: Yes.

18 DR. WONG: -- is do we believe that
19 efficacy has been established?

20 CHAIRMAN HAMMER: Absolutely.

21 Okay, I'd like to --

22 Dr. Armstrong?

23 DR. ARMSTRONG: I just have a couple of
24 comments to make. You know, I think I was asked here
25 because I've had three decades of experience in trying

1 to make early definitive diagnoses of fungal
2 infections, primarily candida and aspergillus. Over
3 those three decades, I have continuously failed to
4 develop a definitive method of making a diagnosis.
5 The only reassuring fact is that I'm in very good
6 company. There are no definitive tests for
7 aspergillus or for candida that we have at this time
8 that we can depend on, particularly beforehand, but
9 even afterwards. So, gone are the days when we had
10 post-mortems to find our mistakes, and not have come
11 the days when we have good definitive tests. I think
12 that's why we have to depend on other outcomes than
13 definitive diagnoses in this kind of study.

14 One more point is Dr. Walsh, in whom I
15 have great faith, should not ask me to have faith in
16 data that's not presented. I wouldn't ask him to have
17 faith in me without presenting data.

18 Tom, I can see you're going to reply.

19 CHAIRMAN HAMMER: Can we please keep this
20 brief? We've been over this.

21 Dr. Walsh?

22 DR. WALSH: Sure, okay, but I do think
23 that this is fair. In confidentiality, I could not
24 present it. It is the FDA's responsibility, who has
25 this data, to share with the Advisory Panel -- and I

1 would strongly encourage them to do so in closed door
2 session. I anticipate that in good faith, that they
3 will do so. But in confidence, I can not present this
4 in public forum.

5 CHAIRMAN HAMMER: Okay, thank you.

6 Thank you, Dr. Armstrong.

7 Dr. Mathews, questions?

8 DR. MATHEWS: One brief question of the
9 sponsor and one to the Agency.

10 I was a little perplexed by that fusarium
11 MIC that you showed, the major point of that slide
12 being that the drugs had equivalent activity. What is
13 the basis of that data for fusarium?

14 DR. GURWITH: I forget -- do you know,
15 Peter, how many isolates that represents? So, that's
16 about 20 isolates, but that was the MIC₉₀ which means
17 that 90 percent of the organisms had MICs below -- 90
18 percent had below the value of 16 that was presented
19 on the slide. We have successfully treated fusarium
20 and fusarium infections are part of the fungal
21 infections that were listed under other filamentous
22 fungi.

23 DR. MATHEWS: Okay.

24 And a question for Dr. Shen. I was really
25 intrigued by the discussion you presented relating to

1 the dilution of the treatment difference. I'm
2 wondering whether in the setting of empirical therapy
3 trials where perhaps the majority of patients who are
4 randomized are not at risk for the outcomes that are
5 to be observed, whether the deltas that are specified
6 in sample size calculations can be looked at as sort
7 of fixed quantities of either 10 percent or 20
8 percent? Because it sounds like from your discussion
9 that this is a generic problem in these kinds of
10 studies and that it's not a sample size problem, per
11 se, since your slide really was talking about the
12 point estimates of the fact.

13 DR. FEIGAL: Maybe I could comment. In
14 the points to consider document from which there are
15 some general guidance on equivalence, what you see is
16 a general approach that is suggested as a starting
17 point. But there are many clinical situations and
18 diseases where it is modified. Where the confidence
19 interval is actually made tighter or in some
20 situations, where it's looser depending on the
21 severity of the illness and the adequacy of other
22 therapies.

23 So, part of what we're looking at today is
24 the issue of how to best define equivalence. The
25 thing to remember is that a product though does not

1 need to even meet equivalence to be approved. There
2 are products which actually demonstrate that they are
3 somewhat inferior to a standard therapy and still are
4 approved. And in that setting, what the issue often
5 is is how precisely do we know how well this product
6 works? If we know exactly what the trade-offs are,
7 there is often a role for a product which comes in on
8 the low side.

9 So, in general, I think even if we were to
10 specify something for this condition -- and that may
11 well be useful -- we would still maybe keep in mind
12 that it's there kind of as a benchmark to show us how
13 precisely we know what we know.

14 DR. MATHEWS: David, it seems to me that
15 the data that Dr. Shen presented was not so much about
16 precision of estimate, but bias and that it was
17 predictable.

18 DR. FEIGAL: No, I think it's more -- the
19 confidence interval is inflated, if you will. This
20 may be a semantic distinction between whether it's
21 bias or precision. But I think the problem was with
22 precision rather than with bias because the data that
23 Dr. Shen presented doesn't affect the point estimate.
24 It simply affects the width of the confidence interval
25 around it by taking into account how diluted the

1 effect is.

2 I think your point about needing to
3 account for that is very well taken because studies
4 with the same drug effect, as Dr. Shen presented,
5 could appear to have very different clinical outcomes
6 based simply on how much of a dilutional effect there
7 is. The dilution certainly does affect the absolute
8 result, but typically with an equivalence design,
9 we're looking at the relative difference. I don't
10 think the difference would be -- the point estimate of
11 the difference would be biased. It would probably
12 remain the same with dilution but the confidence
13 interval would falsely narrow as you got more and more
14 dilution.

15 CHAIRMAN HAMMER: Thank you.

16 Dr. Hernandez, do you have any questions?

17 DR. HERNANDEZ: Yes, I wanted to sort of
18 follow-up on the toxicity data associated with
19 infusion of this drug and ask sort of two questions.
20 One is, from this study or from your prior NDA, is
21 there any sense that you could get away with using a
22 lower dose of Amphotec and reduce some of these acute
23 transfusion associated effects, the hypoxia, chills
24 and rigors from any of these studies? Secondly, sort
25 of how do we explain the fact that it, in fact, had

1 higher toxicity in that regard as opposed to
2 traditional amphotericin B in terms of its physical
3 properties?

4 DR. GURWITH: Well, the first part is
5 could we lower the dose and have less of these acute
6 reactions and still maintain efficacy?

7 DR. HERNANDEZ: Right.

8 DR. GURWITH: Well, among other things,
9 that's one of the things we're looking at in similar
10 types of trials, documented infections or empiric
11 therapy. So, obviously, that's a question. A lot of
12 antibiotics have been developed with a higher
13 effective dose and then people work down to see if you
14 can use less, and sometimes it goes the other way.
15 So, it is possible.

16 The reactions, again, their toxicity but
17 they're not really -- you know, they're fairly easy to
18 manage. This was a study so people just tend to stop
19 patients. Because we had the study design issues,
20 you had to stop if you reached a certain level of
21 toxicity. That doesn't mean that in real life that
22 you necessarily would do that.

23 So, there is the possibility we could
24 achieve better efficacy with lower doses and we're
25 investigating it. But in contrast to nephrotoxicity

1 which --

2 DR. HERNANDEZ: No, I understand the
3 nephrotoxicity data.

4 DR. GURWITH: Okay.

5 DR. HERNANDEZ: I'm asking about the data
6 -- I mean, you had six patients that withdrew from the
7 study for that reason alone.

8 DR. GURWITH: Right.

9 DR. HERNANDEZ: Certainly with
10 amphotericin, people develop acute toxicity, you treat
11 it and/or reduce the dose. The question is, do you
12 have any data from either study about dose reduction
13 and reducing side effects and maintaining comparable
14 efficacy?

15 DR. GURWITH: Not yet, at least.

16 Now, your other question was mechanism.
17 Why do we get seemingly more toxicity? This may be a
18 dose issue. This particular study looked at doses of
19 four. We do have dose efficacy in studies at doses of
20 three. In some general way, maybe this is wrap-it-up
21 tape by macrophages and release of cytokines.

