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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE
OPEN SESSION

Wednesday, July 16, 1997

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P R O C E E D I N G S

Call to Order

1
2
3 DR. HAMMER: Good morning. I would like to open
4 this session of the Antiviral Drugs Advisory Committee
5 Meeting. Today, we are here to consider the application of
6 AmBisome for the empirical treatment of febrile neutropenia.
7 I would like to welcome the sponsor, Fujisawa and begin by
8 having the members seated at the table introduce themselves
9 for the record. I will start with David.

10 DR. FEIGAL: Good morning. I am David Feigal,
11 FDA.

12 DR. GOLDBERGER: Mark Goldberger, FDA.

13 DR. MURRAY: Jeff Murray, FDA.

14 DR. HAMMERSTROM: Tom Hammerstrom, FDA.

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

17 DR. MATHEWS: Chris Mathews, U.C., San Diego.

18 DR. FEINBERG: Judith Feinberg, University of
19 Cincinnati.

20 DR. HAMMER: Scott Hammer from the Beth Israel
21 Deaconess Medical Center and Harvard Medical School in
22 Boston.

23 MS. STOVER: Rhonda Stover, FDA.

24 DR. LIPSKY: Jim Lipsky, Mayo Clinic.

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

3 DR. ELASHOFF: Janet Elashoff, Cedar Sinai Medical
4 Center and UCLA Medical Center.

5 DR. KAN: Virginia Kan, V.A. Medical Center,
6 Washington, D.C.

7 DR. HAMMER: Thank you.

8 I would like to turn, now, to Rhonda Stover who
9 will read the conflict of interest statement.

10 **Conflict of Interest Statement**

11 MS STOVER: The following announcement addresses
12 the issue of conflict of interest with regard to this
13 meeting and is made a part of the record to preclude even an
14 appearance of such at this meeting. Based on the submitted
15 agenda for the meeting and all financial interest reported
16 by the committee participants, it has been determined that
17 all interests in firms regulated by the Center for Drug
18 Evaluate and Research present no potential for a conflict of
19 interest at this meeting.

20 In the event the discussions involve any other
21 products or firms not already on the agenda for which an FDA
22 participant has a financial interest, the participants are
23 aware of the need to exclude themselves from such
24 involvement and their exclusions will be noted for the

1 record.

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

6 DR. HAMMER: Thank you.

7 Before getting to the business at hand, we are
8 going to have an informational digression. David is going
9 to assist the committee with understanding the
10 organizational changes that are at hand.

11 **Announcements**

12 DR. FEIGAL: Thank you. I am sorry I don't have
13 an overhead for this, but I think you have a transparency.
14 At one level, actually, the reorganization is relatively
15 simple. About three or four years ago, Dr. Woodcock began
16 looking at the large divisions that had gotten even larger
17 with the almost 400 positions that came into the Center for
18 Drugs User Fee Act.

19 Many of the divisions which had groupings of
20 products that had been put together for convenience like
21 Pulmonary and Oncology were split apart into separate
22 divisions to make them a little smaller and to flattening out
23 the structure of the Center for Drugs.

24 The two divisions in the Office of Drug Evaluation

1 IV, where I am the Office Director, were the two largest
2 divisions. The two of them combined actually were six times
3 larger than the smallest division. We began looking at ways
4 that we could reconfigure the division so that we would have
5 somewhat smaller divisions and also we could balance the
6 workload a little bit better.

7 The two divisions have different types of products
8 but there was a need for a little bit of adjustment. So
9 what we have done is we have take the Antiviral Division and
10 the Antiinfective Division and we have taken parts of both
11 and created a new division.

12 The Antiviral Division, as many of you know, had
13 not only antiviral products but also the types of
14 opportunistic infections that are common in patients with
15 immunocompromised states, the deep fungal infections,
16 microbacterial, other types of opportunistic infections,
17 some of which have been brought to this committee, and we
18 also had the transplantation products, again one of these
19 groupings that had to go somewhere. Since those patients
20 got our diseases, that seemed as logical as any place else.

21 The Antiinfective group has the traditional
22 products that people think of as antibiotics, antimicrobial
23 agents for bacterial pathogens. It also had all of the
24 parasitic and tropical diseases. So what we did with the

1 new division was that we left all the viruses in Antiviral
2 and we left the traditional bacterial indications in the
3 Antiinfective Division and we moved the opportunistic
4 infection and the parasitic diseases into the new division.

5 The new division also, for workload balancing,
6 took on the responsibility for the quinolone class of
7 antimicrobial agents. So there are now essentially three
8 divisions with the Office of Drug Evaluation IV which are
9 dealing with antiinfective products.

10 The division of labor is still somewhat arbitrary
11 but we hope it will help us balance some of the workload.
12 We do not anticipate creating a new advisory committee for
13 the new division. In fact, I think they are products that
14 could go to either this advisory committee or to the
15 Antiinfective Committee depending on the nature of the
16 problem and the similarity to other things, the expertise of
17 the committee.

18 Dr. Mark Goldberger who has introduced himself
19 this morning is the Acting Division Director of the new
20 division. The antifungal drugs are part of that division.
21 The other thing that you will notice on the organizational
22 structure is that we have taken advantage of the fact that,
23 while we are one of five new drug evaluation offices within
24 the FDA, we are the only one where all of our products are

1 very closely related.

2 We have taken advantage of that by creating some
3 matrix structures where we will have teams that will serve
4 all three divisions, draw on the resources of the three
5 divisions. These are modeled after successful programs or
6 programs that we hope to initiate.

7 The Antiviral group, for example, has had a pre-
8 IND program where they will provide consultation to a range
9 of types of IND holders from individual investigators who
10 have never taken out an IND and don't know how to do it to
11 large companies that are concerned about exactly what are
12 the steps that they need to get started with the first
13 trials in humans.

14 We will extend that pre-IND team not just to the
15 antiviral drugs but across all three divisions to the three
16 teams.

17 There is another team that deals with applications
18 in biopharmaceutics and clinical pharmacology. The purpose
19 this team is to take a look at the products that are based
20 very heavily on pharmacokinetic studies and chemistry and
21 manufacturing. These are often much smaller submissions
22 because they don't have the large bulky clinical data.

23 They are typically things that are commonly
24 referred to as product-line extensions. Although, from a

1 chemistry standpoint, they are often as complex as any other
2 new formulation, the evidence for their clinical
3 effectiveness is much more circumscribed and fast to review.

4 We wanted to actually highlight these products and
5 pull them out of the cue of the normal large NDAs because
6 this is where many of the pediatric products. Many of the
7 pediatric product-line extensions are here.

8 We would like to be able to work with industry to
9 speed up the clock on this and to have some dedicated
10 resources that will work on this particular area. We also
11 we have a team that cuts across all three divisions that
12 begins to more systematically build interactions between
13 many of the post-marketing functions including our
14 epidemiology and safety programs in the agency, the labeling
15 and promotion and the other kinds of things that happen
16 during the post-marketing period where labels frequently
17 need to be changed and updated.

18 Traditionally, this has been an area that has been
19 somewhat slow and not as affected by the User Fee Program.
20 If you look at the diagram, it is a little bit fussy and
21 busy. There are some other components on it, I think, that
22 are self-explanatory, but we hope to make the process as
23 transparent as possible. Many of the people that have moved
24 as products have gone to divisions have followed their

1 products so we anticipate there will be a fair amount of
2 continuity with that.

3 The final change that I would like to mention is
4 sort of a two-fold on a more personal note. One of them is
5 that Dr. Donna Freeman who has been with the FDA in the
6 Antiviral Drug Products for at least seven years, maybe it
7 is eight years, will actually be leaving government service
8 in September.

9 Because Donna has played a very important role as
10 the Acting Division Director for Antiviral Drug Products for
11 a fairly long period, I would like to thank her for having
12 served in that role.

13 As most of you know, we are actively recruiting
14 for new division directors for the new divisions. When we
15 did the reorganization, we weren't encumbered by having any
16 leadership at some of the levels in the organization. So it
17 allowed us to deal with a somewhat less territorial process
18 than when you have division directors in place. But now it
19 is time to get on to the business of the division directors.

20 The other announcement is that on September 1, I
21 will be moving to the Center for Biologic Evaluation and
22 Research as the Medical Deputy Director of the Center for
23 Biologics where I will be working in particular with blood
24 and vaccine products.

1 That was a difficult decision to make and, as most
2 of the division is tired of hearing me mention, one streak
3 that will eventually be broken is the fact that I have been
4 at the table of every meeting of this committee. I think
5 the count is around 30, having started as a committee member
6 before I joined the agency.

7 We had to get Fred Valentine out of the way for me
8 to have that record, but we succeeded in doing that. So
9 this is kind of a transitional period for us, but I think it
10 is going pretty smoothly. We look forward, particularly in
11 some of the areas where we are going to have a new emphasis,
12 to being able to improve on what is already some of the best
13 performance in the agency.

14 DR. HAMMER: Thank you. I think I can speak for
15 my colleagues. There will probably be a standing invitation
16 to future Antiviral Drug Products Advisory Committee
17 meetings.

18 Let's move on, then, to the official business. We
19 are going to start with some FDA introductory remarks by
20 Mark Goldberger.

21 **AmBisome (liposomal amphotericin B for injection)**

22 **Fujisawa USA, Inc.**

23 **Empirical Treatment of Febrile Neutropenia**

1 activity.

2 We believe that, based on the amount of
3 information available, at least from our perspective, it is
4 really not possible at present to define the level of this
5 activity vis-a-vis the comparator arm which was almost
6 invariably amphotericin B. So we will not be making any
7 statement about that, certainly at this meeting.

8 We have not completed any types of labeling
9 discussions with the company but we felt it would be helpful
10 for you, in your consideration of this application, to have
11 that information. We have also asked the applicant to
12 include in their presentation information about the
13 treatment uses of this product.

14 We have also included it in our background package
15 to you so you would have some perspective on that. Of
16 course, you are free during the discussion periods to ask
17 questions as you see fit regarding that issue.

18 We have requested in the past, several months ago,
19 your advice on this indication. We think, however, given
20 the clinical information that will be presented this
21 morning, it was, in fact, a reasonable thing to go ahead and
22 have this advisory committee which is, in no way, a
23 reflection on the quality of your advice several months ago
24 which we found to be quite good.

1 background, AmBisome is currently approved and marketed in
2 26 countries including the U.K., Germany, Sweden, Belgium
3 and Spain.

4 Fujisawa USA has licensed the rights to AmBisome
5 in the United States from NEXstar Pharmaceuticals,
6 Incorporated.

7 [Slide.]

8 Fujisawa is the sponsor of the AmBisome NDA which
9 was submitted to the Division of Antiviral Drug Products,
10 FDA, on November 8, 1996. The NDA was amended on April 25,
11 1997 with the final report of Study 94-0-002, a major U.S.
12 clinical study of the empirical indication. You will hear
13 much more about this study as the morning proceeds.

14 [Slide.]

15 The proposed indication for AmBisome to be
16 discussed this morning is empirical therapy for presumed
17 fungal infections in febrile neutropenic adult and pediatric
18 patients.

19 [Slide.]

20 Our presentation this morning will begin with an
21 overview of AmBisome and its unique liposomal structure.
22 This will be followed by a presentation by Professor Grant
23 Prentice from the Royal Free Hospital in London, England.

24 As Dr. Goldberger mentioned, at the April 14, 1997

1 meeting of this advisory committee, it was requested that
2 documentation of a product's ability to treat fungal
3 infections be included as a part of any presentation of the
4 use of the product in empirical treatment.

5 Both the FDA and we felt it is appropriate to
6 include the brief overview presentation on the use of
7 AmBisome to treat fungal infections and this will be the
8 subject of Professor Prentice' presentation this morning.
9 Professor Prentice has been a clinical investigator of
10 AmBisome and has been using AmBisome to treat patients for
11 several years.

12 Our presentation will conclude with Dr. Walsh
13 presenting the key results from the U.S. study of the
14 empirical indication involving nearly 700 patients. Dr.
15 Walsh, from the National Cancer Institute, was the principle
16 investigator for this U.S. study. This study was also
17 conducted in collaboration with the Mycosis Study Group of
18 the NIH.

19 As you may recall, during the meeting of this
20 advisory committee on April 14, of this year, Dr. Sugar
21 presented information documenting the use of traditional
22 amphotericin B as the standard of care in empirical
23 treatment. This topic, thus, will not be addressed this
24 morning.

1 stable bilayer. Note that cholesterol, a sterol found in
2 mammalian cell membranes, is part of the liposome. Small
3 cohesive liposomes with cholesterol escape initial complete
4 removal by the reticuloendothelial system and persist in the
5 circulation for prolonged periods.

6 In the AmBosome bilayer, the amphotericin B
7 molecules are bound in this stable membrane through
8 interaction with cholesterol as illustrated in the next
9 slide.

10 [Slide.]

11 This indicates the presence of amphotericin B
12 molecules held by hydrophobic and charge interactions in the
13 membrane. Because of this binding, there is very little
14 free amphotericin B available to cause toxicity as the
15 intact sphere circulates to the tissues of the body. This
16 stability has been shown by several different techniques.
17 Using size-exclusion columns, no unbound amphotericin B can
18 be detected.

19 It has also been found that the amphotericin B
20 molecules remain bound in the sphere when incubated for 24
21 hours in plasma.

22 [Slide.]

23 This slide shows the results of a hemolysis study.
24 Red cells were incubated with the drugs for two hours at

1 33 degrees Centigrade. Traditional amphotericin B at a
2 concentration of 1 mcg/ml causes 92 percent hemolysis while
3 AmBisome at 100 mcg/ml caused only 5 percent hemolysis.

4 [Slide.]

5 This slide shows the results of an experiment
6 designed to study the release of potassium from rat red
7 cells. The release of potassium provides a quantitative
8 measure of membrane damage. In this experiment, washed red
9 cells were incubated with increasing concentrations of
10 amphotericin B in the traditional formulation and as
11 AmBisome.

12 It can be seen that potassium release is delayed
13 by several orders of magnitude when the amphotericin B is
14 presented as AmBisome.

15 [Slide.]

16 We now turn our attention to the mechanism of
17 action of AmBisome.

18 [Slide.]

19 AmBisome is found to have activity in vitro
20 comparable to the traditional formulation of amphotericin B.
21 Several examples are presented here.

22 You can see treatment the inhibitory and
23 fungicidal concentrations are virtually the same. The
24 fungicidal activity of AmBisome is accomplished through the

1 interaction of the liposome with the fungal cell wall. This
2 mechanism is illustrated in the next two slides.

3 [Slide.]

4 The liposomes first attach to the surface of the
5 fungal cell.

6 [Slide.]

7 The amphotericin-B-containing liposome then loses
8 membrane integrity and the fungal cell is killed.

9 [Slide.]

10 The AmBisome spheres can be shown in vitro to
11 attach to the surface of both yeast and filamentous fungi.
12 This attachment also occurs with what we call empty
13 liposomes which do not contain amphotericin B.

14 In this electron micrograph, labeled empty
15 liposomes are seen against the intact fungal cell. The
16 black material is an electron-dense label incorporated into
17 the bilayer. These are the liposomes on the outside of an
18 intact fungal cell.

19 Following binding, the amphotericin-B-containing
20 liposome becomes disrupted and there is killing of the
21 fungal cell.

22 [Slide.]

23 This electron micrograph is from the experiment in
24 which AmBisome spheres are incubated with the fungal cells.

1 Here, AmBisome spheres have undergone disruption and lipid
2 material from the liposome is found inside the dead fungal
3 cell.

4 [Slide.]