22 CHAIRMAN HAMMER: Can I just ask, unless
23 you've got really the specific answer, we need to move
24 on because the Committee really needs to get to the
25 questions to help wrestle with things. Well, if you

1 have it, please, but it relates to what Dr. Masur
2 asked earlier.

3 DR. MARTIN: With regard to mechanism, as
4 I pointed out in my earlier presentation, the tissue
5 distribution of Amphotec in this initial period is
6 completely different from amphotericin B. It is taken
7 up whole by macrophages as a complex, whereas
8 Fungizone distributes by lipoproteins to more tissues.
9 This is just evidenced by the uptake in Kupffer cells
10 in liver by Amphotec versus amphotericin B in a
11 preclinical model.

12 My answer to your question is that this
13 macrophages are probably being activated more-so with
14 Amphotec than with amphotericin B because it's a
15 particle being taken up into the internal part of the
16 cell. It's like a bacterium being swallowed up by the
17 cell. So, mediators like ILI, T and F are probably
18 released by the cells.

19 CHAIRMAN HAMMER: And Dr. Feinberg?

20 DR. FEINBERG: Hi. I've got one question
21 each on how the efficacy data and the toxicity data
22 were interpreted and presented to us.

23 I guess I'm a little thrown by the fact
24 that the renal toxicity has kind of had a tripartheid
25 definition, some parts of which seem less serious to

1 me than others. Whereas, you told us, for example,
2 for the infusion related problems for the Amphotec,
3 that they were mild and short-lived and easily dealt
4 with, you actually never showed us any data about
5 reversibility, severity or duration of nephrotoxicity.

6 I'm further concerned because your primary
7 tripartheid endpoint includes a doubling or an
8 increase of one milligram per decaliter. If you turn
9 to the study -- because you also showed us that 12
10 patients discontinued in the amphotericin B arm as
11 opposed to only one on the Amphotec arm due to renal
12 toxicity -- but in the study, therapy could have been
13 discontinued prior to even reaching grade three as
14 long as the patient's creatinine had increased by 1½
15 milligrams or doubled from baseline.

16 You know, to some extent, I feel that when
17 you show us the discontinuation rates, you know,
18 you've built that into the study. You wrote the rules
19 of the study that permitted people to ditch when they
20 reached a doubling of their baseline creatinine. You
21 know, people who start with a creatinine of .7 and go
22 to 1.4, that's not the same thing as people going to
23 a creatinine of four or five. So, I'm concerned about
24 how that was delineated to us and wonder if you did a
25 more stringent analysis based on something, for

1 example, only looking at a 50 percent decrease in
2 creatinine clearance?

3 DR. GURWITH: Well, first of all, you're
4 right. That was a tripartheid endpoint, but actually,
5 these were calculated creatinine clearances and so
6 they tracked completely with the doubling of the serum
7 creatinine. So, patients who met one criteria met
8 both. In fact, most patients met all three criteria.
9 I think there were a couple -- the figures are
10 actually in the original report and available. But I
11 think a couple in the Amphotec group made that
12 criteria only on the increase of one milligram and a
13 few in the amphotericin B group. Most patients met
14 all three.

15 DR. FEINBERG: All right. Also, in Dr.
16 Wu's presentation, she showed us that the differences
17 about a .4 milligram per decaliter between the two
18 arms as it tracks. Can you tell us something about
19 the duration or reversibility? You know, if it hinges
20 on sparing of renal function, then I think we'd like
21 to know more about how disastrous was the renal
22 function problem?

23 DR. GURWITH: Sure. Well, first of all,
24 what she showed and what's in our analyses are mean
25 values. You could look at individual values too,

1 obviously, and that gets to one of the earlier
2 questions.

3 You know, this was a study so people came
4 off study because they developed nephrotoxicity. But
5 I think this is what happens in reality. Physicians
6 know -- I certainly know when I continue to give
7 amphotericin and the creatinine goes up, it's going to
8 go up even more and it's just a matter of time. Now,
9 I'm sure there's exceptions. It may reverse when you
10 stop, but then you're stopping your therapy.

11 So, you're right. In the context of this
12 study, we didn't force them to continue to even a
13 higher level.

14 DR. FEINBERG: Oh, well, you know there's
15 plenty of modifications that people make. I guess the
16 study wasn't set up to do that, to go to every-other-
17 day dosing or something else.

18 I think along the lines of efficacy, it's
19 mentioned in one of your tables that where there's 52
20 successful outcomes out of 106 -- and then there's a
21 little asterisk that says that there was never
22 appropriate complete follow-up for three of those
23 patients. If you take the most conservatives, sort of
24 worst case scenario, and assume that the three
25 patients for whom you didn't have data had failed to

1 have a successful outcome, then that number is 49 out
2 of 106. By my rough arithmetic, that's 46 percent,
3 not 49 percent.

4 You know, I'm not a statistician, so I
5 can't do any sort of off-the-cuff comparison. But it
6 was 46 percent versus 42 percent in the amphotericin
7 B arm. I think that may shift your statistical
8 outcomes and your confidence intervals.

9 DR. GURWITH: Yes, it would shift a
10 little. Let me give you the data on those three
11 patients. One of them, actually, we got the follow-up
12 form after the database was closed so he's not
13 included. But he was alive and no fungal infection 28
14 days after treatment. Another one discontinued only
15 after one dose due to acute reactions. He was known
16 to be alive at least, 28 days later. The third one
17 discontinued when his neutrophil count recovered at
18 Day 14. We had a follow-up exam 26 days later and he
19 was alive. His physical exam was normal, but there
20 was no specific information about the fungal
21 infection. So, we're more confident that these
22 patients didn't develop fungal infections, but you're
23 correct about that.

24 CHAIRMAN HAMMER: Thank you.

25 Dr. El-Sadr?

1 DR. EL-SADR: I have a question, first,
2 regarding the follow-up. I think in Dr. Wu's
3 presentation, she mentioned that -- I wasn't clear.
4 There was no follow-up beyond seven days? Just
5 clarify that issue?

6 DR. WU: Follow-up was limited to patients
7 who had --

8 DR. EL-SADR: Who received at least --

9 DR. WU: -- had received at least seven
10 doses of a study drug.

11 DR. EL-SADR: So, those who did not
12 receive at least seven doses, they're still included
13 in the intent to treat and we have outcomes on them,
14 right?

15 DR. WU: Right.

16 DR. EL-SADR: So, what do you mean by no
17 follow-up on them?

18 DR. WU: It means follow-up, as it was in
19 the original protocol, was designed after study drug
20 treatment discontinued. Week 2, Week 3 and Week 4 are
21 supposed to have culture results, radioactive and lab
22 data.

23 DR. EL-SADR: I see. So, you do not have
24 complete follow-up, but you have outcome?

25 DR. WU: We did not have those data in the

1 case report forms.

2 DR. EL-SADR: You don't have anything at
3 all?

4 DR. GURWITH: Just to clarify that a
5 little more, what happened was, the protocol was
6 designed exactly the way Dr. Wu said. If you
7 remember, original successful outcome definition did
8 not include information about fungal infections in the
9 seven day follow-up, post-treatment follow-up period.
10 When it was suggested we should get this information,
11 we went back to each site and got as much information
12 as we could from the hospital records. The
13 investigator assessed each patient and said they did
14 or did not have a fungal infection based on hospital
15 records in the seven day follow-up.

16 The three patients that were just
17 described were three where the hospital records were
18 being microfiched and so, weren't available.
19 Originally, the protocol did not collect that follow-
20 up, but the successful outcome rates that I
21 demonstrated and the fungal infection rates are based
22 on that complete follow-up, though it is, to some
23 extent, more retrospective than the earlier data.

24 DR. EL-SADR: Another issue which I think
25 actually was raised before is that the data presented

1 on the function of the dilution of the effect by the
2 rate of fungal infection. I guess I'm a little bit
3 worried about that because in my mind, I think of
4 empiric therapy is that you're doing something,
5 although it's a subclinical infection. You know, that
6 you don't really know the true underlying rate of
7 infection in these individuals and it doesn't matter,
8 to a certain extent, because it's not treatment. It's
9 empiric therapy.

10 So, I guess I'm wondering, what do you
11 think the value is of this analysis if there's no way
12 for us to know what the true risk is, I guess -- risk
13 of some sort of clinical infection in this population
14 is, in any case?

15 DR. WU: Well, the dilution effect is true
16 to all clinical endpoints used by Sequus protocol. We
17 chose defervescence as one parameter to illustrate the
18 result based on so-called mixed patient population.
19 Exactly like you said, we do not know what is the
20 exact fungal infection incidence rate at the time
21 those empiric patients entered into trial. The
22 dilution effect affects all clinical efficacy
23 endpoints.

24 DR. EL-SADR: Right. But this looking at
25 the endpoints, I mean, I guess, in a way, you're

1 looking at what they come in with almost as a criteria
2 for enrollment. How many of them have some sort of
3 subclinical disease, right? And since there's no way
4 for us to know that and we don't have any tests or
5 anything to help us out, we're almost in a bind. I'm
6 not sure that in the group that there may be -- we're
7 treating something even though these patients don't
8 have anything that we can put our fingers on in terms
9 of a fungal infection.

10 DR. WU: Well, to me, it seems to be
11 obvious that is the dilution factor we are talking
12 about.

13 DR. EL-SADR: So, you're worried about
14 that in terms of the 20 percent that was mentioned by
15 Dr. Walsh earlier today?

16 DR. WU: I don't know the exact number.
17 The number I used was the most optimistic number, 33
18 percent, and it was 15 years ago. So, nowadays, I
19 think the number is probably lower than 33 percent.

20 DR. EL-SADR: Right.

21 DR. WU: So, that is the number we were
22 focusing on, with that low number in the presence of
23 majority of patients who are likely not to be fungal
24 infected. They're all mixed in the same patient
25 population, so how are we going to deal with that?

1 This is the problem.

2 DR. EL-SADR: Right. But it seems that
3 this analysis really highlights that for me for
4 empiric therapy in a group where you know, maybe, very
5 small percentage has the disease or has the infection,
6 that the more important issue is the toxicity safety
7 rather than efficacy.

8 DR. WU: Well, I think what we'd like to
9 see both.

10 DR. EL-SADR: Right.

11 DR. WU: The toxicity is important, but we
12 would like to know whether the drug is truly doing
13 something otherwise.

14 DR. EL-SADR: In the small number.

15 DR. WU: A placebo might have the same
16 effect.

17 CHAIRMAN HAMMER: Thank you.

18 Dr. Murphy, do you have any questions?

19 DR. MURPHY: Well, first of all, I wanted
20 to make sure that we had some laudatory comments to
21 this company for their pediatric development. Almost
22 one-quarter of the patients were children. We
23 certainly do have a number of children who could
24 benefit by alternative therapies and have fungal
25 infections.

1 Which really brings me to my question
2 though. In a way, one of our larger groups of
3 children who have fungal infection or
4 immunocompromised are neonates and very young
5 children. Your data indicated that of the 49
6 children, none of them in the Amphotec were under a
7 year of age, and you had some in the amphotericin B
8 group who were under a year of age. Since that group
9 may also have some other renal problems, I was trying
10 to find out, did you have anybody under six months of
11 age in the amphotericin group?

12 DR. GURWITH: I don't believe so in this
13 study. I think we have had one or two in other
14 studies.

15 DR. MURPHY: Okay. And then my second
16 question is not a pediatric question. In breaking out
17 the mortality, you have your multi-organ failure
18 group. I know that you had a respiratory failure
19 group and you told us in the other group, who was in
20 the other. But in the multi-organ failure group which
21 was twice as high in the Amphotec group, was
22 respiratory failure a prominent problem in the multi-
23 organ because it was not just respiratory? It got
24 lumped into the multi-organ.

25 DR. GURWITH: I don't think so. Multi-

1 organ failure is a kind of a catch-word for the
2 patient dying of their underlying disease, usually
3 hepatic sepsis, you know, from bacterial infection.
4 So, it gets lumped in a COSTART term because we can't
5 describe each individual death, or at least we don't
6 by a paragraph or something like that. But I don't
7 think there was any suggestion of multi-organ failure
8 in either group being related to study drug.

9 DR. MURPHY: Okay.

10 CHAIRMAN HAMMER: Dr. Masur?

11 DR. MASUR: In terms of the infusion
12 related toxicity, is there any evidence that the
13 chills and rigors are as readily treatable with the
14 usual adjunctive therapies as they are with
15 conventional amphotericin? I mean, is it conceivable
16 with a higher dose, that it is harder to abort them
17 with medicine? Do you have data on that?

18 DR. GURWITH: Well, I guess we don't
19 really have comparative data to say that one dose --
20 you know, a certain dose or certain cocktail is
21 better, works better with amphotericin than with
22 Amphotec, but certainly Amphotec patients respond
23 similarly to the amphotericin B patients when they get
24 their premedications. As you may know, they're not
25 always standardized.

1 DR. MASUR: Right. Well, I mean, this
2 study, since there were fewer and fewer immediate
3 reactions on consecutive days, is that because they
4 were being treated or was treatment being withheld to
5 see whether there was tachyphylaxis?

6 DR. GURWITH: No. The protocol stated
7 that no pre-medication for the test dose. Then they
8 had to have pre-medication for the first dose and then
9 after the first dose, it was as the physician felt was
10 needed. So, in some cases, the pre-medications may
11 have been discontinued or decreased and discontinued
12 as dosing went on.

13 DR. MASUR: Do you know whether pre-
14 medication was comparable in the two groups?

15 DR. GURWITH: The number of days of pre-
16 medications were comparable. That's about all because
17 it's hard to compare doses.

18 DR. MASUR: All right. And then the other
19 question -- presumably, Dr. Hammer is allowing two
20 complex questions -- is in terms of the
21 nephrotoxicity, I wasn't clear on your responses
22 before in terms of the time to return to baseline. If
23 you looked at either tubular wasting or the creatinine
24 elevation, was there any suggestion that it took a
25 longer period of time to return to baseline with

1 Amphotec than with amphotericin? In other words, is
2 it conceivable that with a higher dose you've given
3 with Amphotec that there might be a longer time to
4 return to baseline?

5 DR. GURWITH: That's something maybe we
6 can analyze. I'm not sure -- we certainly -- since we
7 don't -- once the patient went off study, then they
8 could get some other drug and they might even get
9 amphotericin because, again, this was a blinded study.
10 So, it's a little hard for us to analyze what happened
11 to them off study. So, I guess that we can do
12 something else, but we certainly don't have that
13 available right now.