5 The concentrations of amphotericin B found in the
6 circulation after AmBisome administration are substantially
7 higher than seen with conventional amphotericin B. This can
8 bring high concentrations of amphotericin B to the sites of
9 fungal infection.

10 [Slide.]

11 These plasma concentrations are from a rabbit
12 study in which animals with pulmonary aspergillosis were
13 treated with traditional deoxycholate amphotericin B at
14 1 mg/kg or AmBisome at doses of 1, 5 or 10 mg/kg. The
15 differences in concentrations of circulation amphotericin B
16 achieved are quite dramatic.

17 We have seen very similar serum concentration
18 patterns with increasing AmBisome doses in mice, rats and
19 dogs.

20 [Slide.]

21 These are serum-concentration time profiles of
22 amphotericin B measured in a Phase I, pharmacokinetic study
23 conducted by Fujisawa USA in febrile neutropenic patients.
24 The doses administered were 1, 2.5, 5 or 7.5 mg/kg/day. For

1 reference, shown here in grey, as the expected levels from
2 an administration of traditional amphotericin B at 1 mg/kg.
3 This reference concentration is based on the publication by
4 Heinemann in June, 1997, Antimicrobial Agents and
5 Chemotherapy.

6 In six patients receiving traditional amphotericin
7 B at 1 mg/kg, the maximum concentration ranged from 1.0 to
8 2.1 mcg/ml. AmBisome can result in levels that reach 50 to
9 100 times those achieved with the conventional drug. As one
10 increases the administered dose from 1 to 7.5 mg/kg, there
11 is a non-linear increase in serum concentration.

12 In our AmBisome animal pharmacokinetic studies,
13 even higher plasma concentrations of amphotericin B were
14 measured. However, a similar dose-related disposition
15 profile was observed. These results suggest that there is
16 some saturation of reticuloendothelial uptake so that more
17 AmBisome is found in the plasma compartment with higher
18 doses.

19 Despite these high circulating levels of
20 amphotericin B, there was no evidence of dose-related
21 toxicity including nephrotoxicity in this Phase I study.

22 [Slide.]

23 I can report that our dose-escalation efforts have
24 continued with a maximum tolerated dose study being

1 conducted in patients with infection with Aspergillus or
2 other filamentous fungi. Data have not yet been submitted
3 and reviewed by the FDA in this study.

4 In this ongoing study, doses of 10, 12.5 and
5 15 mg/kg of AmBisome have been successfully administered in
6 repeated daily doses. The maximum tolerated dose of
7 AmBisome has not been reached and patients have continued to
8 be entered on therapy at 15 mg/kg/day of AmBisome. We have
9 now entered a total of 20 patients at this high dose level.

10 [Slide.]

11 An extensive series of animal studies have been
12 performed looking at the efficacy and toxicology of
13 AmBisome. Many of these studies suggest that one can
14 achieve improved efficacy with AmBisome because of the
15 increased doses that can be administered safely.

16 [Slide.]

17 In this model system, granulocytopenic rabbits,
18 protected with antibiotics including aminoglycosides, have
19 experimentally inducted pulmonary aspergillosis. Groups of
20 rabbits were treated with traditional amphotericin B at
21 1 mg/kg/day and with AmBisome at doses of 1, 5 and
22 10 mg/kg/day.

23 You have just seen the serum concentration curves
24 from this animal experiment. Survival results in infected

1 rabbits that were treated with no antifungal, traditional
2 amphotericin B and increasing doses of AmBisome are
3 presented here. It is apparent that the treatments with
4 AmBisome result in substantially improved survival.

5 In this study, nephrotoxicity was seen with the
6 traditional drug at 1 mg/kg and with AmBisome at 10 mg/kg
7 but not with AmBisome at 1 or 5 mg/kg. As you can see,
8 AmBisome, at 5 mg/kg, resulted in 100 percent survival.

9 [Slide.]

10 These results are from an immunocompetent mouse
11 experiment in which animals were injected with Candida
12 organisms and treated two days later with a single dose of
13 amphotericin B or AmBisome at increasing doses. In this
14 model of systemic candidiasis, greater survival was obtained
15 with higher doses of AmBisome which were beyond those that
16 could be administered as conventional AmBisome.

17 Note at the higher AmBisome doses, the median
18 survival exceeded the completion of the experiment at
19 42 days. Also, six to eight of the eight animals in the
20 AmBisome groups survived compared to far fewer in the
21 amphotericin groups.

22 [Slide.]

23 When the drug administration was delayed until
24 three days after fungal inoculation, no amphotericin B

1 animals survived while good survival was seen at doses of
2 5 mg/kg or higher in the AmBisome groups.

3 [Slide.]

4 In this background overview of AmBisome, we have
5 stressed several features of this drug product.
6 Amphotericin B is firmly incorporated in the membrane layer
7 of the liposome. The ability to deliver increasing doses of
8 AmBisome results in high plasma concentrations of
9 amphotericin B. These high concentrations have been
10 demonstrated in patients and in multiple animal-model
11 experiments.

12 AmBisome attaches to the fungal cell and then
13 disperses with resultant fungal-cell killing. In animal-
14 model systems, AmBisome can be administered at higher doses
15 and shows improved efficacy beyond that possible with
16 traditional amphotericin B.

17 Little drug-related toxicity was seen with doses
18 up to 7.5 mg/kg/day administered to empirical-therapy
19 patients. Doses as high as 15 mg/kg have been administered
20 to patients with fungal infections.

21 [Slide.]

22 To complete this overview presentation, I will
23 briefly mention the U.S. studies which are listed on this
24 slide. I have already discussed the Phase I pharmacokinetic

1 study. In the MTD study that I mentioned, 15 mg/kg has been
2 given to adults subjects and we are currently performing a
3 similar study in children and have successfully administered
4 7.5 mg/kg.

5 Study 94-0-002 is the pivotal empirical-therapy
6 trial which is the focus of today's discussion. Study MSG
7 29 and Study 94-0-013 are comparative, double-blind trials
8 of AmBisome and traditional amphotericin B in AIDS patients.
9 Both are currently active.

10 Over 40 patients have been enrolled in the
11 histoplasmosis study which is being conducted by the Mycosis
12 Study Group. Over 220 patients have been enrolled in the
13 cryptococcal meningitis study. An open-label trial is
14 available for patients who require antifungal therapy with
15 amphotericin B and whose physicians have selected AmBisome
16 as an appropriate therapy.

17 Many of these patients have had poor tolerance or
18 poor response to other amphotericin-B formulations.

19 I thank you for your attention. The next
20 presentation on the therapeutic use of AmBisome will be by
21 Professor Grant Prentice of the Royal Free Hospital, London.

22 **Treatment of Fungal Infection**

23 DR. PRENTICE: Good morning Chairman, members of
24 the committee, ladies and gentlemen. My name is Graham

1 Prentice. Actually, my full name is Hugh Grant Prentice. I
2 guess this was another modification made by Fujisawa at the
3 last moment.

4 I am a clinical hematologist. My main interest is
5 in the management of hematological malignancies. I have a
6 major interest in the application of cytokines in the
7 developments of leukemia vaccines but I have a longstanding
8 interest in the prevention and treatment of infections in
9 the neutropenic patient.

10 I am head of a large department of hematology in
11 London. We now have nine years experience in the use of
12 AmBisome. We have treated in excess of 600 patients with
13 this drug.

14 [Slide.]

15 The initial experience in treatment of fungal
16 infections with AmBisome came through a compassionate-use
17 protocol. This was performed in Europe between November
18 1988 and February 1990. The categories of patients enrolled
19 in the study are shown in the following slide.

20 [Slide.]

21 Patients with a diagnosis of invasive fungal
22 infection were eligible to receive AmBisome under protocol
23 10-400 if they had failed treatment by conventional
24 amphotericin B, if they had developed nephrotoxicity as a

1 consequence of amphotericin B therapy or if they had
2 preexisting renal insufficiency that contraindicated the use
3 of amphotericin B.

4 A total of 140 episodes of fungal infection in 133
5 patients was treated under this study.

6 [Slide.]

7 This slide presents the clinical responses
8 recorded by the investigators. Clinical success was good
9 regardless of the reason for enrollment. Almost half of the
10 patients enrolled due to amphotericin B failure were cured.
11 62 percent of patients enrolled due to amphotericin B
12 nephrotoxicity were cured and 70 percent of patients entered
13 with renal insufficiency were cured.

14 [Slide.]

15 The investigators also provided mycological
16 assessments of the rates of eradication of specific types of
17 fungal infection. The results for the three major pathogens
18 are presented here. AmBisome was effective as rescue
19 therapy for the broad spectrum of patients who had a need
20 for treatment with amphotericin B but were precluded from
21 receiving the conventional formulation.

22 As a result of these studies, AmBisome was
23 approved for rescue use in the United Kingdom, many
24 countries in continental Europe and elsewhere. AmBisome

1 first became available for study in 1988. Since approval in
2 the early 1990s, it is estimated that over 25,000 patients
3 have been treated with this formulation.

4 In addition to this compassionate use experiment,
5 a number of experiments have been conducted which allow us
6 to examine the role of AmBisome in the treatment of invasive
7 aspergillosis, candidiasis and cryptococcosis. I shall now
8 deal with these.

9 [Slide.]

10 Data are available on 134 episodes of
11 microbiologically confirmed invasive aspergillosis. In
12 addition to the compassionate use experiment just shown, the
13 data are extracted from three other trials outlined in the
14 following slide.

15 [Slide.]

16 The largest of these trials was a randomized study
17 which compared two doses of AmBisome, 1 or 4 mg/kg/day.
18 This trial was performed by the European Organization for
19 Research and Treatment of Cancer, the major European cancer
20 trials organization.

21 The other two studies noted were randomized
22 comparative trials of AmBisome versus amphotericin B as
23 treatment of confirmed mycoses. The overall results in
24 trials that entered patients with confirmed invasive

1 aspergillosis are presented in the following slide.

2 [Slide.]

3 Therapy was considered a clinical success if the
4 patient survived the infection and had clinical cure or
5 improvement. The overall clinical-response rate was 85 of
6 134 episodes, or 63 percent. Because of the invasive
7 procedures involved, repeat mycology was less often
8 obtained.

9 However, it can be seen that amongst evaluable
10 patients, the mycological eradication rate is 52 percent.
11 Both results are quite good from what one has come to expect
12 in treating aspergillosis. There is one point from this
13 experiment that is worthy of mention. In the EORTC study,
14 success was seen both at the 1 mg and at the 4 mg/kg/day
15 dose.

16 This is reminiscent of responses seen at these
17 doses in animal models.

18 [Slide.]

19 Once there has been more of a focus on the
20 management of Aspergillus infections, invasive candidiasis
21 has also been successfully treated with AmBisome. The
22 numbers in the following slide represent either candidemias
23 in compromised hosts or biopsy-proven cases and do not
24 include urinary infections or gastrointestinal candidosis.

1 [Slide.]

2 The clinical success rate is 84 percent.
3 Mycological eradication was documented in 79 percent of
4 cases. Now, while candidiasis is not often the subject of
5 anecdotal or case reports, it is interesting to note that in
6 Europe, a number of reports of successful treatment of
7 disseminated candidiasis and of aspergillosis have been
8 recorded in premature and low birth-weight infants.

9 [Slide.]

10 Among the life-threatening mycoses, cryptococcal
11 meningitis offers one of the best opportunities to correlate
12 clinical response with mycological eradication because the
13 cerebrospinal fluid can be resampled. As a result, it has
14 been possible to compare therapeutic regimens with respect
15 to conversion of fungal cultures from positive to negative.

16 [Slide.]

17 In this infection, AmBisome appears most
18 promising. Not only are the overall clinical and
19 mycological success rates quite good, but the hallmark of
20 AmBisome treatment has been the rapidity of culture
21 conversion within one to three weeks from the start of
22 therapy.

23 This may relate to the doses administered which
24 have been from 3 to 4 mg/kg/day for AmBisome. By contrast,

1 the dose of conventional amphotericin B that can be
2 administered has been of the order of 0.7 mg/kg/day.

3 [Slide.]

4 This rather complex slide presents the rates of
5 culture conversion at three weeks. For AmBisome, in fact,
6 already at one week, six of these patients had converted to
7 negative culture. It also presents the overall success rate
8 at ten weeks and, of course, these patients received three
9 weeks of either AmBisome or amphotericin B followed by
10 fluconazole maintenance therapy.

11 This trial was conducted both in the Netherlands
12 and in Australia. The results are filed in the NDA. They
13 were also presented at the recent ICAC conference and will
14 soon appear in the literature.

15 The standard of therapy for this disease has
16 become two to three weeks of amphotericin B induction
17 therapy followed by oral fluconazole consolidation and
18 maintenance therapy. These results suggest that AmBisome
19 may become the preferred option for initial therapy.

20 [Slide.]

21 This slide lists a number of less frequently
22 encountered fungal species for which there have been reports
23 of successful therapy with AmBisome. These reports suggest
24 that the full spectrum of activity of amphotericin B has

1 been retained in the liposomal product.

2 [Slide.]

3 In Europe, we have completed two studies comparing
4 AmBisome and amphotericin B as empirical therapy in febrile
5 neutropenic patients nonresponsive to four days of broad-
6 spectrum antibiotic therapy.

7 One of these studies, 104-10, included 134 adult
8 patients. The second trial, Study 104-14, involved 205
9 pediatric patients. A summary of the results of these
10 trials can be found in your briefing document. These
11 studies were open-label and had smaller enrollments than are
12 now considered optimal.

13 They do, however, provide support evidence that
14 AmBisome can be successfully utilized for empirical therapy.

15 [Slide.]

16 I have made the following points this morning.
17 AmBisome can successfully treat patients with invasive
18 mycosis who cannot receive standard amphotericin B therapy.
19 Furthermore, AmBisome has verified therapeutic efficacy
20 against aspergillosis, candidiasis and cryptococcosis.

21 [Slide.]

22 AmBisome has been widely used in Europe and in
23 other countries throughout the world. The data which have
24 been presented thus far and those which will be presented by

1 increased morbidity and mortality in this very vulnerable
2 patient population.

3 [Slide.]

4 The rationale for empirical antifungal therapy is
5 to provide early therapy for undiagnosed fungal infections
6 or systemic prophylaxis for high-risk patients.

7 Amphotericin B is currently the drug of choice despite its
8 toxicity profile.

9 A lipid formulation of amphotericin B may provide
10 a better option of reducing toxicity while preserving
11 antifungal efficacy.

12 [Slide.]

13 Two workshops were sponsored by the Food and Drug
14 Administration in 1994 and 1995 leading to the
15 recommendation of a study design for evaluating liposomal
16 antifungal agents for empirical antifungal therapy in
17 persistently febrile neutropenic patients.

18 [Slide.]

19 These workshops lead to the recommendation that
20 the study should compare a lipid formulation of amphotericin
21 B versus traditional amphotericin B, that the study should
22 be a double-blinded, randomized equivalence trial, that the
23 study should utilize a direct confidence-interval approach
24 for efficacy and, finally, that resolution of fever alone

1 was inadequate as a primary endpoint.

2 [Slide.]

3 These findings lead to a randomized, double-blind
4 multicenter trial of AmBisome versus traditional
5 amphotericin B in what is known as the pivotal trial 94-0-
6 002. This study was designed according to the
7 recommendations of the aforementioned FDA-sponsored
8 meetings. It was also developed in collaboration with the
9 National Institute of Allergy and Infectious Diseases,
10 Mycosis Study Group, and involved 32 centers.

11 [Slide.]

12 The trial design was double-blind and randomized 1
13 to 1. The inclusion criteria included ages 2 to 80 years,
14 chemotherapy, absolute neutrophil count less than 500, a
15 fever greater than 38 degrees Centigrade, broad-spectrum
16 antibacterial therapy for more than 96 hours and, finally, a
17 serum creatinine less than twice the upper limit of normal.

18 [Slide.]

19 The sample size determination was based on an
20 anticipated febrile response rate of 70 percent for
21 amphotericin B. The study had an 80 percent statistical
22 power to determine differences of 10 percent within a
23 95 percent two-sided confidence interval. Such a study
24 design required 330 evaluable patients per treatment group.

1 [Slide.]

2 Patients were stratified by center as well as by
3 risk factor. Patients were divided into low-risk and high-
4 risk groups, among the high-risk-group patients who had
5 received prior empirical amphotericin B, the presence of
6 allogeneic bone-marrow transplantation and those who had
7 relapsed acute leukemia.

8 [Slide.]

9 This study design was for patients to be treated
10 initially with the standard dosage of AmBisome seen here at
11 3 mg/kg/day and amphotericin B at 0.6 mg/kg/day. Following
12 appropriate guidelines with in the protocol, dosages may
13 have been elevated to intermediate dosages, as indicated
14 here, at 4.5 mg/kg of AmBisome and 0.9 mg/kg of amphotericin
15 B, or at 6 mg/kg of AmBisome or 1.2 mg/kg of amphotericin B
16 in the high dosage.

17 Should the patient develop toxicity, lowered
18 dosages of such drug were permitted at 1.5 and 0.3 mg/kg
19 respectively as seen in the left column.

20 [Slide.]

21 Patients continued on antifungal therapy until
22 neutrophil recovery and up to three days after recovery.
23 Patients were permitted to remain on study for a maximum of
24 42 days unless a positive fungal infection by culture was

1 obtained. The duration of therapy with confirmed fungal
2 infection was for 14 days following a negative culture.

3 [Slide.]

4 Success was determined using a composite endpoint.
5 All of the following were required to occur; survival for
6 seven days after study drug, resolution of fever during the
7 neutropenic period, resolution of microbiologically
8 confirmed study entry fungal infection, no proven or
9 presumed fungal infections during drug therapy or within
10 seven days after the last dosage of study drug and, finally,
11 study drug was not prematurely discontinued due to toxicity
12 or lack of efficacy.

13 In addition, the primary composite endpoint,
14 secondary efficacy variables included in incidence of proven
15 emergent fungal infections.

16 [Slide.]

17 In assessing safety parameters, the overall
18 incidence of adverse events, incidence of Grade 3 or Grade 4
19 toxicity, infusion-related reactions, nephrotoxicity,
20 hypokalemia and hepatotoxicity were specified in the
21 protocol for evaluation.

22 [Slide.]

23 In assessing infusion-related reactions during the
24 infusion of blinded study drug or within one hour of

1 infusion, the following parameters were monitored
2 prospectively; fever spike, chills, rigors, nausea, vomiting
3 and other reactions including cardiorespiratory events.

4 [Slide.]

5 We will now address the results of the study by
6 first examining the patient population.

7 [Slide.]

8 347 patients were enrolled onto the AmBisome arm
9 and 355 onto the amphotericin B arm. A modified intent-to-
10 treat analysis was performed on the 343 AmBisome and 344
11 amphotericin-B-treated patients who were randomized and
12 received at least one dose of study drug.

13 Patients were equally stratified as high risk, 117
14 and 119, respectively, and low risk, 226 and 225,
15 respectively.

16 [Slide.]

17 Treatment groups were comparable for age including
18 patients 2 to less than 13 years, 13 to less than 65 years,
19 and greater than or equal to 65 years of age. Treatment
20 groups were also comparable for sex and race. It is a
21 strength in our study that enrollment included more than
22 10 percent pediatric patients and approximately 12 percent
23 elderly patients.

24 In addition, nearly half of the patients in each

1 treatment group were women.

2 [Slide.]

3 Among the patient characteristics, patients were
4 equally distributed for bone-marrow transplantation and for
5 chemotherapy. Approximately one-third of the bone-marrow
6 transplantation were allogeneic and two thirds were
7 autologous. Patients were also equally distributed for
8 solid tumors and for hematological malignancies including
9 leukemia and lymphoma.

10 [Slide.]

11 In assessing patients undergoing premature
12 discontinuation, there was a relatively equally frequency of
13 discontinuation, 26 percent on AmBisome, 29 percent
14 amphotericin B. However, there was a significant reduction
15 in the frequency of premature discontinuation due to
16 infusion-related reactions in AmBisome at 2 percent versus
17 amphotericin B at 6 percent.

18 [Slide.]

19 Efficacy was assessed using the composite endpoint
20 of success as well as its five components. The overall
21 success rate of AmBisome versus amphotericin B using the
22 composite endpoint was similar and approximately 50 percent
23 on each arm.

24 [Slide.]

1 The results were also similar between AmBisome and
2 amphotericin B for each parameter of success including
3 survival through seven days post study drug, fever resolving
4 during the neutropenic period, premature discontinuation of
5 study drug due to toxicity or lack of efficacy and
6 resolution of baseline fungal infections.

7 However, there was a difference between the
8 presence of proven emerging fungal infections which we will
9 discuss at greater length. The parameter here on the third
10 line reflects both proven and presumed invasive fungal
11 infections.

12 [Slide.]

13 The confidence intervals for overall success,
14 survival and fever resolution during neutropenia are
15 presented here. These are tightly confined within 10
16 percent. For the parameter of overall success, the
17 confidence interval demonstrates that AmBisome may be from
18 6.8 percent less to 8.2 percent more effective than the
19 traditional amphotericin B using the composite endpoint.

20 [Slide.]

21 As shown here by the 95 percent confidence
22 intervals, the therapeutic equivalence between AmBisome and
23 amphotericin B was independent of the patient's age and risk
24 factor and was also independent of whether the patient

1 received baseline antifungal prophylaxis or recombinant
2 colony-stimulating factors.

3 The bottom axis depicted here reflects the
4 breakdown farther of adults versus pediatrics, high-risk
5 versus low risk, baseline antifungal prophylaxis and no
6 baseline antifungal prophylaxis, recombinant colony-
7 stimulating factors and no recombinant colony-stimulating
8 factors.

9 [Slide.]

10 We have established the equivalence of AmBisome
11 and amphotericin B based upon the composite endpoint of
12 success. We will now shift our attention to a discussion of
13 proven emergent breakthrough fungal infections. The
14 protocol specified the incidence of emergent fungal
15 infections as an efficacy endpoint.

16 It has been estimated that as many as one-third of
17 neutropenic patients who remain febrile despite broad-
18 spectrum antibiotic therapy will, if untreated, have a
19 documented invasive fungal infection.

20 [Slide.]

21 This next slide indicates the effects of using
22 empirical antifungal therapy in this setting. The left
23 histogram demonstrates the group at potential risk for
24 invasive fungal infection. As demonstrated in the right

1 histogram, we would expect that some of these patients will
2 have no manifestations of fungal infection as shown in
3 green.

4 We would also expect that some may develop
5 clinical evidence of fungal infection which was not
6 microbiologically or histologically confirmed. These will
7 be patients with presumed fungal infections.

8 Finally, even with a potent drug such as
9 amphotericin B, some patients will still have the emergence
10 or breakthrough of a proven fungal infection shown here in
11 red. In this randomized study, the absence of an emergent
12 fungal infection was one of the criteria for success. The
13 criteria for diagnosis of a proven fungal infection were
14 specified in the protocol.

15 These criteria were developed with input from
16 experts in antifungal therapy, from the investigators and
17 from the FDA medical reviewers. The purpose of specifying
18 these criteria was to insure proper documentation of
19 invasive fungal infections in this study population.

20 The blinded investigators were asked to indicate
21 whether a fungal infection was proven or presumed on the
22 study case-report forms. It became apparent that there were
23 more proven emergent fungal infections designated in the
24 amphotericin B group. Conversely, there were more presumed

1 infections on AmBisome.

2 We, therefore, reviewed all the emergent fungal
3 infections using the strict protocol criteria for proven
4 infections.

5 [Slide.]

6 This slide demonstrates the infecting fungal
7 species for the blinded investigator-designated proven
8 infections, 16 patients in the AmBisome arm and 32 patients
9 in the amphotericin B arm. Some of the emergent fungal
10 infections designated by the investigators as proven did not
11 appear to meet the strict protocol-specified criteria for
12 proven infection.

13 Because of this, and, in addition to our
14 interpretation, we requested that all fungal infections
15 listed as emergent by the investigators be reexamined in a
16 blinded, independent evaluation. This evaluation, using the
17 strict protocol-specified criteria, was performed by Dr.
18 John Wingard of the University of Florida at Gainesville.
19 Dr. Wingard was not a participant in this study.

20 I will now present how the emergent fungal
21 infections were further analyzed based upon the strict
22 protocol-defined criteria.

23 [Slide.]

24 The independent reviewers blinded reclassification

1 for the AmBisome group is presented in this slide. Six
2 infections were reclassified from proven to presumed.
3 Positive urine or stool culture, or the recovery of Candida
4 species from bronchoalveolar lavage fluid was not considered
5 definitive.

6 For sinus aspergillosis, nasal culture also was
7 not considered definitive. The independent reviewer also
8 examined all presumed infections in the AmBisome group.
9 This review of the presumed emergent fungal infections in
10 the AmBisome group did not reveal any additional proven
11 invasive fungal infections.

12 As a result of this analysis, the AmBisome group
13 was determined to have ten patients with proven emergent
14 breakthrough invasive fungal infections.

15 [Slide.]

16 This slide presents the results of the blinded
17 review of this amphotericin B group. Six infections were
18 reclassified from proven to presumed. This, again, was due
19 to the lack of definitive cultures or histology.

20 The review of the investigator-designated presumed
21 emergent fungal infections in the amphotericin B group did
22 not reveal additional proven fungal infections. As a result
23 of this analysis, the number with proven invasive fungal
24 infections in the amphotericin B group is now 26 patients.

1 [Slide.]

2 This slide presents the analysis of all patients
3 with infections designated as presumed by the investigators.
4 None of the reported presumed infections meet the criteria
5 for proven infection. However, an additional six patients
6 in each treatment group were reclassified to presumed from
7 the proven category.

8 Some of the patients had a separately diagnosed
9 proven infection in addition to their presumed infection.
10 Therefore, these patients were already included under the
11 proven category. The remaining are patients with only
12 presumed fungal infection.

13 [Slide.]

14 In the advisory committee's briefing document,
15 three reviews of proven emergent fungal infections are
16 presented; the investigator's review, the sponsor's review
17 and Dr. Wingard's independent review, all of which were
18 blinded. The results of the sponsor's review and the
19 independent blinded review were similar. Therefore, we are
20 summarizing only the investigator's and the independent
21 reviewer's assessments.

22 [Slide.]

23 As indicated on this slide, 16 patients in the
24 AmBisome arm versus 32 patients in the amphotericin B arm

1 had investigator-designated proven fungal infections for a
2 p-value of 0.021 by Cochran Mantel Haenszel chi square. The
3 blinded review using the strict protocol criteria
4 demonstrated 10 in the AmBisome arm versus 26 in the
5 amphotericin B arm for a p-value of 0.007.

6 [Slide.]

7 The sites of infection for these invasive mycoses
8 accepted as proven by the protocol criteria are presented
9 here. There were three instances of candidemia during
10 AmBisome therapy versus 12 during traditional amphotericin B
11 therapy. There were four instances of documented
12 breakthrough invasive respiratory aspergillosis for AmBisome
13 versus 9 for traditional amphotericin B.

14 For the key pathogens, Candida and Aspergillus,
15 the numbers are clearly lower for AmBisome. The less
16 frequent infections are also shown, Fusarium, Mucor,
17 Cryptococcus and Ulocladium.

18 [Slide.]

19 This slide now returns to our original construct
20 of possible outcome of empirical therapy. It can be seen
21 that AmBisome is more effective in preventing proven
22 invasive fungal infections. However, both drugs have
23 reduced the number of emergent infections from the 30
24 percent that would be expected in the absence of therapy.

1 [Slide.]

2 I would like to now address the issue of survival
3 outcomes for these patients.

4 [Slide.]

5 There was a trend toward a reduction in the number
6 of deaths on AmBisome, 25 versus 36 on amphotericin B.
7 However, this difference was not statistically significant
8 with a p-value of 0.143.

9 [Slide.]

10 There also was a difference in the frequency of
11 fungal infections as a primary or contributing cause of
12 death with 4 in the AmBisome arm versus 11 in amphotericin
13 B.

14 [Slide.]

15 These data relate death rates to invasive fungal
16 infection. As might be anticipated, patients with no
17 evidence of fungal infection had the lowest rate of death.
18 This was 6 percent for both study groups. Patients with
19 presumed fungal infections had a 15 and 29 percent mortality
20 respectively on AmBisome versus amphotericin B.

21 Patients with proven fungal infections had the
22 highest mortality; 33 percent versus 46 percent respectively
23 on AmBisome versus amphotericin B. In both the presumed and
24 the proven fungal-infection categories, there were lower

1 rates of death in the AmBisome group.

2 [Slide.]

3 In the next two slides, the fungal-related deaths
4 are listed for the emergent fungal-infection groups, proven
5 and presumed. Two of the four fungal-related deaths in
6 AmBisome were in patients with proven fungal infections.
7 Nine of the 11 fungal-related deaths for amphotericin B were
8 also in the proven-infection group. The species and sites
9 of infections related to death are also given here.

10 [Slide.]

11 The other two fungal-related deaths in each group
12 occurred in patients with presumed fungal infections. The
13 sites and causative species are again listed.

14 [Slide.]

15 We will now turn our attention to safety.

16 [Slide.]

17 Three different categories of adverse events were
18 prospectively defined and recorded on separate case-report
19 forms. These categories were infusion-related reactions,
20 non-fungal infections and non-systemic fungal infections,
21 and all other toxicities.

22 [Slide.]

23 This slide demonstrates the frequency of severe
24 Grade 3 or Grade 4 toxicity from any of these adverse-event

1 categories. There was a significant reduction in the
2 overall incidence of these events as well as in the
3 incidence as indicated here of chills, fever, dyspnea,
4 nausea and vomiting in the AmBisome arm versus the
5 amphotericin B arm. All other events had similar frequency.

6 [Slide.]

7 As noted previously in the presentation, infusion-
8 related reactions were prospectively defined as adverse
9 events; fevers, chills, rigors, nausea, vomiting, et cetera
10 which occurred during study-drug infusion or within one hour
11 of completion of study-drug infusion. It is important to
12 emphasize that patients were not premedicated prior to the
13 initial infusion of study drug.

14 The primary physician had the option of
15 premedicating on subsequent infusions or treating patients
16 who developed infusion-related toxicity during the course of
17 the drug administration.

18 [Slide.]

19 This slide demonstrates significantly fewer
20 febrile responses in AmBisome versus amphotericin B on the
21 Day 1 of infusion. Please note that the differences were
22 observed using several different fever-spiked criteria as
23 indicated here at greater than 0.3 degrees Centigrade,
24 greater than or equal to 0.6 degrees Centigrade and greater

1 than or equal to 1 degree Centigrade.

2 [Slide.]

3 Also, as indicated, there were significantly fewer
4 incidences of chills and rigor as well as other reactions
5 with AmBisome which we will detail farther.