14 CHAIRMAN HAMMER: Dr. Lipsky?

15 DR. LIPSKY: Thank you.

16 One, a question which may be complex,
17 related to kinetics. It's fairly fascinating that
18 over 80 percent of the drug perhaps can not be
19 accounted for by area under the curve on an
20 amphotericin equivalence. I wonder has anybody
21 accounted for what happens to the rest of the drug?
22 Do we know where it goes? For instance, it's
23 intriguing that you get into trouble with the lung.
24 Can it be going to the lung? Does it do anything with
25 surfactant, et cetera, et cetera?

1 DR. MARTIN: We're intrigued by the same
2 question. The drug distributes to the RES, to the
3 liver. And in multi-dose animal studies, more and
4 more drug goes to the liver with each successive dose
5 until you actually saturate the liver. Then there's
6 spill-over into other organs such as the spleen. But
7 there's no toxic consequences, apparently, of this
8 buildup in the organs. My interpretation is that
9 you're injecting more drug. It's going into these
10 cells, macrophages as a complex. There is a delay in
11 the drug being freed from the complex and reentering
12 the circulation in the form of lipoprotein bound drug.

13 DR. LIPSKY: But you're talking about a
14 massive amount extra. You're talking about, you know,
15 four-fold time. This should be staying around for a
16 long period of time and also, eventually, getting the
17 lipoproteins, kidney, et cetera unless you believe
18 it's solely a bolus phenomenon that avoids the kidney.
19 I realize that's not really germane to the efficacy,
20 but it's just amazing that it displays these kinetics.

21 DR. MARTIN: The benefit of this drug is,
22 in fact, its distribution to the RES because, in that
23 way, it avoids the kidney exposure. So, it's the
24 other side of the coin. You load up these other
25 organs but at the doses we're talking about, the

1 plasma levels after each dose are equivalent. So, one
2 would expect the antifungal activity to be equivalent
3 and there are no toxic consequences to this buildup in
4 the organs, such as the liver and spleen.

5 DR. LIPSKY: And you state in the brochure
6 that there's less accumulation of this drug in the
7 kidney, significantly less. How much less as compared
8 to amphotericin?

9 DR. MARTIN: Five to seven-fold less in
10 animal studies.

11 DR. LIPSKY: Okay, so that's dramatic.

12 Okay, and finally, a question on efficacy.
13 Where does the company stand on an indication for
14 candida infection?

15 DR. GURWITH: For candida, we've submitted
16 data, as I mentioned before, with the original NDA
17 that had to do with candida infections in patients,
18 second line patients, starting or have started a trial
19 in oral pharyngeal candidiasis, Fluconazole resistant
20 oral pharyngeal candidiasis in AIDS patients. We're
21 approved and the drug is used in Europe for candida
22 infections. We're also considering, actually, a dose
23 finding study in candida, a randomized trial, to
24 answer some of the issues that have been brought up.

25 DR. LIPSKY: Thank you.

1 CHAIRMAN HAMMER: Thank you.

2 Now it's time for the Committee to do its
3 work.

4 Dr. Feigal, the charge to the Committee?

5 DR. FEIGAL: Well, I'll keep my comments
6 brief. I think we're asking the Committee essentially
7 to address two things for us. One is to consider this
8 application for the supplementary indication for this
9 product. The first question asks you whether or not
10 you find that this product meets that standard.

11 Then secondly, we'd like, having heard the
12 discussions this morning and have thought about this
13 issue at other times, to get your comments and
14 guidance on endpoints for this particular condition.
15 There are some things that we don't dispute with the
16 company. We don't dispute that empiric therapy in
17 this setting with antifungal agents is a life-saving
18 therapy. But there are many challenges to studying
19 that and establishing the effectiveness and the safety
20 of products in this area. We would appreciate your
21 reflections on these issues as well.

22 CHAIRMAN HAMMER: Thank you.

23 There were two questions for the Committee
24 and the first will result in a vote. The second
25 question is more for discussion.

1 I'd like to ask the Committee members to
2 comment first, prior to the vote, on the first
3 question which I will read. I'd like to go around the
4 table in opposite order. Please keep your comments
5 brief, but hopefully, to the point addressed by the
6 question which is:

7 "On the basis of the data presented in
8 this NDA, does the Committee find that the applicant
9 has adequately demonstrated the safety and efficacy of
10 Amphotec in comparison with Fungizone as empiric
11 treatment in febrile and neutropenic patients?"

12 I'll start with Dr. Lipsky.

13 DR. LIPSKY: On the issue of safety, it
14 appears that it has demonstrated a favorable
15 comparison. To the data presented to the Committee on
16 efficacy, it would appear that there is not enough
17 data presented to make that decision. I believe this
18 is a bit different than just saying this is like a
19 generic amphotericin, does it have similar levels, et
20 cetera, et cetera? Based on the black labeling, in
21 the package insert, in workshops, et cetera, it's
22 feeling of the scientific community that they want
23 more than just a comparison of serum levels.

24 It would be interesting that if we saw the
25 data -- you know, the European data, on the efficacy

1 for candida and, you know, we already have it for
2 aspergillosis. Then everything would certainly make
3 sense that this will work. But just from what we've
4 seen this afternoon, I'd say no.

5 CHAIRMAN HAMMER: Thank you.

6 Dr. Masur?

7 DR. MASUR: Well, I think it's commendable
8 that this study is being evaluated to see if enough
9 data can be mined for it to add efficacy to the safety
10 data that is derived. As Dr. Lipsky said, I think
11 that although there are some unresolved issues about
12 safety, I think that there's enough data to suggest
13 that there are advantages of this preparation over
14 Fungizone.

15 In terms of efficacy, admittedly, this is
16 a very difficult -- it's very difficult to establish
17 appropriate endpoints. But it's also a problem in
18 this era of fluconazole prophylaxis, in this area of
19 GCSF. It's very difficult to determine whether this
20 drug is as effective as amphotericin or as ineffective
21 as amphotericin. It's hard to really know where this
22 stands. So, I think that the efficacy issue is one
23 that is very difficult to pull out of the data as it
24 is currently presented.

25 CHAIRMAN HAMMER: Thank you.

1 Dr. Murphy?

2 DR. MURPHY: Actually, I have a little bit
3 different take on the safety. I think, certainly, the
4 nephrotoxicity is appealing, or the lack thereof, that
5 you've presented. I think the whole concept and
6 approach is very, obviously, appealing, exciting.
7 However, I think that we actually have a balance of
8 toxicities here which people will need to continue to
9 work on how they're going to control them. So, I
10 think that, yes, safety has been demonstrated that's
11 equivalent, if you will, because you have a balance of
12 issues.

13 The efficacy, I feel that the data is not
14 sufficient at this time as a first line indication.

15 CHAIRMAN HAMMER: Thank you.

16 Dr. El-Sadr?

17 DR. EL-SADR: This is a very difficult
18 decision. I guess we're being asked not to say if
19 it's better than amphotericin, but if it's an
20 alternative to amphotericin for this indication for
21 empiric therapy. These are very difficult studies to
22 do. I think it's sort of appreciated that it is very
23 difficult because of the population. Also, because of
24 this whole issue of empiric therapy and what it is and
25 what it isn't.

1 I think it would have been nice if the
2 Committee had seen some data on candida, on the
3 treatment of candidiasis because we actually had
4 nothing in our packet on the treatment of candidiasis.
5 You've told us that the data does exist and has been
6 submitted -- that they do exist and have been
7 submitted, and that this agent -- I guess maybe the
8 FDA can confirm this. I don't know -- has been shown
9 to work for treatment of candidiasis. I think that's
10 very important in making a decision on whether to use
11 it for empiric therapy.