6 Reduction in the incidence of infusion-related
7 events were further seen in the subgroup of children less
8 than 13 years of age including a reduction in the incidence
9 of fever spikes, chills and rigor, nausea and vomiting and
10 other reactions. There also was a reduction of patients
11 receiving premedication on subsequent infusions in 176
12 AmBisome recipients versus 251 amphotericin B recipients.

13 These reductions included, as indicated here,
14 reductions in the use of acetaminophen, diphenhydramine,
15 meperidine, hydrocortisone and lorazepam.

16 [Slide.]

17 The increased use of meperidine and hydrocortisone
18 in patients using amphotericin B is further apparent when we
19 examine the total number of doses administered. It can be
20 seen also that these agents were used in only 4 percent and
21 7 percent of AmBisome infusions respectively.

22 [Slide.]

23 In assessing the nonfebrile infusion-related
24 reactions during all infusions, there was a substantially

1 lower overall incidence of these events as well as fewer
2 patients with chills and vomiting in the AmBisome versus the
3 amphotericin B arm.

4 Of note, there were more patients who sustained a
5 flushing or vasodilatation reaction on the AmBisome arm
6 versus the amphotericin B arm at 5.2 percent versus
7 0.6 percent.

8 [Slide.]

9 This slide shows a constellation of
10 cardiorespiratory events including dyspnea, hypotension,
11 tachycardia, hypertension and hypoxia. These infusion-
12 related events were significantly less frequent in the
13 AmBisome versus the amphotericin B arm.

14 [Slide.]

15 There also was a significant reduction in the
16 incidence of nephrotoxicity as defined by a 1.5 times or
17 2 times increase from baseline in creatinine in AmBisome
18 versus amphotericin B. There was also a significant
19 reduction in the frequency of hypokalemia but no difference
20 in the frequency of hepatotoxicity.

21 [Slide.] In this patient population, potentially
22 nephrotoxic agents are frequently prescribed. The lower
23 incidence of nephrotoxicity on AmBisome is seen in patients
24 administered increasingly additional nephrotoxic drugs as

1 one proceeds from 0 or 1 medication, 2 concomitant
2 nephrotoxic agents or greater than 3 nephrotoxic agents.

3 [Slide.]

4 In patients undergoing allogeneic bone-marrow
5 transplantation, an immunosuppressant with nephrotoxic
6 potential is often required. The lower incidence of
7 nephrotoxicity for AmBisome and amphotericin B is shown here
8 for this subgroup of patients.

9 [Slide.]

10 There were fewer patients in the AmBisome arm who
11 discontinued drug due to an infusion-related adverse event.
12 Fewer patients in the AmBisome arm had their dose reduced
13 due to either a non-infusion-related adverse event or an
14 infusion-related adverse event.

15 As treating physicians, we have long been
16 concerned about the frequent need to interrupt or
17 discontinue amphotericin B in these high-risk patients. It
18 is likely that the efficacy benefits of AmBisome
19 demonstrated in this study are due both to the higher
20 dosages administered and to the lessened need to reduce
21 dosages.

22 [Slide.]

23 In summary, this randomized, double-blind,
24 controlled trial of AmBisome versus amphotericin B

1 demonstrated that AmBisome was equivalent to amphotericin B
2 using a composite endpoint. AmBisome was more effective in
3 preventing proven invasive fungal infections and fungal-
4 infection-related deaths.

5 This study also demonstrated that AmBisome was
6 significantly less nephrotoxic, was associated with fewer
7 cardiorespiratory adverse events, was associated with fewer
8 severe adverse events and had significantly reduced
9 infusion-related toxicity.

10 I thank you for your attention.

11 DR. HAMMER: Thank you very much for a very clear,
12 efficient presentation.

13 We are running a little ahead of schedule so it
14 gives us the opportunity, I think, now to take a few minutes
15 for questions for the sponsor's presentation. We will have
16 some time to return to this later. I was wondering if there
17 are immediate questions.

18 DR. FEINBERG: I have a question about the study
19 design in terms of what was done with the dosing. It was
20 stated that the doses could be increased per protocol from
21 initial doses of 3.0 mg/kg for AmBisome or 0.6 mg/kg for
22 amphotericin B. But you didn't indicate what decision-
23 making drove these increases.

24 It was made clear that decreases were for toxicity

1 and I don't believe the data showed whether patients
2 actually did have their doses increased or decreased. So I
3 wonder if you could speak to that.

4 DR. BUELL: Yes. When we were constructing the
5 protocol and we had all of the participating sites there in
6 the protocol design, they requested an option to be able to
7 increase the dose within the blinded study either by a
8 50 percent or 100 percent amount.

9 The decision was based, basically, on their
10 clinical concern or estimate for the patient, the way they
11 might treat a patient if they were treating with
12 amphotericin B in the ordinary circumstance. If they saw
13 pulmonary infiltrates or something that troubled them, they
14 might make a decision to increase the dose to the point
15 where it is tolerated by the patient.

16 So it was really the investigator's clinical
17 judgement. We did set one criterion for recommending the
18 reduction and that was based on nephrotoxicity. But they
19 could either interrupt or reduce the dose or they might
20 interrupt for a few days and start at the lower dose if they
21 were encountering toxicity problems, all within the blinded
22 study.

23 DR. FEINBERG: So do you have data, then, on how
24 many patients in each group were, in fact, either dose-

1 increased or dose-reduced?

2 DR. BUELL: Yes. Can we see the last 3-day slide?

3 In both groups, it was blinded and so the investigators
4 didn't know which drug the patient was on. But, in both
5 groups, there was some raising of dosage and in both groups,
6 there was some lowering.

7 [Slide.]

8 This reflects whether they were on standard,
9 intermediate or high doses on average during the last three
10 days of receiving study drug. It is one way we have of
11 representing this. You can see that there were somewhat
12 more patients on AmBisome, in yellow, on intermediate and
13 high doses and a bit more on amphotericin B that had been
14 reduced to the lower dose.

15 Let me just add that Dr. Walsh did show, in one of
16 his last slides, that we looked at the number of times the
17 dose was reduced or interrupted and that was greater in the
18 amphotericin B arm.

19 DR. WONG: I am interested by the difference you
20 find in proven versus presumed fungal infections. Nowhere
21 in the briefing book or presentation today did you define
22 these terms precisely for us. So I was wondering if you
23 would do that. And then, kind of follow ups to that, how
24 many patients in each group had autopsies and how many

1 patients in whom it was decided had proven infections would
2 have been classified as presumed infection had they not had
3 autopsies?

4 DR. BUELL: The autopsies were done in a limited
5 number of patients. In the sponsor's review, we noted two
6 patients who had the findings of invasive fungal infection
7 at autopsy that were done outside the seven-day cutoff for
8 the study. I included those two as proven infections in the
9 sponsor's analysis.

10 DR. WONG: Could you define for us what proven
11 infection is as opposed to presumed infection?

12 DR. BUELL: Yes. That took three pages of an
13 appendix to the protocol. The one that was most completely
14 detailed was for the pulmonary infections where, for
15 Aspergillus, you had to have the clinical picture and you
16 had to have a positive biopsy or a positive recovery by
17 bronchoalveolar lavage. It would be similar for other
18 filamentous fungi.

19 For candidiasis, the recovery of Candida organisms
20 from a BAL was not considered definitive and that would have
21 required transbronchial biopsy or other biopsy to show the
22 presence of the infection. So that is for pulmonary.

23 Candidemias are clear. You had to have the
24 positive cultures. For other sites such as disseminated or

1 chronic candidiasis, we required a scan that was positive
2 and a prior identification of having had a fungemia or, in
3 some instances, there were actually biopsies done.

4 So those were the primary ones. The others all
5 required the culture of a normally sterile site with the
6 fungal infection--for example, pleural fluid. For something
7 like invasive candidiasis, you had to have a biopsy
8 confirmation showing invasive fungal elements.

9 Superficial infections were not considered proven
10 infections for purposes of this study.

11 DR. WONG: But a positive blood culture was
12 sufficient for candida?

13 DR. BUELL: Yes.

14 DR. WONG: I wonder if you just have those three
15 pages that you could share with us.

16 DR. BUELL: I have them with the protocol. We
17 were thinking of making a projection but they were a little
18 too cumbersome. I will be happy to show them to you.

19 DR. ELASHOFF: I have two questions. The first
20 has to do with the study seems to have been powered for the
21 fever endpoint which doesn't seem to be one of the primary
22 endpoints.

23 DR. BUELL: We had to have a rationale for
24 selecting a sample size. We took the results of a prior

1 study by the EORTC with a fever-resolution rate of
2 70 percent and did our sample calculation based on our need
3 to have a 10 percent delta. And that came to 330. Once we
4 had arrived at the sample-size calculation, we ran kind of a
5 reverse analysis to see, at various incidences, what delta
6 we were capable of detecting.

7 At 50 percent incidence, we would have been able
8 to detect a 12 percent difference based on the sample size.

9 For the proven emergent fungal infections, which
10 we have been looking at, our power to detect differences for
11 the results we have seen was 88 percent.

12 Does that address your question?

13 DR. ELASHOFF: The second thing I wanted to ask is
14 how successful, in this study, was blinding especially since
15 many adverse events were probably felt by investigators
16 beforehand to be more typical of the amphotericin B. Part
17 of the reason I am asking about this is if specific
18 additional things like culture or biopsy are necessary for
19 proven infections, then there is a potential bias in what
20 the investigator orders if blinding is not successful.

21 So what additional information do you have about
22 whether blinding was successful or not?

23 DR. BUELL: I was thinking of actually bringing a
24 prop for this answer. We went to great lengths to assure

1 that the study was blinded. AmBisome is a cloudy yellow
2 solution and amphotericin B is clear. We had two
3 techniques. One involved using a sleeve-like plastic
4 material, almost like a trash bag.

5 You can see through it enough to see bubbles but
6 you can't tell whether it is cloudy or clear.

7 Alternatively, we had a particular kind of infusion pump
8 called the provider pump which had an orange tubing that was
9 light protective. That also effectively blinded it.

10 The investigators have told us that they couldn't
11 tell. If we can look for a minute at the reactions.

12 [Slide.]

13 The one that would be most of a clue that it was
14 amphotericin B rather than AmBisome would be the chills and
15 rigors. But these patients have fever spikes anyway because
16 of their condition and chills were frequently seen. If you
17 look here, imagine in the double-blinded situation, you
18 have, overall in the course of your experience, 37 percent
19 having chills here and 74 percent here.

20 So this wouldn't be enough to really give you the
21 accurate one. On the Day-1 infusion reactions, it was, I
22 believe, 18 percent versus about 38 percent. I don't have
23 that slide in front of me. So there wasn't enough, really,
24 of an early clue.

1 Also, these were administered by nurses on the
2 wards and the investigators weren't really there looking at
3 this all the time.

4 DR. ELASHOFF: Did you, in fact, ask investigators
5 to guess in this study? They do that in some studies.

6 DR. BUELL: I have asked investigators personally
7 if they knew, and they said they didn't. I can tell you one
8 story of a patient who had a biopsy at entry that came back
9 as Mucor. The lesion faded and cleared while the patient
10 was neutropenic. This investigator thought that this
11 indicated that AmBisome was a good drug.

12 And I asked him why. He said the patient had no
13 reactions and his creatinine didn't budge. That patient, in
14 fact, was an amphotericin B patient. So amphotericin B
15 patients don't always show this. We are comfortable that we
16 had adequate blinding.

17 Tom, do you have any comments about it?

18 DR. WALSH: We really took major efforts to try to
19 ascertain that the study was blinded as extensively as
20 possible. I won't recapitulate the points that Don had made
21 but mechanically one could clearly not make the distinction.
22 Indeed, we had major concerns from the nurses,
23 predominantly, that they were not able to distinguish the
24 difference and there, there was no vested interest other

1 than, clearly, that the patient be well cared for.

2 But, nonetheless, we were able to convince all the
3 participating centers, nursing departments within standard
4 operation procedures to literally have the bags blinded as
5 well as the tubings literally all the way down to the
6 patient catheter access site.

7 What also was quite apparent, however, was not
8 only a somewhat higher frequency on AmBisome than what, in a
9 sense, the conventional might think of total absence of
10 infusion-related toxicity, but, also, surprisingly lower
11 amounts on amphotericin B. Sometimes in the literature, we
12 read 80, 90 percent attributable infusion-related
13 toxicities.

14 Instead, when one looks very carefully, much of
15 this fever, if it is not carefully prospectively monitored,
16 which we did with a separate bedside data-retrieval sheet,
17 one can then confuse the baseline fever associated with the
18 infection, be it a bacterial or fungal infection, with
19 infusion-related toxicity.

20 As one anecdote deserves another, I would share
21 with you that my research nurse and I, during the early
22 phase of this blinded study, were called urgently to the
23 bedside just as our patient was going to start receiving her
24 infusion. My research nurse, Maureen McAvoy, had stepped

1 away and had returned and then she paged me.

2 We both ran to the bedside and the patient was
3 having marked rigors and chills. The IV infusion was going
4 and the nurse asked, "Shouldn't we premedicate this
5 patient?" I said, "Well, the protocol doesn't require that
6 but if we do have infusion-related actions during therapy,
7 we can intervene."

8 At that point, Maureen McAvoy looked up at the
9 infusion bottle and asked, "Well, don't you think we should
10 turn the pump on at the point?" So, indeed, the fever which
11 was being attributable to the compound actually was due to
12 the underlying infection.

13 It is not as easy to discern cause of fever unless
14 you carefully, meticulously, in a blinded way, prospectively
15 document it. To my knowledge, this is the first study that
16 really has characterized that.

17 DR. LIPSKY: A few questions about kinetics. Is
18 there not both liposomal-associated and non-associated
19 amphotericin in the plasma of patients?

20 DR. BUELL: Our assay does not allow us to
21 distinguish that. We believe that it remains tightly bound
22 in the AmBisome because, at the high levels that we have,
23 even if there were 1 or 2 percent association, we would
24 expect to have nephrotoxicity in these higher doses that we

1 are administering.

2 So we believe it is bound and we are developing
3 the assay to look at that specifically.

4 DR. LIPSKY: Can you account for what happens to
5 the amphotericin after it is administered? Can you do a
6 tabulation of where it goes, how much is eliminated, how
7 much stays behind in the body?

8 DR. BUELL: We did provide pharmacokinetic
9 parameters with clearance and volume and distribution and
10 those sorts of things. Here we have a product which can
11 circulate and is also taken up by the reticuloendothelial
12 system. We envision there is some sort of interaction
13 there.

14 We did a study in animals where we administered
15 the drug for 90 days and then we looked at the washout.
16 That was our 90-day tox study with follow up. You could see
17 high concentrations or large amounts in the liver and spleen
18 primarily, but also lesser amounts in other tissues at the
19 end of that and you could watch those decrease over time
20 over three to four weeks.

21 In that situation, if you look at the serum, you
22 can detect low levels for prolonged periods of time. As far
23 as specifically what happens, we have been talking for some
24 time about doing a double-labeled study with the tritium in

1 the amphotericin and C14 in the liposome. That is something
2 that is of great interest to us but we haven't achieved it
3 yet.

4 DR. LIPSKY: So, after the administration of this
5 compound, which is, what, fivefold, approximately, greater
6 than you would administer amphotericin, you presume there
7 would be a prolonged body burden of amphotericin after the
8 discontinuation?

9 DR. BUELL: Yes. We do believe that. Why don't
10 we show the 90-day tox. The slide is there. Let's look at
11 that. I can just point out--

12 [Slide.]

13 As you see, these are 1, 4 and 12 mg/kg
14 administrations, 91 days. So it was a longer-term toxicity
15 study. Then the drug was stopped. But you can see, liver
16 and spleen are the predominant organs that contain the
17 material, kidney lung. There would be trace amounts or
18 small amounts in other tissues including the brain; then, of
19 course, larger amounts at the higher doses.

20 Then, if you look over time, 1, 2 and 3 weeks
21 later, you can see it disappearing from the issue. So it is
22 exactly as you have described it.

23 DR. EL-SADR: I apologize if I missed this. I had
24 to step out. The study follow-up period was how long after

1 completion?

2 DR. BUELL: The drug was discontinued when the
3 patient recovered from neutropenia or else had a premature
4 discontinuation. The patients were followed for seven days
5 after that and had a follow-up assessment at that point.

6 DR. EL-SADR: So you don't have mortality or any
7 other data beyond seven days after discontinuation of study?

8 DR. BUELL: We didn't systematically follow and
9 collect data after seven days after therapy.

10 DR. HAMMER: Can you detail the presumed
11 infections a little bit more? I think that is really one of
12 the points that the group needs to see. You must have a
13 table of what those are and some hypothesis as to whether
14 these were blunted or what you feel about these. I think
15 they were driven by pulmonary syndromes if I remember the
16 table correctly.

17 DR. BUELL: That's exactly right. Let's look at
18 this slide, Slide 78.

19 [Slide.]

20 When I became aware of these findings where the
21 proven ones were primarily in amphotericin B but there were
22 more presumed in AmBisome, I took a very careful look at
23 what the reasons were for making these diagnoses and also
24 looked at what the suspected organisms were.

1 I laid it out in this slide. The majority were
2 based on X-ray infiltrates and not often a classic
3 infiltrate of something like a halo sign that you associate
4 with Aspergillus but sometimes rather just descriptions of
5 diffuse infiltrates.

6 Sometimes, a radiologist would say this was
7 consistent with Aspergillus and, as soon as that happens, of
8 course, it becomes a highly suspect thing, although if you
9 read the description of the X-ray, it might not necessarily
10 have been characteristic.

11 So the investigators were suspecting that there
12 might be Aspergillosis or Candida pneumonia. This was
13 usually because they had other positive cultures in the body
14 for Candida and had an infiltrate. In both groups, there
15 were pulmonary reasons. Sometimes, they were just going on
16 the basis of the chronic prolonged fever. Rarely, they
17 might have a scan which showed some lesions in the liver but
18 without any confirmatory mycology.

19 So these are the sites and kind of the suspected
20 organisms in the presumed group.

21 DR. HAMMER: Did most or all of those have an
22 isolate from some either top superficial site or--because
23 they classified it as Aspergillosis or Candida. I assume
24 that was made because they had a culture of the surface or--

1 DR. BUELL: The Aspergillus was usually based on
2 seeing infiltrates in the chest. I was somewhat surprised
3 at how nondescript--even some were described as ground glass
4 which you usually think of, like, in adult-respiratory
5 distress picture. But even then sometimes that was called a
6 presumed infection. They usually blamed Aspergillus if they
7 didn't have Candida. If they had heavy Candida growth which
8 you often can find in the throat or stool, then they were
9 more suspicious of it being due to candidiasis.

10 DR. HAMMER: I also noticed that there appeared to
11 be more antibacterial agent modification in the AmBisome
12 group than the amphotericin B group if I remember that
13 correctly from the briefing document, and what contribution
14 that may have made to the defervescence component of the
15 success criteria.

16 DR. BUELL: This came up at the prior advisory
17 committee meeting looking at empirical therapy. Let's look
18 at the slide on that.

19 [Slide.]

20 You need to add 71 and 128, and that is 199. And
21 45 and 154 is 200. So 199 AmBisome patients and 200
22 amphotericin B patients revolved their fever during the
23 neutropenic period. We have looked at that group for
24 antibiotic modification.

1 We defined antibiotic modification as the addition
2 of a new antibacterial, the addition of a new antiprotozoal
3 or new antifungal agent that was not being administered at
4 study entry. When there were no changes, you can see, fever
5 resolution was 88 percent in both groups. There were
6 slightly more patients that had antibiotics modified on
7 AmBisome.

8 The response to fever was comparable, though, in
9 both these populations that had antibiotic modification. It
10 is almost kind of a reverse thing. If the patient's fever
11 isn't responding, I think there would be more of a tendency
12 to be manipulating the other treatments in addition to the
13 fact that these patients were both on antifungal agents in
14 the study.

15 DR. ELASHOFF: I'm sorry. I can't understand this
16 slide.

17 DR. BUELL: Let's put it back up. What we showed
18 was the success parameters.

19 DR. ELASHOFF: The issue is that I thought you
20 said that the 200 patients in each group represented here
21 are people who had fever that went down and then you have
22 got an 80 percent rate of people whose fever went down. So
23 there is some aspect of either who is represented in the
24 slide or what the success rate is that I didn't understand.

1 DR. BUELL: Let me clarify. This population is
2 patients whose fever responded during the neutropenic
3 period. I meant to say that we looked at the success
4 parameter and it was 88 percent and 88 percent, not fever
5 response. That was a mistake on my part. And the success
6 was 82 and 74.

7 So here, we are looking at the impact of
8 antibiotic modification on the success parameter and we are
9 looking at, for those whose fever responded, what role did
10 antibiotic modification play. So the data was right, but my
11 statement was not quite right.

12 DR. MATHEWS: I have one question on the dosage
13 equivalency between amphotericin B and AmBisome. What is
14 that based on, that 5 to 1 ratio, and the standard dose of
15 3 mg/kg?

16 DR. BUELL: In the European study, compassionate
17 experience that Dr. Prentice mentioned, the average dose
18 that was administered to patients in Europe had been about
19 2.8 mg/kg. So we decided that that is likely to be an
20 effective dose for the study. We brought it up to 3 just to
21 have the even number.

22 The 0.6 mg/kg of amphotericin B was an agreed-upon
23 dose that seemed reasonable to the investigators when we
24 gathered the investigators from the 30 sites in writing the

1 final version of the protocol. Some used less routinely.
2 Some used a little bit higher dose routinely. Because they
3 had the flexibility to modify the doses, they agreed on the
4 0.6 and they felt that the 0.6 was likely to be a reasonable
5 effective dose for empirical therapy.

6 DR. MATHEWS: It is curious because only about
7 4 percent of the product is actually amphotericin; right?

8 DR. BUELL: I just need to clarify. When we say
9 that we are administering 3 mg/kg of AmBisome, we are always
10 talking about the amount of amphotericin B in the product
11 that is being administered. That is not the total product
12 with the sucrose and everything else.

13 DR. MATHEWS: Okay. That wasn't clear.

14 DR. BUELL: That is how we get--in the animal
15 studies I showed you where they both received 1 mg/kg, that
16 is based on the amount of amphotericin B.

17 DR. MATHEWS: Okay. Thank you.

18 DR. BUELL: And then the in vitro sensitivity
19 tests.

20 DR. MATHEWS: And then I have a few questions on
21 the clinical trial. Was there any time-to-event analysis of
22 the proven infections that emerged during therapy and did it
23 differ--did the times during which these infections were
24 diagnosed differ between the treatment groups?

1 DR. BUELL: I don't have that data to show you. I
2 can tell you that we ran a Kaplan Meier type look at the
3 time of appearance of emergent fungal infections using the
4 investigator's designation, the sponsor's and the blinded
5 reviewer.

6 The curves did separate and the p-values were on
7 the order of 0.014 on the Kaplan Meier. But, I'm sorry, I
8 don't have that because that was not our primary analysis.
9 We used the Cochran Mantel Haenszel on analyzing that.

10 DR. MATHEWS: But the event time was time of
11 diagnosis? Say, if there was an infiltrate, what would be
12 the date that was assigned to when the event occurred? A
13 biopsy date? An infiltrate date on X-ray? Or what?

14 DR. BUELL: The mean time-to-diagnosis for the 16-
15 -this is the investigator's designation as the number that
16 we have--for the 16 that were considered to be proven by the
17 investigators, the mean time-to-diagnosis for AmBisome was 7
18 days and for amphotericin, the mean time-to-diagnosis was 11
19 days.

20 But I like to look at it with the Kaplan Meier
21 because it shows the separation of the curves as well. This
22 is the mean time-to-diagnosis for a smaller number of
23 infections for AmBisome. Some of those in the
24 investigator's assessment were urinary or stool. They might

1 have been made fairly promptly.

2 DR. MATHEWS: With regard to the independent
3 investigator's review, what data sources did he have to
4 review in making those designations?

5 DR. BUELL: He had the case-report forms,
6 themselves. The case-report forms contain no designation as
7 to the drug being administered. We set the concentration so
8 that, for a given weight patient, they would receive the
9 same volume, whether it was amphotericin or AmBisome. So
10 there was no designation at all on the case-report form of
11 which drug the patient was on.

12 He worked from the X-ray descriptions, from the
13 sheet that the investigator filled out indicating that there
14 was a proven or presumed infection. He had the culture
15 data, everything that was in the case-report form. Of
16 course, this was blinded.

17 DR. MATHEWS: Was their medical record, actual
18 text of the medical record, included in what--

19 DR. BUELL: No; there was not text of the medical
20 record. This was from the case-report form, captured data.
21 We did 100 percent source verification on all data in the
22 case-report forms by our monitors. And Dr. Wingard had the
23 protocol and the strict criteria laid out in the protocol to
24 work from. This was all sent down to Florida and he did

1 that down there.

2 DR. MATHEWS: Having done hundreds of medical-
3 record reviews and chart abstractions for various studies, I
4 find you learn an enormous amount from looking at the
5 medical records themselves because there are often five or
6 six different physicians involved in the care of patient
7 writing notes and they often contradict one another or have
8 different impressions.

9 So what appears in the case-report form may only
10 be a snapshot of the range of opinions in a given case.

11 DR. BUELL: That is quite possible. We do monitor
12 to be sure that the information put in the case-report form
13 is actually verified by patient record. Our monitors also,
14 with respect to safety, do look for other mentions in the
15 record of adverse events.

16 DR. MATHEWS: The last question is do you have any
17 measure of diagnostic intensity in the pursuit of these
18 treatment-emergent infections? Was there comparable use of
19 invasive procedures, biopsies and so on?

20 DR. BUELL: I can say that on the basis of the
21 BALs which, I think, were about the same in both groups, and
22 there were a number that were documented by actual biopsy in
23 both groups--I can't give you 100 percent answer. My sense
24 of it is that it was approximately the same. Again, I truly

1 believe that the investigators were blinded to the study
2 drug that was being administered when they were looking and
3 working up these fungal infections.

4 DR. MATHEWS: Thank you.

5 DR. DIAZ: A lot of the data that you presented
6 was based upon all of the patients combined, irrelevant of
7 whether they received one dose or multiple doses of drug.
8 Did you do any stratification or looking at the data in
9 terms of your success and some of the indicators, fever,
10 resolution of neutropenia, sort of based upon numbers of
11 days treated or numbers of doses received in the
12 amphotericin B group versus the AmBisome groups?

13 DR. BUELL: Yes; we did. In fact, we
14 prospectively defined a criteria of at least three doses as
15 a subgroup to analyze. I can show you on the success
16 parameter the outcome on that.

17 [Slide.]

18 Of the 343 that received at least one dose, 324 in
19 AmBisome went on to get at least three doses and similarly a
20 good percentage in the amphotericin B group. The success
21 parameter, again, was equivalent between the two groups. So
22 I can't give you information on a week's dosing. We don't
23 have that breakdown. But we thought three was sufficient
24 time to have gotten in a fairly good amount of antifungal

1 therapy.

2 DR. DIAZ: Just back to these patients with
3 presumed infections, the majority of them being presumably
4 pulmonary in nature. In terms of the patients that were
5 treated with AmBisome, I noticed that there were a higher
6 percentage, at least, of patients who developed pleural
7 effusions and vasodilation. Can you make any comment in
8 terms of those complications or reactions associated in
9 these presumed pulmonary patients, or patients with presumed
10 infections.

11 DR. BUELL: Pleural effusions were infrequent
12 enough that I don't think they made it to our cutoffs for
13 the slides. The vasodilation was something that was kind of
14 a flushing that happened when they received the
15 administration, itself. It was an infusion-related
16 reaction. I don't think that that would get translated into
17 something like the exudative phenomenon that you sometimes
18 see with things like IL2. It is nothing anywhere near like
19 that, if that is what you were thinking about.

20 We had pleural effusion in 12.5 percent of
21 AmBisome patients and 9.6 percent of amphotericin B. The
22 actual numbers were 43 patients on AmBisome and 33 on
23 amphotericin B. I suspect those were related to other
24 disease processes and not a drug-related situation.

1 DR. HAMMER: On the vasodilatation; have you seen
2 that in your other studies? Is this a consistent finding
3 and is it a histamine-release reaction or do you know what
4 that is?

5 DR. BUELL: I am told that other liposomal
6 products such as the liposomal daunorubicin can give a
7 reaction like this. So I think it is a liposome thing that
8 is some kind of a vascular--there are some events that
9 happen that we think are part of this kind of liposomal
10 reactivity that may be histamine-sensitive, in fact.

11 DR. HAMMER: But you saw a diminished pulmonary--
12 the dyspnea reactions, et cetera, were lower in the AmBisome
13 group and some other lipid preparations if I remember
14 correctly sometimes give more of a dyspnea reaction.

15 DR. BUELL: Let's look at the respiratory, Slide
16 90.

17 [Slide.]

18 These are cardiorespiratory infusion reactions, if
19 this is what you are referring to. These are the number of
20 episodes. We have known about this for a long time, that
21 amphotericin B can cause this. Hypoxia was mentioned at the
22 last meeting here. We only had one episode called hypoxia
23 in an AmBisome patient. So we were very encouraged about
24 that because we are infusing a lipid substance and it goes

1 into the circulation and it can get to the lungs.

2 So we were quite reassured by our safety data on
3 the respiratory symptoms.

4 DR. HAMMER: Just a last brief question. Do you
5 have fungal susceptibility data on the emergent proven
6 infections?

7 DR. BUELL: No; we don't. Dr. Walsh wishes that
8 we did, but we don't have the isolates to do that testing.

9 DR. WONG: I have one last question. On one of
10 your slides, you listed outcomes in people who had fungal
11 infections at entry to the study. I think 8 of 11 in one
12 group and 9 of 11 in the other group improved.

13 DR. BUELL: Yes.

14 DR. WONG: Could you tell us something about those
15 patients and how it was decided that they had fungal
16 infections and what is meant by the result.

17 DR. BUELL: Slide 53, analysis of the baseline
18 infections.

19 [Slide.]

20 One of the things that we felt was when a patient
21 enters the study, you strongly suspect they have a fungal
22 infection and you start the empirical therapy. If, on the
23 day that you start the study, you draw a culture and it
24 comes back positive, you find out that they, in fact, did

1 have the fungal infection and you have found it out because
2 you happen to start the drug that day and draw the culture
3 just before.

4 We felt that these were really the category of
5 patients that empirical therapy is intended to treat. So we
6 didn't drop them from the study. And we required as a
7 marker of efficacy that these infections be controlled
8 because they would be the same as one that we just happened
9 not to detect.

10 So we kept them in the study. When we analyzed
11 these, there were 11 reported as baseline fungal infections
12 by the investigator. We felt that one of these was not
13 documented and was presumed, so we felt there were 10 and
14 11. These were candidemias or blood infections and there
15 were subsequent negative cultures in 8 of 11 and 7 of 10.

16 Some were removed from study with this finding, I
17 think, by the investigator because of concern and a desire
18 to treat them in an open-label fashion. So this was the
19 outcome on that parameter.