12 DR. WU: Yes, I agree with you. But the
13 data have not been scrutinized by FDA, so we can not
14 answer your question whether in favor or not in favor
15 of sponsor's conclusion.

16 DR. EL-SADR: I think, again, it's a very
17 tough decision. I mean, even when I think about even
18 asking that question, I'm not sure how relevant that
19 question is to the issue of empiric therapy. Although
20 I think it is relevant because the most common
21 infection would be candida infections in these
22 patients.

23 Again, I do not think that it has been
24 demonstrated that it is similar to amphotericin, but
25 I think mainly because I agree on the safety. I'm

1 comfortable that it is no worse than amphotericin,
2 maybe better for renal insufficiency. But I think
3 without having any information at all on candidiasis
4 treatment, it's difficult for me to say that it has
5 similar efficacy in empiric therapy.

6 CHAIRMAN HAMMER: Thank you.

7 Dr. Feinberg?

8 DR. FEINBERG: Well, I guess I share Dr.
9 Murphy's feeling more-so than some of the other panel
10 members that I think the data show that there is
11 different kinds of toxicity for these two different
12 compounds. In my experience, it's unusual to have
13 such extraordinary problems that are unmanageable in
14 terms of amphotericin nephrotoxicity that you know,
15 the FDA analysis, to me with the .4 milligrams per
16 decaliter difference was, you know, fascinating and
17 compelling for -- the fact that it was a difference,
18 but I'm not sure whether it's a clinically relevant
19 difference in many patients.

20 Like many of the other members, I'm
21 troubled by the efficacy data. I think the data that
22 have been presented here today sort of point out the
23 problem of using data generated by a study that had a
24 different goal and a different statistical
25 underpinning, and you know, different data collection

1 requirements, and then trying to turn that into
2 something that is an equivalent study. I guess I feel
3 that there's enough uncertainty about where these
4 confidence intervals really lie that I'm also not, you
5 know, overwhelmingly convinced that efficacy has been
6 proven here.

7 CHAIRMAN HAMMER: Thank you.

8 Dr. Hernandez?

9 DR. HERNANDEZ: I think that the
10 nephrotoxicity safety data is one that really warrants
11 our endorsement, particularly since there are many
12 patients where amphotericin alone may be manageable,
13 but in combination with other therapies that may not
14 be the case. I was likewise though concerned on the
15 safety issue of the other toxicities that Amphotec
16 has, that amphotericin B does too, although not as
17 prominent, apparently. I would certainly share that
18 at least from what we've seen, it's difficult to
19 really make a finding a comparable efficacy for
20 Amphotec.

21 CHAIRMAN HAMMER: Thank you.

22 Dr. Mathews?

23 DR. MATHEWS: Well, for once, I think I'm
24 going to disagree with the majority opinion. I think
25 there's substantial advantage for this agent in terms

1 of the nephrotoxicity profile. I think that the
2 protocol perhaps stopped treatment a little too early
3 to allow a more convincing demonstration of that
4 effect. But I agree with the sponsor, at least in my
5 experience, once the creatinine starts rising and you
6 continue high doses of these drugs, it's going to get
7 worse.

8 With regard to the efficacy issue, I think
9 there was a consistent effect across the components of
10 the outcomes that they examined. I think while one
11 doesn't know that either agent in this setting
12 benefitted the patients, I agree with the sponsor's
13 interpretation that they were comparable effects and
14 that the Agency's analyses were post hoc analyses.

15 The one that I was most impressed with,
16 namely the dilution argument, made the critical
17 assumption that the outcome events were comparable --
18 the distribution of outcome events were comparable
19 among patients who had fungal infections and who
20 didn't. If you use the example as you did of the
21 defervescence, I'm not sure that's a reasonable
22 assumption. Because if the drug is working to treat
23 fungal infection, you wouldn't expect defervescence
24 rates to be comparable in groups that had infection
25 compared to those that didn't.

1 So, on balance, I'm more in favor of
2 approving this.

3 CHAIRMAN HAMMER: Thank you.

4 Dr. Elashoff?

5 DR. ELASHOFF: In terms of safety, yes,
6 they did demonstrate improved safety using their
7 definition of nephrotoxicity. In terms of overall
8 adverse events, no confidence interval was given to
9 compare those rates and make a claim of equivalence.

10 In terms of the treatment study, there was
11 a historical control only, so I don't regard that as
12 proof of efficacy and I don't think the main trial
13 demonstrates efficacy or equivalence. If fungal
14 colonization at baseline is an important risk factor,
15 then the two groups had a different mix of patients
16 which would bias estimates of differences in efficacy.
17 Even if they were the same mix, the dilution effects
18 mean that the drugs may appear equivalent even if they
19 are not, or if neither one works. Therefore, I don't
20 think they've demonstrated efficacy.

21 CHAIRMAN HAMMER: Thank you.

22 Dr. Sugar?

23 DR. SUGAR: In terms of the safety, I
24 would give it a qualified yes, that the company has
25 showed that Amphotec is less toxic than amphotericin

1 B. However, I think that I'd like to see more
2 clinically relevant nephrotoxicity data, specifically
3 grade 3 and grade 4, because I'm not convinced that
4 what we've seen is clinically relevant. I'm also very
5 concerned about the systemic toxicity, given the large
6 numbers of patients that will be receiving this drug
7 without any real need for it because of the problems
8 in diagnosis.

9 In terms of the efficacy, I think that
10 there are trends and suggestions that there is
11 equivalence. But given the study design, it's a
12 problem in -- and I like the expression used before --
13 mining the data because that's what's been done. The
14 study really wasn't put together to prospectively
15 identify an efficacy here.

16 CHAIRMAN HAMMER: Thank you.

17 Dr. Wong?

18 DR. WONG: I think that the Amphotec has
19 been shown to be less nephrotoxic. I'm concerned
20 about the hypoxia. I think that warrants further
21 study and is a potentially serious problem. I think
22 that efficacy has not been demonstrated.

23 CHAIRMAN HAMMER: Thank you.

24 Dr. Kan?

25 DR. KAN: I share some of the concerns

1 with the other members of the Committee in regard to
2 lowering the renal toxicity. I think that has been
3 shown, given the parameters of the present data. My
4 other concerns are for the acute toxicities at the
5 time of infusion. I think more needs to be done to
6 delineate the nature of those toxicities.

7 With regard to the efficacy data, I think
8 there's been insufficient data presented at this time
9 to warrant an indication for empiric therapy.

10 CHAIRMAN HAMMER: Thank you.

11 Just adding my comments briefly, they
12 concur with the consensus we've heard so far.
13 Certainly, with the safety, the nephrotoxicity
14 potential does seem to be less -- there's full
15 agreement on that -- versus the dose of amphotericin
16 that was studied.

17 I agree that the infusion reaction here is
18 really problematic. In the sense that we don't quite
19 understand it, we don't know how prevalent that
20 problem is. And as lipid complexed or liposomal
21 compounds of this variety get increasingly used, this
22 is something we need to know more about. I would
23 encourage some basic work in this regard. We have
24 hypotheses, but we really don't know. Given the
25 nature and the severity of illness of this patient

1 population, acute hypoxic pulmonary reactions are
2 certainly not trivial. But there's no question, I
3 think, about the nephrotoxicity.

4 On the efficacy side, it comes down to a
5 question, I think -- if I could express, perhaps, the
6 sense of the Committee -- we would have liked to have
7 seen a study that clearly demonstrated this because
8 there is a need for a safer agent. I think what we're
9 really the victim of is insufficient information. I
10 think we really don't know. We're being put in the
11 position of not having adequate data, really, to make
12 a conclusion in the sense that the sample size is
13 small; the study as has been gone over was originally
14 designed for another primary objective which was
15 safety. Yes, it doesn't look like there's much
16 difference but we really do not know whether there is
17 a difference or there isn't a difference.