20 DR. KAN: Some of the patients that you described
21 had concomitant use of nephrotoxic drugs. It appears that
22 more amphotericin B patients were involved with that
23 concomitant usage. I wonder if you had done some analysis
24 of those subsets of patients on nephrotoxic drugs other than

1 those that you already described with FK506 and
2 cyclosporine.

3 [Slide.]

4 DR. BUELL: What we did here was to separate--this
5 is a nephrotoxicity parameter as measured by a doubling from
6 the baseline serum creatinine. It was a rather standard
7 definition for nephrotoxicity we have used across all our
8 studies that we have submitted to the Agency.

9 We were looking at the effect of having additional
10 nephrotoxic agents. So if there were none, 0 or 1, you saw
11 this degree of difference on this parameter of
12 nephrotoxicity. If the patients had been receiving two of
13 these potentially nephrotoxic meds, we had the 16 versus 36.
14 This approximated what the overall study results showed.

15 Then, with the higher number of meds, you might
16 say the threshold goes higher. Some of these patients in
17 the AmBisome are probably having this phenomenon related
18 more to the other drugs.

19 Can we show the slide I think just before this
20 one? No; it is the backup slide with the agents, just to
21 explain the agents that we considered in this analysis.
22 They are listed here.

23 [Slide.]

24 So we did include FK506, tacrolimus, cyclosporine

1 and some of these drugs that frequently need to be given to
2 this patient population. The population that received
3 cyclosporine in our studies were the allogeneic transplant
4 patients. In that group, I believe the incidence of
5 nephrotoxicity on amphotericin B reached as high as about 75
6 or 76 percent.

7 But it was also correspondingly higher in the
8 AmBisome but the difference was still there in the amount of
9 nephrotoxicity.

10 DR. KAN: One additional question related to the
11 long-term effects of the liposomal preparation. Since you
12 showed that in, particularly, the organs involved in the
13 reticuloendothelium system, the liver and the spleen, having
14 such a high degree of amphotericin remaining after 91 and
15 121 days, were longer-term follow up available for patients
16 receiving, or just up to the seven days post infusion?

17 DR. BUELL: Within the study that were are talking
18 about, the primary large empiric therapy study, we followed
19 the patients for seven days gathering data. I think in the
20 kind of experience that Dr. Prentice described where this is
21 widespread usage throughout the world of this agent, there
22 are many patients who have received it and have gone on to
23 live their lives.

24 I guess we could show the surveillance slide. It

1 is Slide 96. In countries where the drug has been approved
2 where there is a good post-marketing surveillance, we have
3 recorded the number of spontaneously reported adverse
4 events. That is where you might pick up something of low
5 frequency that you wouldn't appreciate in the trials.

6 It is rather amazing, I think.

7 [Slide.]

8 These are the total reports of things that have
9 come out of the post-marketing surveillance with relatively
10 few events having been described. These tend to be more
11 associated with the administration of the product. There
12 wasn't anything that came, that I am aware of, that suggests
13 there is some sort of longer-term problem.

14 As we said, this product has been used quite a
15 while throughout the world.

16 DR. HAMMER: Thank you very much. Brian, one last
17 question and then we will take a break.

18 DR. WONG: Just to follow up on the people with
19 the fungal infections at baseline. You said some were taken
20 out of the study because that fungal infection was
21 diagnosed. Can you break down for us, of the patients that
22 were randomized to receive amphotericin B and those who were
23 randomized to receive AmBisome, how many of the people who
24 were proven to have fungal infections at entry completed

1 their therapy with the assigned drugs and improved.

2 DR. BUELL: I don't know that we can give you that
3 information here. Jay, do we have that in the book
4 somewhere? We might be able to find it. If I get it, I
5 will present that to you. But it appears that at least 8
6 and 7 stayed in the study and had the documentation of the
7 cured or improved. So they, at least, stayed in. So I
8 think we are talking about a small number of patients here,
9 maybe 2 or 3 in each group that we might not be sure of it
10 happening.

11 DR. HAMMER: If you can find that during the
12 break, you can let us know.

13 Let's break for 15 minutes and then return.

14 [Break.]

15 DR. HAMMER: We are now going to continue with the
16 FDA presentation and Joyce Korvick.

17 **FDA Presentation**

18 **Clinical Efficacy**

19 DR. KORVICK: I am Dr. Korvick. I am the primary
20 medical reviewer for the NDA-5740, the amphotericin B
21 liposomal preparation.

22 [Slide.]

23 As others have done before me, I would like to
24 welcome you to the first advisory committee for the Division

1 of Special Pathogens and Immunologic Drug Products.

2 [Slide.]

3 Before I continue with my remarks, I would like to
4 acknowledge the people that were on the review team. Dr.
5 Hammerstrom and I will be presenting the FDA remarks for
6 today.

7 [Slide.]

8 First I will make introductory remarks and briefly
9 comment on the activity of AmBisome for the treatment of
10 fungal infections. However, the majority of our
11 presentation will focus on the empirical use of AmBisome for
12 the treatment of the febrile neutropenic patient. Dr.
13 Hammerstrom will present the statistical comments for the
14 empirical therapy indication and I will continue with some
15 medical comments.

16 Finally, we will turn to the safety considerations
17 here, pediatric use and then state the questions for the
18 advisory committee.

19 [Slide.]

20 As was mentioned previously, the sponsor has
21 submitted AmBisome for several indications. The top one is
22 empirical therapy, treatment of systemic and deep mycosal
23 infections, and, also, prophylaxis and treatment of visceral
24 Leishmaniasis.

1 As was previously mentioned, we have had several
2 discussions, FDA-sponsored meetings, and the committee's
3 consideration at the last advisory for how these kinds of
4 studies should be designed. Some of the comments from the
5 last advisory committee, I think people were interested in
6 knowing what the demonstrated antifungal activity was for
7 the agent and, also, they were interested in a well-designed
8 clinical study of empirical therapy, febrile-neutropenic,
9 patient and a lot of discussion centered the usefulness of
10 fever as a primary endpoint.

11 As many of you participated in those discussions,
12 I think you will be familiar with those considerations.

13 [Slide.]

14 The treatment studies presented by the applicant
15 have demonstrated clinical and mycological activity when
16 AmBisome was administered for the treatment of invasive
17 fungal infections with Aspergillus, Candida and
18 Cryptococcus. There were too few definitively confirmed and
19 evaluable fungal infections in the comparative studies to
20 determine an actual rate of efficacy for AmBisome compared
21 to conventional amphotericin B.

22 However, studies such 09, a study of cryptococcal
23 meningitis in HIV-infected patients, give a certain degree
24 of comfort when one considers that cryptococcal meningitis

1 is fatal if left untreated.

2 In the collection of studies submitted by the
3 applicant, AmBisome appears to have similar activity to
4 amphotericin B with improved tolerability for the treatment
5 of deep fungal infections. Overall, these study data are
6 supportive of a secondary-line indication for AmBisome for
7 the treatment of these infections.

8 There are ongoing studies of these infections in
9 the United States which will support additional indications
10 including histoplasmosis and cryptococcosis. However, those
11 studies are ongoing.

12 [Slide.]

13 I will now turn to the subject of interest today,
14 the empirical treatment of febrile neutropenic patients.

15 [Slide.]

16 As the sponsor had mentioned, there were three
17 studies submitted for this indication in the NDA. There was
18 a study in pediatric population. These two studies on the
19 top were done in Europe and you can see that they were dose-
20 comparison as well as comparative studies with amphotericin
21 B, both of them using 1 and 3 mg of AmBisome, comparing that
22 to a 1 mg/kg dose of amphotericin B.

23 These are the study n's. So you can see those
24 were large trials. However, the study that was presented by

1 Dr. Walsh, the 002 study, was substantially larger. Some
2 problems that we have with the European studies were that
3 the definitions for some of the endpoints were applied
4 retrospectively in the study.

5 The studies also permitted patients who were
6 failing on amphotericin B to switch over to AmBisome.
7 However, the reverse was not true. Therefore, you might get
8 a little bit of bias or you might dilute the effect of the
9 AmBisome.

10 Finally, all of these studies do use the composite
11 endpoint. The two studies from Europe were using fever,
12 fungal infection and need-to-discontinue-drug. We think
13 that the composite endpoint that was defined in Study 002
14 was much more thoroughly established and took a lot more
15 serious look at the influence of various parameters on the
16 overall outcome.

17 [Slide.]

18 I am going to give the podium over to Dr.
19 Hammerstrom for some comments on the efficacy of this study.

20 **Statistical Summary**

21 DR. HAMMERSTROM: I am Dr. Hammerstrom. I will be
22 giving the FDA analysis of the efficacy in Trial 002 and the
23 European trials.

24 [Slide.]

1 My talk can be divided into four components. I
2 will describe the study endpoints and planned analyses. I
3 will then review the protocol-specified primary endpoint
4 which is the composite endpoint. Third, I will talk about
5 findings regarding emergent fungal infections. And,
6 finally, I will discuss the other supportive empirical
7 trials.

8 [Slide.]

9 The applicant has listed one primary endpoint
10 which is a composite of several criteria. At the previous
11 advisory committee meeting, concerns were raised regarding
12 this endpoint. It was noted that a relatively high
13 proportion of non-fungally infected patients may be enrolled
14 in the trial.

15 The inclusion of such subjects may lead to an
16 overstatement of the success rate for both treatment arms
17 and a lack of sensitivity in evaluating equivalence. The
18 protocol also lists four secondary endpoints, three that are
19 related to duration of fever and one which directly
20 addresses antifungal activity, the emergence of new fungal
21 infections.

22 The applicant also developed an analysis plan
23 prior to unblinding the data. In this plan, fungal
24 infections were specifically required to be proven

1 infections. At this time, three additional endpoints were
2 also added; fever resolution, yes or no; duration of
3 survival and time-to-success.

4 [Slide.]

5 The method of assessing results on secondary
6 endpoints is not specified a priori. There are, in fact, at
7 least nine chances for demonstrating superiority. The
8 primary endpoint, itself, could be tested for superiority
9 and not just equivalence, and the seven listed secondary
10 endpoints described in the data-analysis plan in the
11 protocol could be tested.

12 Finally, percent surviving, an endpoint which is
13 always examined in treatment for a frequently fatal disease
14 could be tested for superiority. Since no formal analysis
15 plan was developed which addressed the multiple-comparison
16 issue, it is possible that combinations of the secondary
17 endpoints would also be of interest.

18 This means that p-values, unadjusted for multiple
19 endpoints, may be misleading. But since there is ambiguity
20 regarding what types of decisions could have been reached
21 based upon the secondary endpoints separately and together,
22 a formal adjustment procedure cannot be developed post hoc.

23 Therefore, we must rely upon a subjective
24 assessment of the overall pattern seen in the data.

1 [Slide.]

2 The prespecified primary endpoint is a composite
3 of the listed items. You have seen these listed before on
4 the applicant's slide as well. This endpoint was discussed
5 at the previous advisory committee. A concern was raised
6 that success would be declared for subjects who had a fever
7 from nonfungal causes.

8 This could lead to a reduction in sensitivity for
9 distinguishing between the two drugs. Also, the inclusion
10 of toxicity makes this endpoint a mixture of safety and
11 efficacy. We will examine the endpoint of this issue based
12 upon the data presented.

13 [Slide.]

14 The applicant has given the number of failures by
15 each mode, listed in the previous slide, but in ways where
16 the categories overlap. Subjects could have failed for more
17 than one reason. This table shows failures ordered in a way
18 recommended by the FDA medical reviewer.

19 Each successive group of failures here contains
20 only people who have not failed for one of the earlier
21 reasons. The first cause of failure is death. Here
22 AmBisome was somewhat superior to amphotericin B, 25 versus
23 36, starting with equal numbers enrolled. We will comment
24 on the statistical significance of this below.

1 Among the survivors, more were still febrile on
2 AmBisome so that, at this point, by the time you look at the
3 first two causes of failure, essentially equal numbers were
4 afebrile survivors.

5 The third failure mode in this ordering was
6 emergent fungal infections, EFIs. Here this is both proven
7 and presumed. Note that the 14 and 13 EFIs for the two arms
8 listed here do not include any EFIs who either died or were
9 still febrile so the total number of EFIs will be larger
10 than the 14 and the 13.

11 These 27 EFIs were those who were still alive and
12 afebrile at the end of the trial. One should also notice
13 that failures due entirely to adverse events or toxicity
14 were quite low here so the concern that this is a mixture of
15 a safety and an efficacy endpoint is not particularly
16 serious.

17 [Slide.]

18 The NDA contains a number of different ways to
19 count emergent fungal infections, as this slide shows.
20 Investigators initially classified them as either proven or
21 presumed. The applicant reviewed the investigators' case-
22 report forms. Finally, Dr. Wingard, an outside reviewer,
23 also did so in a blinded fashion.

24 Finally, the FDA medical reviewer also blinded

1 reviewed the data and agreed, case by case, with the
2 applicant. In what follows, we will use the applicant's and
3 the FDA reviewer's numbers although the results that we will
4 be reporting are generally fairly robust to which choice of
5 these you make.

6 [Slide.]

7 This table shows the counts and percents of fungal
8 infections for each arm, the difference in the rates,
9 AmBisome rate minus amphotericin B rate, and the Cochran
10 Mantel Haenszel p-values for testing equality of the rates.
11 The p-values here are unadjusted for multiple endpoints and
12 are computed using the same stratification as was used in
13 the randomization; that is, they were stratified by both
14 site and by high and low levels of baseline risk.

15 Two points to be noticed here. Among fungal
16 infections overall, there was essentially no difference in
17 the rates but, secondly, proven and presumed infections went
18 in the opposite directions. The difference in each case was
19 of sufficient magnitude to be equally likely or unlikely;
20 that is, the p-values are essentially the same but the sign
21 of the difference is opposite.

22 [Slide.]

23 This slide shows the same statistics as the
24 previous slide for death and fungal infections combined. We

1 usually complement any examination of a non-fatal endpoint
2 with a look at that endpoint or death as a combined adverse
3 outcome.

4 There are three points worth noting here. First,
5 there are fewer deaths on AmBisome, although the difference
6 is not statistically significant, with a p-value unadjusted
7 of 0.14. Second, the difference is somewhat larger when one
8 considers death or proven fungal infections with a p-value,
9 unadjusted for multiple comparisons, below 0.05.

10 Third, deaths in subjects without any EFI look as
11 if they were evenly split between the two arms. That might
12 suggest that including these deaths in the combined endpoint
13 mainly serve to add noise to the simple endpoint of proven
14 fungal infections.

15 [Slide.]

16 There were two other trials in Europe that address
17 empirical antifungal therapy with AmBisome. These trials
18 were primarily intended to use the combination endpoint
19 based on empiric-therapy outcome. They were of smaller
20 sample size and there is some question as to whether
21 emergent fungal infections were assessed as carefully as in
22 Trial 002. Apropos of this latter concern, we note that the
23 FDA medical reviewer reexamined the case-report forms in
24 Trial 10 and increased the number of EFIs detected from 5 to

1 9.

2 There was no clear definition of proven or
3 presumed infections in the European trials. The observed
4 rate of emergent infections was about half as high as in
5 Trial 002. You can compare those rates. This may reflect
6 either the use of a population at higher risk in Trial 002
7 or a higher false-negative rate with respect to what was a
8 secondary endpoint in the other two trial.

9 [Slide.]

10 This slide shows the 95 percent confidence
11 intervals for the difference in confirmed fungal-infection
12 rates in all three trials. Here we have used both the
13 applicant's and the FDA medical reviewer's counts in Trial
14 10 so there are two confidence intervals for Trial 10.