18 It is difficult for this Committee to say
19 when we're asked the direct question "is there
20 evidence of efficacy?", and there just basically is
21 insufficient evidence. Even if we would will it or
22 would want it to show that, when asked the objective
23 question, my own feeling is that however much we would
24 have liked it, we have not been shown enough data
25 given also the problems in the analysis and study

1 design and the way endpoints were looked at -- which
2 was not a fault of the original design of the study,
3 but in just what's happened subsequently to try to put
4 it into a supplemental NDA -- that my personal feeling
5 is that efficacy for the empiric indication has not
6 been shown. I basically, however, think that it may
7 well be there. We just can't be sure about it from
8 the data presented.

9 With that, I think formally, we should
10 take a vote. So, I'll read it again for the record.
11 "On the basis of the data presented in this NDA, does
12 the Committee find that the applicant has adequately
13 demonstrated the safety and efficacy of Amphotec in
14 comparison with Fungizone as empiric treatment in
15 febrile and neutropenic patients?"

16 Let me remind the Committee members that
17 only the Committee members and not the consultants and
18 guests are eligible to vote. So, that's Drs. Lipsky,
19 Masur, Murphy, El-Sadr, Feinberg, Hernandez, Mathews,
20 and me. So, the question is, all those in favor --
21 actually, we'll split that question -- adequately
22 demonstrated the safety comparison to Fungizone and
23 we'll do a 1A. How many individuals believe that the
24 safety has been adequately demonstrated?

25 1B, has the efficacy been adequately

1 demonstrated for empiric indication? All those in
2 favor?

3 There's one vote in favor, Dr. Mathews.

4 All those opposed?

5 I see no abstentions. Okay.

6 Now, we'll move on to the discussion
7 question. This is an important issue I think for this
8 sponsor and for other sponsors who are either here or
9 will see the output from this Committee as to how to
10 study this extremely difficult disease process, and to
11 try to get an indication for empiric therapy. So, I
12 will read this. I'll ask the Committee to comment
13 individually. Again, please try to keep your comments
14 to the point. If there are also comments in addition
15 to the bullet points listed, please feel free to
16 include them as far as helpful suggestions to the
17 sponsor.

18 The specific point for discussion is: "In
19 addition to documented fungal infection, what other
20 endpoints would the Committee find useful?
21 Specifically: suspected fungal infections;
22 defervescence in the presence of antibiotic
23 modification; a composite endpoint which would combine
24 both efficacy and toxicity events?"

25 So, feel free to comment on each of these

1 and to add anything else to try to sort through this
2 maze. I'll start with Dr. Kan.

3 DR. KAN: I think that in addition to the
4 documented fungal infections, I think a stringent
5 criteria need to be met for suspected fungal
6 infections and probably be monitored by an independent
7 board. Specifically, recommendations or criteria that
8 were set by the MSG or IDSA may be a good starting
9 point.

10 I think that the analyses that were done
11 by Drs. Wu and Shen at the FDA where they looked at
12 defervescence and the presence or absence of
13 neutrophil recovery as well as antibiotic
14 modification, those were worthwhile measures.

15 The last point, to have a composite
16 endpoint that would incorporate both efficacy and
17 toxicity events. I think they need to be given enough
18 sample size to adequately demonstrate both rather than
19 either. Otherwise, I think we might run into the
20 difficulties that we had with the first question.

21 CHAIRMAN HAMMER: Thank you.

22 Dr. Wong?

23 DR. WONG: I guess my recommendation would
24 be not necessarily to try to answer all the questions
25 in the context of a single trial. I think an

1 empirical antifungal therapy trial is probably very
2 well able to answer tolerance and toxicity questions.
3 But whether the treatment is effective for fungal
4 infection, in my mind, has to be addressed in patients
5 who are known to have fungal infection. The best
6 place to find those may not be in the context of an
7 empirical trial.

8 So, if there were clear-cut evidence with
9 good controls, in this instance, you know, of efficacy
10 in candida patients and efficacy, let's say, also in
11 aspergillus patients, that might be enough. So, I
12 guess I would recommend that efficacy should be
13 established, not necessarily in precisely the context
14 that the request for an indication is being made.
15 That might make it easier.

16 I think this question about a composite
17 endpoint -- you know, combining several different
18 criteria, some of which are efficacy criteria and some
19 of which are toxicity criteria, are just asking to get
20 into circular arguments. I would advise to, if at all
21 possible, to avoid that.

22 CHAIRMAN HAMMER: Thank you.

23 Dr. Sugar?

24 DR. SUGAR: I think in looking at the
25 design of an empirical therapy trial, the way I look

1 at it is the patient develops an onset of neutropenia
2 and then at some point resolves. If the empirical
3 antifungal therapy is successful, the patient goes
4 from point A to point B without developing any
5 manifestation of fungal infection. So that documented
6 fungal infection, suspected fungal infection, and all
7 of the clinical correlates of that -- and it's very
8 difficult because of all the adjunctive things going
9 on that affect fever, for example, with the
10 antipyretics and transfusion, but they have to be
11 looked at. I think they can be if the study is
12 prospectively organized in a way that these are
13 specific components of that trial. So, I would agree
14 with those.

15 The composite endpoint -- I agree with
16 Brian -- it may be a very complicated parameter.

17 CHAIRMAN HAMMER: Thank you.

18 Dr. Elashoff?

19 DR. ELASHOFF: I think it makes sense to
20 have survival as an endpoint. Possibly, some
21 composite efficacy endpoint, but I certainly would not
22 combine toxicity and efficacy in a single endpoint.

23 CHAIRMAN HAMMER: Thank you.

24 Dr. Mathews?

25 DR. MATHEWS: I find the endpoint of

1 documented fungal infection itself problematic in this
2 setting because if you consider who are the people
3 that are enrolled in the studies like this, there's
4 the one group that aren't at risk at all for the
5 outcome because they're not colonized and at risk.
6 Then there are people who have mild infections that
7 are already established but not manifest, for whom the
8 treatment will abort the infection and therefore, it
9 will not be detected. Then there are people who have
10 established infection which may or may not be manifest
11 at baseline or during the early treatment period who
12 would be counted as advanced because it would worsen,
13 say, during the early part of the treatment period and
14 then be diagnosed. That would be counted as an
15 outcome, where in fact, that subset of patients had
16 the infection to begin with and may have had their
17 lives prolonged or saved by that treatment. Yet, they
18 would have been counted as failures.

19 We didn't really get into a discussion in
20 this data set on when, during the course of the
21 treatment period, the various infections were
22 diagnosed or should be diagnosed, to be counted as
23 outcomes. Something that happens that is diagnosed
24 four days into the treatment period seems to me was
25 very likely to have been present and established on

1 Day 1 or Day 0. So, I think that issue needs to be
2 thought of. I'm sure the MSG has dealt with this in
3 much greater depth than I have in just a few minutes.
4 So, that's my major issue.

5 I think suspected fungal infections is an
6 even worse issue to deal with because it is so totally
7 ambiguous. You know, I don't know whether this is
8 even feasible to say -- although I suspect it could be
9 accomplished -- in that patients who enroll in trials
10 like this where there are alternative therapies that
11 don't require that they be randomized, a great effort
12 should be made to either get autopsies or agreement to
13 invasive procedure so that, at least for the patients
14 on these trials, the outcomes can be verified.

15 CHAIRMAN HAMMER: Thank you.

16 Dr. Hernandez?

17 DR. HERNANDEZ: Well, I guess I would sort
18 of start from the bottom and work up. I think that
19 the composite endpoints really makes it difficult, and
20 it's even hard to imagine in a very large study, how
21 you could separate out efficacy from toxicity events
22 using kind of composite endpoints. So, I'm less
23 inclined in that way.

24 Likewise, I think defervescence, while we
25 would like these patients to be afebrile and it's an

1 important clinical parameter, it is impacted by so
2 many other variables, not the least of which are all
3 the other drugs that these patients get and the
4 diagnoses that they have themselves in the case of
5 malignancies. That likewise, that one doesn't make me
6 feel any better.

7 I think if you could design a study where
8 suspected fungal infection could be very clearly
9 identified and reviewed in some very consistent way to
10 determine who's eligible for it would probably be the
11 next best after actually studying efficacy in people
12 with known infection.

13 CHAIRMAN HAMMER: Thank you.

14 Dr. Feinberg?

15 DR. FEINBERG: On the face of it, you
16 know, my first response to this idea of looking at
17 suspected fungal infections was clearly yes. Then I
18 agree with what Dr. Hernandez just said. You'd need
19 to have some very clear -- and what Dr. Mathews said
20 -- I think you'd need to have some very clear
21 guidelines as to what constituted it and you probably
22 ought to have, you know, a group of investigators or
23 experts blinded to study drug assignment to actually
24 review it in some way. It's not necessarily easy, but
25 it's doable.

1 Similarly, defervescence is not
2 necessarily easy at all, as Dr. Wu showed us today,
3 but probably doable because it's such an important
4 clinical feature and what keys physicians to be
5 concerned about these patients to begin with. It's
6 what triggers ordering systemic antifungal therapy in
7 this setting. But I think I do agree with the others
8 that I think it requires a fairly sophisticated
9 approach. And that, again, I think it's doable but it
10 wouldn't be easy.

11 I want to also weigh in against the
12 composite endpoint. I'm mindful of the fact that I
13 don't remember what the package insert looks like, but
14 atovaquone, the pivotal trial for atovaquone for
15 pneumocystis pneumonia hinged on a composite endpoint
16 that was effective clinically against the pneumonia
17 and did not lead to dose-limiting toxicity. That's
18 not the way the label reads though, huh?

19 DR. FEIGAL: Well, approval was based on
20 survival.

21 DR. FEINBERG: Survival?

22 DR. FEIGAL: The approval was based on the
23 survival data, yes. It was inferior but it was well
24 enough characterized so that you could know what the
25 advantages and disadvantages.

1 DR. FEINBERG: Okay.

2 DR. FEIGAL: So that the toxicity was
3 described separately. So, they were kept separately.

4 DR. FEINBERG: Okay.

5 DR. FEIGAL: But you're right. There have
6 been PCP studies that have had treatment success
7 defined as being able to complete therapy on the
8 initial randomized therapy with the rationale that
9 that tells you that that therapy, in and of itself, is
10 adequate in some patients who don't have to stop it
11 for side effects, for example.

12 DR. FEINBERG: Right. Well, I was a party
13 to helping devise that. I think at the time, we all
14 thought it was very clever, but in retrospect, I think
15 it's much less clever than we originally thought.
16 Really, when physicians need to consider what they're
17 going to, especially in a potentially life threatening
18 situation, the toxicity calculation that you make in
19 your mind and the clinical efficacy calculation that
20 you make in your mind are separate. Then you conjoin
21 them.

22 So, I think it's more important for
23 physicians to know how well a drug works and then they
24 can weigh, in a given patient, the risks of using that
25 drug than to set up the study a priori so that the two

1 things are mixed together. Because I think in the
2 end, it gives you a much murkier kind of guidance.

3 CHAIRMAN HAMMER: Thank you.

4 Dr. El-Sadr?

5 DR. EL-SADR: I actually had no problems
6 with the endpoints that were picked for the study
7 because it's a very, very difficult issue. The study
8 and the complexities of the management of these
9 patients are very real.

10 I think though the others on the Committee
11 have mentioned the important criteria which is that
12 they're decided on ahead of the study and then
13 collected appropriately and prospectively, whatever
14 the endpoints are, including suspected or confirmed
15 fungal infections; and that someone adjudicates the
16 findings and decides to categorize one way or the
17 other. I think it's very important that it's done
18 prospectively rather than going back through charts
19 and trying to determine what fits which diagnosis. I
20 think that's one of the weaknesses of some of the
21 findings from this study. But I do think that it is
22 such a complex area that you have to go with composite
23 endpoints.

24 I actually don't have a big problem with
25 the combination of efficacy and toxicity. I think in

1 a situation like this where we suspect that the
2 numbers of people who actually have the disease or
3 have the infection are small, and where you're going
4 to give the drug to large numbers who don't have what
5 you think you're treating, then in this setting, it's
6 particularly valuable, maybe, to do a composite
7 efficacy/toxicity as an endpoint.

8 I also think that looking at with and
9 without antibiotic modification is appropriate. I
10 think these studies need to reflect real life and the
11 decisions that clinicians have to make as they go
12 along managing these patients. I'd be careful about
13 trying to prescribe too many things in the study
14 conduct itself. But in the answer, that can be one of
15 the analyses that can be done.

16 CHAIRMAN HAMMER: Thank you.

17 Dr. Murphy?

18 DR. MURPHY: Really, I would just word it
19 slightly differently than the others as far as a
20 composite. I do think though I would keep the
21 efficacy separate from the toxicity, even though
22 eventually that's what you do, conjoin, as was stated.
23 I do think though that even though you may not be
24 statistically able to prove some points, it is the
25 full weight of the trends that are consistent that

1 will come to bear upon the final decision.

2 So, the composite would have -- even
3 though you may not have that many absolute fungal
4 infections. And then the clear definition of the
5 suspected -- which I think that there was definitely
6 room for improvement in that part of the study. Then
7 even, you could have probable, but you could have
8 clearly defined definitions of these. Look at them
9 separately; look at them together. It would be the
10 consistency of the trend that would be important.

11 I also agree with the fact that even
12 though we need to reflect the real world, it would
13 have been useful to look at -- if I want to look at
14 defervescence, I would have looked at it for longer
15 than 48 hours. I mean, I think that was another issue
16 here. The weight of the evidence would have been more
17 convincing if we could have had it longer than 48
18 hours and we could have a trend when there was no
19 antibiotic modification, again, in that area,
20 combining that data, looking at it separately.

21 CHAIRMAN HAMMER: Thank you.

22 Dr. Masur?

23 DR. MASUR: I think it's a wonderful
24 opportunity to have these liposomal drugs to add to
25 the armamentarium, so I would hope that the sponsors

1 don't get the impression that these are not valued.
2 They're real opportunities.

3 The data that's available on the efficacy
4 for fungal diseases is a little bit of concern in that
5 the aspergillus data is only compelling to a point.
6 I would agree with the other people that it would be
7 nice to have some more concrete data on candidiasis.
8 Although I think we have to recognize that studies of
9 candidiasis are very difficult to interpret for a
10 whole variety of reasons, but would it not be nice to
11 at least have some data presented about the
12 efficacies. So that we were sure that while the
13 theory was good, that, in fact, for yeast as well as
14 moulds, there was efficacy.