15 The risk of EFI per arm in each trial is given at
16 the bottom. It is worth noting on this slide that all three
17 trials generally support a conclusion of equivalence with
18 95 percent confidence limits for the difference in EFI rates
19 being between plus and minus 10 percent. This one is a
20 little bit outside that interval.

21 [Slide.]

22 In summary, the difference in success rates with
23 respect to the combined endpoint was between -7 and +8 with
24 95 percent confidence. This must be interpreted in the

1 presence of an unknown proportion of non-fungally infected
2 patients.

3 Second, there was an observed difference in favor
4 of AmBisome in the rate of proven emergent fungal
5 infections, between a 1 percent and an 8 percent decrease in
6 proven and fungal EFI rate. There are two difficulties in
7 interpreting this rate. The first is the multiple
8 comparison problem alluded to earlier. The second is that
9 the presumed infections show a treatment difference in the
10 opposite direction.

11 This leads to result 3, that there is no apparent
12 difference in the rates of all EFIs between a negative
13 4 percent and a plus 6 percent with 95 percent confidence.
14 The applicant has contended that presumed infections are so
15 poorly defined that they may not be fungal disease. If this
16 were the case, one would expect a rough parity between the
17 two arms or at least a small advantage in favor of AmBisome.

18 In fact, we have a result that is at least as
19 striking as for the proven infections but in the other
20 direction. Finally, the European studies support a
21 conclusion that AmBisome is at least as effective as
22 amphotericin B.

23 I would now like to reintroduce Dr. Korvick for
24 the rest of our presentation.

1 and proven, as Dr. Hammerstrom described. We thought what
2 is the clinical significance of the presumed category since
3 everybody is happy with the proven. However, the difference
4 is significant in the opposite direction for the presumed.

5 [Slide.]

6 The majority of the presumed infections were
7 designated as pneumonia by the investigators and, upon
8 closer inspection of these, only three had potential proven
9 infections which were only based on CT findings. There were
10 no cultures for those three patients. They were evenly
11 distributed among the groups.

12 The remainder of the patients had chest X-rays
13 which were non-specific as described previously. On the
14 basis of those chest X-rays and in the absence of culture
15 results, the investigators made an attempt at diagnosing
16 them. In each group, approximately 50 percent of these
17 pneumonias were designated as Aspergillus and 50 percent
18 Candida by the investigators.

19 [Slide.]

20 We attempted to further evaluate the clinical
21 significance of the presumed infections by comparing
22 mortality rates for patients with presumed, proven or no
23 emergent infection for each of the treatments. If presumed
24 fungal infections carried the same significance as proven

1 fungal infections, one would expect mortality rates for
2 these categories to be similar.

3 While the numbers are small for some of the cells,
4 the mortality rates for the proven emergent fungal
5 infections appear to confer a worse prognosis than in the
6 presumed. We are looking forward to further discussion by
7 the committee on the usefulness of the fungal endpoint as a
8 potential primary endpoint for future studies.

9 I will now turn my comments to the safety of
10 AmBisome. In general, we agree with the applicant's review
11 of the safety data. This NDA package contained a safety
12 database which included 1580 patients, 923 having been
13 treated with AmBisome, 536 with amphotericin B and 130 with
14 placebo.

15 The most frequently utilized dose of AmBisome was
16 3 mg/kg/day. There were some patients who received higher
17 doses and some studies included doses up to 7.5 mg/kg/day
18 and one child had received 15 mg/kg/day.

19 The comparison of adverse-event rates for AmBisome
20 and amphotericin B are best described in the prospective
21 comparative studies. We will use those to describe several
22 of the safety parameters of interest including
23 nephrotoxicity, hepatotoxicity, infusion-related reactions
24 and the pediatric safety database.

1 Reductions of the known drug-related toxicities of
2 amphotericin B have been seen and, in all studies reviewed,
3 the AmBisome appeared to have a better safety profile than
4 amphotericin B.

5 [Slide.]

6 Hepatotoxicity appeared as a concern in the
7 preclinical data in mice and rodents and this was
8 scrutinized by the FDA as well as you have seen the
9 presentation by the company. In Study 002, these are the
10 comparative rates of hepatotoxicity and this was a
11 predefined endpoint. You can see that they are similar for
12 both groups.

13 We looked at the number of patients that were
14 withdrawn from study drug due to hepatotoxicity. There were
15 six in the AmBisome group and two in the amphotericin B
16 group. The numbers were small and there was no overall
17 pattern regarding which specific enzyme was affected. In
18 all cases, when study drug was withdrawn, the patient's
19 liver functions returned toward baseline.

20 [Slide.]

21 You have seen this slide already and we are in
22 agreement with the company that overall infusion-related
23 reactions appear to be less in AmBisome than amphotericin B
24 and, specifically, when you focus on the potential

1 cardiopulmonary events, you do see a benefit for the
2 AmBisome preparation.

3 Pulmonary events were looked at in regard to
4 patients who were withdrawing from study drug due to a
5 pulmonary event and, in the AmBisome group, only two
6 patients were withdrawn because of shortness of breath due
7 to infusion-related reactions.

8 On patient had chest pain, back pain and
9 tachycardia in the AmBisome group. When you compared this
10 to the amphotericin B group, there were five patients who
11 were withdrawn from the amphotericin B due to shortness of
12 breath, one due to hypotension and two due to tachycardia.
13 Pulmonary events were not seen more frequently in the
14 AmBisome group compared to amphotericin B.

15 [Slide.]

16 Regarding the pediatric safety profile of
17 amphotericin B and AmBisome, we had looked at the pediatric
18 population in Study 002 as well as the European study.
19 These are some of our conclusions.

20 Overall, there seems to be a similar safety
21 profile in pediatrics for AmBisome compared to adult
22 populations. In general, the nephrotoxicity differences
23 between AmBisome and amphotericin B appear to be less
24 pronounced in the pediatric population but this may be due

1 to the reduced toxicity that is seen in general for
2 amphotericin B in children.

3 Finally, there were no differences in the
4 pediatric population between hepatotoxicity for amphotericin
5 B and AmBisome.

6 [Slide.]

7 I would like to show you a few slides describing
8 the nephrotoxicity. What we did was we looked at the mean
9 change from baseline over time. This is in Study 002. The
10 red line--this is mean change in creatinine from baseline.
11 The red line is amphotericin B and I am tracing where the
12 greenish-blue is. Here you can see that it was much less in
13 the AmBisome group and this was statistically significant.

14 [Slide.]

15 We then did the same plot for the adult trials.
16 You can, again, parallel results. These were different
17 statistically favoring AmBisome. Finally, we looked at the
18 pediatric population. Again, to recall, there were 38
19 patients and 37 patients on the two treatment arms that were
20 in the pediatric category.

21 Here we see the red line and the blue line are
22 very close together, not seeing much difference. Also
23 recall this was in a 0.6 mg/kg dose of amphotericin B.

24 [Slide.]

1 In the European study, we see, though, some
2 additional benefit of AmBisome when you compare that to
3 amphotericin B. These differences start looking a little
4 bit more like what we saw in 002. One reason for this could
5 be the fact that the amphotericin B dose in this group was
6 1 mg/kg compared to the 0.06 used in the U.S. study.

7 [Slide.]

8 In summary, our conclusions are that AmBisome is
9 at least as effective as amphotericin B for the empirical
10 therapy of the febrile neutropenic patients. We are
11 interested in the fungal endpoint and are anticipating
12 comments from the committee. The safety profile for
13 AmBisome is improved when compared to amphotericin B
14 especially for nephrotoxicity and infusion-related
15 reactions.

16 [Slide.]

17 Our committee questions are: Is AmBisome safe and
18 effective for use as empirical therapy for the febrile
19 neutropenic patient. We would like you to comment on the
20 discordant results for the proven and presumed infections in
21 Study 002 and, also, to comment on design issues for future
22 trials for the febrile neutropenic host, especially paying
23 attention to specific endpoints of interest which should be
24 given more emphasis.

1 I would like to turn the podium back to the chair.

2 DR. HAMMER: Thank you very much.

3 **Questions for Clarification**

4 DR. HAMMER: Are there any questions for the FDA
5 presentation?

6 DR. EL-SADR: It seems to me, from the curves you
7 showed, that the longer the patients were on the treatment,
8 the curves seemed to come together in creatinine.

9 DR. KORVICK: Thank you for reminding me. I
10 wanted to make a comment and this also reflects back to some
11 of the toxicity questions the committee was grappling with
12 earlier. On average, these patients were on study drug for
13 14, at most 21, days. So the curves start coming back
14 together because the patient numbers start getting smaller
15 and there are fewer patients on study over time.

16 But, in general, when you look, for the majority
17 of patients in those first two to three weeks, there is a
18 separation in the curve. Also, in the 002 study, I think
19 the patients were on study drug, and you can correct me, for
20 an average of about two weeks.

21 So we are not treating these patients for 90 days
22 like the animal data.

23 DR. WONG: You showed two numbers I guess I am
24 interesting in knowing a little more about. One was for the

1 presumed infections, the pneumonias seem to be quite
2 different. Do you have information about how many total
3 pneumonias of all-cause there were in the two groups, not
4 just pneumonias that were presumed to be fungal in origin.

5 DR. KORVICK: I don't have that data. I don't
6 know if the company does.

7 DR. WONG: The second is you analyzed outcome with
8 respect to mortality according to whether someone had no
9 evidence of fungal infection, proven fungal infection or
10 presumed fungal infection. I guess it comes back to the
11 same question I asked the sponsor. To what extent were
12 people assigned to the category of proven infection because
13 fungal infection was found at autopsy and, therefore, the
14 analysis was circular? I guess that is really the question.

15 DR. KORVICK: Not all of the patients had
16 autopsies when they died. In this group, there were
17 handfuls and I don't remember the numbers. These numbers
18 get small, and there were only a small number that were
19 based on autopsy. But they also had clinical symptoms that
20 were suggestive.

21 DR. WONG: I guess my comment is I would suggest
22 that the data be looked at with that question in mind.

23 DR. KORVICK: The other thing is as we talked
24 about the reclassification of the data, when we were

1 reclassifying, you could see that there were shifts between
2 the presumed and the proven but there was no way to shift
3 people from the presumed to the nothing category.

4 So there could also potentially be an artifact in
5 that regard as well.

6 DR. HAMMER: Were there any site-specific issues
7 with respect to the presumed diagnoses?

8 DR. KORVICK: No.

9 DR. HAMMER: They didn't cluster in a couple of
10 sites.

11 DR. KORVICK: We didn't see any influence by site.

12 DR. BUELL: Just in response to your first
13 question, Dr. Wong, there were 26 additional pneumonias on
14 AmBisome that were considered nonfungal and 30 additional
15 pneumonias in amphotericin that were considered non-fungal.

16 DR. FEINBERG: So I guess what are the criteria
17 for thinking that these pneumonias were nonfungal. Let me
18 add, along the lines that Brian was pursuing, you showed us
19 data for antibiotic changes, but there are other causes of
20 fever and, certainly, for example, other causes of
21 pneumonia. So I wonder if you looked at, for example,
22 ganciclovir, institution of ganciclovir.

23 In other words, are there viral pneumonias? What
24 else is happening in this patient population?

1 DR. BUELL: Let me just kind of give an answer as
2 to how it might be. You have a very sick patient with a low
3 count and he is continuing febrile and has something
4 happening on his chest X-rays. So I believe you tend to
5 pull out all the therapies you can to try to help the
6 patient. I would like to think that all those non-proven
7 pneumonias are nonfungal. But the clinician has to make a
8 judgment at that time and he certainly can't ignore them.

9 DR. KORVICK: We had anecdotes this morning, but I
10 recall when I was running through some of the case-report
11 forms, there was a patient that was in the presumed
12 category, had a non-specific chest X-ray and then had
13 metastatic breast cancer and, at autopsy, at death, it was
14 diagnosed as metastatic breast cancer with no evidence of
15 fungal infection.

16 So these are the kinds of people that you are
17 dealing with and it is difficult.

18 DR. FEINBERG: I am asking specifically, since the
19 prior table that the sponsor showed dealt with antibiotic
20 changes, was antibiotic used loosely as antiinfective
21 changes? Do you have a separate dataset for the institution
22 of therapies aimed at nonbacterial pathogens?

23 DR. BUELL: We did look at them separately as
24 well. As I said, we included all three in our definition of

1 an antibiotic modification because all three might have
2 affected a fever in that analysis, antivirals,
3 antiprotozoals and antibacterials.

4 In reality, the number of antiprotozoals
5 instituted were very few so it was primarily an antiviral
6 drug added, I would say predominantly an antibacterial and
7 then next antiviral. I could get those specific numbers but
8 I can't give them to you straightaway here.

9 DR. KAM: In your discussion about the pediatric
10 subjects in Trial 002, you had a slide with the creatinine
11 changes and it appeared that the AmBisome patients had a
12 more protracted course with a subsequent rise in creatinine.
13 Can you comment on the actual numbers of pediatric patients
14 and whether, again, in the trials done in Europe, for
15 example, pediatric patients have a delayed rise in
16 creatinine, for the sponsor or Dr. Korvick.

17 DR. BUELL: As Dr. Korvick pointed out, I know in
18 our study, the average time on therapy was about ten days.
19 These late rises in creatinine are taking place in patients
20 that are staying on study longer and I think that is for a
21 reason. I think they are neutropenic longer, they are
22 sicker, they probably are getting more nephrotoxic insults
23 from other drugs.

24 We had a suggestion of that when we looked at the

1 reversal of the nephrotoxicity after the drug was stopped.
2 The number of patients nephrotoxic when they left the study
3 at the end of therapy was much lower in AmBisome than
4 amphotericin. Correspondingly, the recovery was greater
5 falling towards normal in the amphotericin and less so in
6 AmBisome.

7 I think that is because what we are seeing with
8 AmBisome and a proportion of the amphotericin patients is
9 nephrotoxicity due to other reasons that may not resolve as
10 quickly and the amphotericin-B-induced toxicity will resolve
11 when you stop the drug.

12 I am not particularly troubled by those late
13 occurrences. We have had patients receiving, in our high-
14 dose studies, AmBisome up to 100 days in one instance, and
15 many times 30 or 40 days, and we didn't see what looked like
16 a buildup of nephrotoxicity due to prolonged dosing.

17 DR. KORVICK: I was also interested--you had
18 wondered about numbers, and just to give you a flavor for
19 that in addition to what he was talking about, one way of
20 looking at this would be the number of people or patients
21 who had creatinines twice baseline.

22 So the kinds of numbers we are talking about, any
23 time during when you were on the study, twice baseline in
24 the 002 study for the pediatric population, you had 10 out

1 of 38 and 6 out of 37 for the AmBisome versus amphotericin.
2 In the European study, this is very similar, for twice
3 baseline anytime during the time you were on study drug, you
4 had 9 out of 71 and 14 out of 64.

5 So that is like 13 and 23 percent AmBisome versus
6 amphotericin. So the numbers, even though you are showing
7 the graphs over time, that might be the most conservative
8 way to look at the data.

9 DR. KAM: I guess, in looking through some of the
10 charts that were shown during the sponsor's presentation,
11 there seemed to be clear differences between the AmBisome
12 and the amphotericin B until you showed your graph about the
13 timing of creatinine rises. And that was something that--

14 DR. KORVICK: I just only wanted to illustrate
15 that, perhaps, a smaller benefit was seen in pediatrics and
16 it was hypothesized that, perhaps, amphotericin is not quite
17 as nephrotoxic in the pediatric population and, therefore,
18 you may not expect to see such a difference as you would in
19 the adult.