15 In terms of, you know, the kinds of
16 endpoints, I guess people have been talking around
17 this point from different perspectives, but it seems
18 to me that we're really looking into strategy. The
19 issue is, if you start this drug versus another drug
20 for empirical therapy, at the end of their
21 hospitalization, is their hospitalization shorter?
22 Have you had more survived? Have there been fewer
23 complications? I would agree with what other people
24 have said that one of the real problems with the
25 current data set is the issues, or the endpoints have

1 not been well defined. But that I would hope we could
2 come up with some kind of composite in that once you
3 know what the relevant amount of toxicity and the
4 relevant amount of efficacy is, then the physician can
5 make his own or her own conclusion as to whether
6 you're willing to accept a little less efficacy for a
7 little more safety.

8 So, I think a composite endpoint as an
9 indication of whether a strategy is more successful or
10 less successful would be desirable. Again, I think
11 that pre-defined endpoints for presumed and defined
12 fungi would go a long way to helping establish that.

13 CHAIRMAN HAMMER: Thank you.

14 Dr. Lipsky?

15 DR. LIPSKY: It seems that if you look at
16 principles here, what do we want with empirical
17 therapy, or what happens? Well, number one, we want
18 to understand what are the organisms that we are
19 empirically treating. Number two, whatever we treat,
20 we want to know that it works for each of those likely
21 organisms. And then finally, given that you know one
22 and then are doing two, does it all matter in
23 empirical therapy?

24 So, looking at that then, what does it
25 mean to really matter? Well, the ultimate means that

1 the patients are surviving and that you have a good
2 clinical outcome. That they're surviving and the only
3 difference -- if you were going to prove that, the
4 only difference that you did between group A and group
5 B is that you had antifungal therapy. So, what does
6 that mean? Well, it seems it could be relatively
7 simple. That first of all, you have survived. Good
8 clinical outcome? Well, some of those aspects have
9 been mentioned. Certainly, you could combine the
10 various systems of decrease in fever, decrease in
11 otherwise support, et cetera, et cetera, et cetera.

12 So, I don't think in the final analysis
13 that, you know, it's going to be too hard to come up
14 with things. The problem will be that it simply may
15 take a fair number of patients to prove that, and I
16 believe other workshops have wrestled with that
17 problem. But still, if one is going to go to the
18 effort to add a treatment in a particular clinical
19 situation, and that may be standard and become
20 important in what people do, then I think there is a
21 strong burden to do it well; to do it right.

22 CHAIRMAN HAMMER: Thank you.

23 Just a few additional comments which
24 mostly strike the consensus. I'll also start from the
25 third bullet point.

1 I think there were two issues to composite
2 endpoints. I would agree, and I think we're trying to
3 prove the point to separate efficacy and toxicity
4 events is important. Clinically, of course, we bring
5 those equations together on every treatment that we
6 administer. So, that's automatic and can be a
7 secondary component of an analysis. But if one is
8 bringing up primary objective and primary endpoints
9 together, I would separate those.

10 However, the composite endpoint here also
11 has a second meaning which is related to the efficacy
12 issues which were brought up both by the presentations
13 as well as by the sponsor in Sequus' presentation
14 today. That's a problem because you need to define
15 what that composite endpoint will be. You also need
16 to choose something for your sample size
17 determination. For example, probably defervescence,
18 however loose and difficult that is, may have to be
19 the endpoint one chooses to calculate a sample size.
20 But within that, one needs to also think about the
21 other issues that have been brought up, documented
22 fungal infections, suspected fungal infections,
23 survival hospital days, additional antibiotic use, et
24 cetera.

25 I don't have a problem -- in fact, I think

1 there's an absolute need, clinically, to have in a
2 clinical trial, a suspected fungal infection component
3 of a composite efficacy endpoint, and something also
4 to be looked at separately in a secondary way. But
5 that needs to be prospectively defined. We do this
6 all the time. It's problematic, but at least if it's
7 prospectively defined, there is some agreement on
8 that. Obviously, we recognize that this is a true
9 issue clinically. So, to ignore it within the context
10 of a clinical trial will separate the trial from real
11 world activity. Plus, I think it's important with
12 respect to supplementing the documented fungal
13 infection issues.

14 We were caught in a bit of a bind today as
15 a Committee because of whether a greater sample size,
16 in fact, would give you enough suspected and true
17 documented fungal infections as secondary endpoints
18 to, actually within this context of a trial, tell you
19 something. I think that's an open question and will
20 have to wait for more data.

21 I would also just modify or supplement the
22 second bullet point, the presence of defervescence,
23 the presence of antibiotic modification have been
24 brought up several times today. I think the issues of
25 plus or minus antibiotic modification, meaning, I

1 believe, antibacterial or other -- or non-antifungal
2 modification needs to be stratified for and looked at,
3 plus or minus imidazole prophylaxis which will be
4 evolving, and plus or minus GCSF are all issues,
5 particularly with regaining neutrophil counts that
6 will determine efficacy questions in this analysis.

7 So, I think we're down to basic issues in
8 clinical trial design and that is a prospective,
9 randomized control trials with enough pre-definitions
10 and pre-specifications that can stand up over time.

11 I think one other issue that needs to be
12 brought in here is adequate follow-up. I think one of
13 the issues that sort of came up today and was
14 difficult for the Committee to grapple with is what
15 was being followed up until what point? I think that
16 there can be definitions as to when the first follow-
17 up is limited, but I think a more extended follow-up,
18 not just until the treatment stops or white count
19 comes back, but X number of days or weeks thereafter,
20 to actually see what happens in the clinical evolution
21 and with survival over a month or two period is
22 important. So, I think adequate follow-up for
23 toxicity resolutions as well as for clinical follow-up
24 is a mandatory component of these. You can have an
25 immediate follow-up and an extended follow-up.

1 I also think one other point in future
2 trials that was brought up here is the issue of if you
3 start treatment and the culture is positive, that
4 those patients are then discounted. I agree with Dr.
5 Wong. This is presumptive therapy. This is not
6 prophylaxis of someone that you think everything is
7 fine and you are instituting antifungal therapy
8 empirically, even though you know it's a small
9 fraction of the individuals because of the fever which
10 you know is a manifestation that something is going on
11 with the patient. So, when a blood culture then comes
12 back positive, it should not be a great surprise that
13 in fact, you've found something.

14 I think what that requires from the
15 comments that were made earlier is that within the
16 context of such trials, you have enough flexibility in
17 follow-up management that, for example, if you need a
18 dose modification when a documented fungal infection
19 occurs, you can do it. You wouldn't be using these
20 drugs if you didn't think they had efficacy against
21 most of the pathogens that would be coming up. If a
22 pathogen comes up to what you know the antifungal
23 agent is ineffective, then of course, you discontinue
24 it. But if it is within the spectrum of organisms for
25 which you know you have either clinical data or in

1 vitro data, it would seem to me that what you want to
2 do is make sure you have the proper dose and see what
3 the effect will be. And that will, I think, only
4 enhance the efficacy analyses in trials such as this
5 in the future.

6 Those are my comments. I've tried to
7 bring some personal comments in also to somewhat reach
8 a consensus, although we don't all agree on each
9 point, of what the Committee has to say. If I've said
10 anything that anyone markedly disagrees with, now is
11 the time to amend it. If not, I would ask Dr. Feigal
12 if there are additional duties that we need to take
13 care of.

14 DR. FEIGAL: No. I'd like to thank you
15 very much.

16 CHAIRMAN HAMMER: Thank you.

17 This meeting is adjourned. Thank you.

18 I'd like to thank the sponsor and the
19 Agency.

20 (Whereupon, the meeting was concluded at
21 2:45 p.m.)

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