20 DR. KAM: Right; if you are getting larger doses
21 of equivalent amphotericin drug and they seem to be
22 receiving the investigational drug over a longer period of
23 time, and it is during the, if you will, latter part of
24 their infusions that you are seeing a rise.

1 DR. LIPSKY: I have a question, actually, if I
2 can, for the sponsor, just to clarify the dose. How certain
3 is it that giving more is better. Some of the animal data
4 didn't look overwhelming. It looked like it may have
5 plateaued early. I know you mentioned even going higher in
6 human studies.

7 It is interesting that in vitro it looks like the
8 drug may be slightly more potent, for whatever that means,
9 than amphotericin.

10 DR. BUELL: Yes. I have never maintained that
11 amphotericin B is an ineffective drug. It is a very potent
12 antifungal agent and it becomes difficult to show
13 superiority to it in a clinical trial situation. In a model
14 like Dr. Walsh's Aspergillus model, you can see if you look
15 at the lungs and the degree of pathology and events like
16 that where the infection is proceeding in a more controlled
17 manner than you ever see in the human experience, the higher
18 concentrations seem to enable the infection to be abrogated
19 more quickly. There is less pathology.

20 So we do believe there is a reason to expect that
21 more is better. It is difficult to show it in human
22 studies. We are hopeful that in diseases like cryptococcal
23 meningitis where there is room for improvement that we will
24 be able to begin to show these kinds of benefits with the

1 higher doses.

2 DR. LIPSKY: Do you get better CSF levels? How do
3 you deliver it to the central nervous system?

4 DR. BUELL: It gets to the inflamed meninges
5 through the circulation. We have known for years that
6 amphotericin B doesn't appreciably cross the barrier yet it
7 is effective therapy, probably because inflammation may let
8 the drug penetrate into the site of infection.

9 What we are saying is we are bringing maybe 50 to
10 100 times the concentration. It is in a liposome so it may
11 not be exactly the same thing but that is where we hope we
12 can see the benefit become manifested.

13 DR. LIPSKY: Finally, for either FDA or the
14 sponsor, in the issue with the presumed infections, is it
15 possible that if you had an efficacious or a treatment that
16 was working, that that would obscure the diagnosis and make
17 it less likely to be definite, as if you were drawing a
18 blood culture and someone was on an antibiotic so,
19 therefore, the blood culture might be negative, if you make
20 an analogy.

21 DR. BUELL: It may be that a disease is trying to
22 manifest itself and is held more in check with the AmBisome
23 than with the amphotericin B. Dr. Walsh mentioned that you
24 sometimes have to cut back on the amphotericin because of

1 toxicity. And that may allow something to emerge and become
2 a proven infection.

3 DR. LIPSKY: But, looking at the actual criteria
4 for presumed infection, could one say, "Gee, yes, we are
5 less likely to get it out of the blood because the drug is
6 working, or we are less likely to biopsy it," or is that
7 just idle speculation.

8 DR. BUELL: It may be that the manifestations were
9 more pronounced that led to a diagnostic finding. We didn't
10 really define the criteria for presumed. We defined it for
11 the proven.

12 DR. EL-SADR: Actually, this question is for Dr.
13 Korvick. I am just curious, in general, in my experience
14 for studies with antiviral, studies in HIV patients, usually
15 it is required at least one month post-last-dose of study
16 medication to collect adverse events and mortality. I am
17 curious for studies like this, I thought it was more
18 traditional to have a four-week post study completion or
19 post study at drug administration as sort of a traditional
20 definition for collection of data.

21 DR. KORVICK: I think we do, in general, like to
22 see longer-term follow-up data at the end. I think when the
23 sponsor designed the study, they were looking at the seven
24 day as a cutoff. Dr. Walsh may want to talk more about the

1 kinds of patients that are enrolled in the study and what
2 the long-term data mean.

3 DR. BUELL: I think you are absolutely correct.
4 Ideally, we would like to see patients followed out for one
5 month and even to address this issue on cumulative
6 nephrotoxicity with the concept of large amounts of
7 deposition of liposomal amphotericin B, does that have an
8 impact.

9 If these patients had a chronic infection and were
10 to receive no more cytotoxic chemotherapy--for example,
11 cryptococcal meningitis--where we would basically be able to
12 follow them out over long term, say, in an HIV setting.
13 That would lend itself very nicely to potentially a 30-day,
14 even 90-day, follow up.

15 The problem becomes the nature of our patient
16 population. Many of them are receiving repeated cycles of
17 cytotoxic chemotherapy. A patient with acute nonlymphocytic
18 leukemia will come in for induction chemotherapy, then will
19 undergo, as soon as the neutrophil count recovers, usually
20 within potentially a week of that, they will then undergo
21 hospital admission again and yet another cycle for induction
22 and then, following that, another cycle for consolidation.

23 So no sooner have they recovered from neutropenia
24 which is the point where we would discontinue antifungal

1 study drug, then, within a week, they are rehospitalized.
2 If we follow them out beyond that, it then becomes
3 exceedingly confusing because they are then into a new cycle
4 of neutropenia.

5 They are then being enrolled, potentially, either
6 into another study. It certainly would be counted as a
7 serious adverse event because any rehospitalization, of
8 course, would be considered an SAE although not directly
9 related.

10 Analysis of the patient beyond that period of
11 neutropenia, then, or within seven days, becomes exceedingly
12 complicated and almost uninterpretable because they are
13 undergoing repeated cycles of neutropenic and
14 immunosuppression. Hence, as much as we would like to
15 follow them out farther, we are really precluded from any
16 meaningful of being able to do that.

17 What we did try to do is capture those patients
18 who were reenrolled in the spirit of trying to understand
19 this better. We thought, "Well, how could we do it better?"
20 One way was basically to be able to capture the patients who
21 were reenrolled on study--and that was permitted--with the
22 intent specifically of addressing that issue.

23 We had a small number of patients, 62, who were
24 reenrolled.

1 DR. HAMMER: Can you repeat that.

2 DR. BUELL: No; they weren't counted in the
3 primary analysis. Pardon me. They were not counted in the
4 primary analysis, but, just looking at that subset, we
5 didn't see any deleterious effect of cumulative amphotericin
6 B. In this unique patient population, then, although a very
7 large population, that is as far as we can really take it
8 with our current limitations.

9 DR. EL-SADR: I understand these studies are very
10 difficult to do but I would imagine that, since you
11 randomize an intent-to-treat, you would sort of--what you
12 are looking for is really sort of difference between the two
13 arms.

14 DR. BUELL: In a way, there is the potential
15 retrospectively. These patients are not lost-to-follow-up.
16 They are captured. There is the potential to then go back
17 retrospectively and ask how did these patients do realizing
18 that it is going to be quite complicated in so far as the
19 repeated cycles.

20 DR. HAMMER: Thank you. Are there any other
21 questions either for the sponsor or the FDA?

22 DR. FEINBERG: I have two questions. The first is
23 the indication, which is for the treatment of presumed
24 fungal infection in febrile neutropenic patients. You

1 didn't say anything about the dose for this indication. The
2 dose in the trial is, again, different from the doses used
3 in other trials or the rest of the database. Is that wide
4 open?

5 DR. KORVICK: I think that the sponsor is looking
6 for the 3 mg/kg, when you look at the data for at least the
7 fever endpoints and so forth in the European studies, they
8 sort of look to favor the higher doses being more active
9 than the lower doses. So I think we are in agreement that
10 that is the dose we are looking to.

11 DR. FEINBERG: Then, for the FDA, in your written
12 summary to us, there was a mention of the fact that what was
13 defined as a proven endpoint in this study included
14 endpoints that, by the MSG criteria--this is an MSG study--
15 included endpoints that would be considered probable by sort
16 of the standard MSG grading system, for example for
17 aspergillosis.

18 DR. KORVICK: That really was the only one. I
19 perhaps worded it poorly.

20 DR. FEINBERG: Did you look at that separately, I
21 guess is what I am asking. Did you look at it by the MSG
22 criteria as well as the sponsor's criteria and did that make
23 a difference?

24 DR. KORVICK: They were the same basically. The

1 sponsor's criteria of proven included the confirmed Mycosis
2 Study Group endpoint with the exception that the probably
3 Aspergillus pneumonia diagnosed by bronchoalveolar lavage
4 culture was included in the proven. So, basically, they
5 paralleled the two with that exception.

6 DR. FEINBERG: Do you happen to recall how many
7 patients got into the proven category on the basis of just a
8 positive BAL culture?

9 DR. KORVICK: It was a small number. I think it
10 was, like, three. I do have that.

11 DR. BUELL: We did incorporate an analysis
12 including the probable infections because many people feel
13 that this could be a significant finding.

14 [Slide.]

15 That's here. It adds 3 in AmBisome and 1 in
16 amphotericin B. These probables were called probable by me
17 and Dr. Wingard. You see the p-value down there is 0.024.
18 So they really don't do anything to the finding about the
19 proven infection difference.

20 DR. HAMMER: Thank you.

21 Any last questions? Thank you.

22 **Open Public Hearing**

23 DR. HAMMER: There is now time for an open public
24 hearing. No individuals have come forward to sign up, but

1 is there anyone here who wishes to speak at the open public
2 session?

3 If not, we are going to, since we are a little bit
4 ahead of schedule, the committee's wish is not to break for
5 lunch but, really, to move on to the charge to the committee
6 and to the discussion.

7 So we will turn to Mark Goldberger to give us our
8 charge.

9 **Charge to the Committee**

10 DR. GOLDBERGER: Dr. Feigal was, as you see, on
11 the agenda scheduled to do this. However, he was called, as
12 they say in Washington, downtown. So he will not be able to
13 do this. He timed it, as you notice, extremely well leaving
14 about three minutes ago.

15 Basically, I thought I would just elaborate a
16 little bit on our questions to you sort of as a starting
17 point. Our first question, I thought, is relatively
18 straightforward, I would hope, at least to ask and,
19 hopefully, will not be too difficult to answer. Is AmBisome
20 safe and effective for use as empirical therapy for febrile
21 neutropenic patients?

22 Our second question has been the subject already
23 of some discussion this morning. We deliberately focussed
24 on it because we think this is an important point to get

1 your opinion on, and that is we would ask you to comment on
2 the discordant results for proven and presumed fungal
3 infections in Study 002.

4 Keep in mind that at one level, what we saw in
5 terms of the fungal endpoints in this trial was not entirely
6 expected; that is, as you know, the previous trials, which
7 have been smaller, have been powered on a composite or
8 febrile endpoint.

9 The trial, initially, was also powered on an
10 endpoint related to fever. The principle endpoint was a
11 composite endpoint as well. The idea that one could
12 actually see an important result in proven fungal endpoints
13 is something that is welcomed, I think, potentially welcomed
14 but was not entirely expected.

15 I think even, perhaps, less expected was the
16 finding that what we seem to see is that the proven
17 endpoints are in one direction, the presumed in the other.
18 I should also keep in mind that, as you can see from some of
19 the discussion this morning, perhaps we were not as entirely
20 prepared prospectively as we might have been in terms of
21 looking at the issue.

22 One of the reasons, therefore, to ask you about
23 is, first of all, to get your opinion about whether, on
24 balance, taking into account both the data that you have

1 heard today and your knowledge of both the pathophysiology
2 of disease and the effectiveness of treatment that what we
3 see here is, perhaps, more likely to be a biologic
4 phenomenon that is going to need some explanation or this is
5 something that, perhaps, just occurred by chance alone,
6 albeit, perhaps, a relatively unlikely occurrence.

7 The second thing which would, perhaps, follow in
8 large part from what you think about the first part of the
9 question is what implications might we draw about our
10 understanding of the activity of AmBisome based upon this
11 issue of the discordance between proven and presumed
12 endpoints and, finally, really, leading into the third
13 question, what implications does this have for future
14 studies.

15 Our third question, at one level, basically, is,
16 obviously, to comment on design issues for future trials
17 with particular attention to the endpoints or endpoints
18 which would be given emphasis. But, obviously, as part of
19 that, we are particularly interested in what you think about
20 presumed endpoint and the things we might be thinking of in
21 advance and the advice that ought to be provided to sponsors
22 about the questions that should be asked, the data
23 collected, so that if this issue occurs again in a future
24 trial, we will be in a better position to evaluate it and we

1 will minimize uncertainty taking into account that when one
2 deals with a presumed endpoint in this clinical setting, it
3 is impossible, I think, to truly eliminate uncertainty.

4 Our goal, therefore, is to minimize it as best we
5 can. Those, basically, are our questions to you.

6 Obviously, you are free to elaborate on any of them during
7 your discussion but these are the things that we would like
8 to get from you during the discussion of questions.

9 DR. HAMMER: Thank you very much.

10 **Open Committee Discussion**

11 DR. HAMMER: I will read the first question again.

12 This is a question that we will first discuss and then the
13 committee will vote on. It is as stated, "Is AmBisome safe
14 and effective for use as empirical therapy for febrile
15 neutropenic patients?"

16 I will begin on the right with Virginia.

17 DR. KAM: First, I will address the safety and
18 then the effectiveness. Certainly, if you take the most
19 stringent criteria--i.e., patient discontinuation--I think
20 there is equivalence between those receiving AmBisome and
21 those receiving amphotericin B.

22 Albeit it has been shown on several slide
23 presentations, there is apparent less nephrotoxicity over
24 long-term usage and less acute reactions during the

1 infusion, I think, because this falls into the empiric
2 category of therapy, I would need to take consideration for
3 patient discontinuation as a more strict criteria for safety
4 issues.

5 So I think, in the equivalence question, it is as
6 safe as amphotericin B. In terms of efficacy, and, again, I
7 apologize if I am overstepping the question numbers, I think
8 that it is important to take into consideration both the
9 proven as well as presumed infections in the analysis of
10 effectiveness because, as the title of the study states, it
11 is for the treatment of presumed fungal infections in a
12 neutropenic setting.

13 Again, they, in my opinion, have shown
14 equivalence. So the AmBisome is as equivalent as
15 amphotericin B for efficacy. Right now, amphotericin is
16 used as a standard of care for neutropenic hosts and it has
17 not got that indication on its own, amphotericin being used
18 for empirical therapy.

19 So I would say that there is equivalent safety and
20 efficacy of this new product compared with a standard that
21 we currently use in the clinical setting.

22 DR. WONG: I think on the safety, the drug has
23 been demonstrated with short-term follow up to be safe. I
24 guess for longer-term follow up, as Dr. Walsh mentioned, it

1 will probably be necessary to look at the results from some
2 of the other trials beside this one in which people are not
3 immediately reenrolled in chemotherapeutic trials so that
4 you can't answer the question.

5 Effective; I guess I pretty much agree with Dr.
6 Kan. Efficacy seems to be at least as good as amphotericin
7 B insofar as this composite endpoint is concerned. I guess
8 my comment would be that I think a separate question is, in
9 this setting, is the new drug as effective as amphotericin B
10 for treatment of proven fungal infections.

11 The small number of patients, 10 or 11 per group,
12 who were shown to have fungal infections at the time of
13 randomization, I think are key for answering that question.
14 When I asked the question, I guess I was assured that most
15 of those patients received their assigned study drug and
16 most of them got better, but I guess I would like to see
17 that analysis really filled out; how many in each group were
18 treated throughout the episode with the assigned drug and
19 what were the outcomes.

20 It is really that group, I think, that tells us
21 whether this is an effective treatment for the infection
22 that we are designing our empirical therapy to treat. I
23 think analysis of even that small subgroup should be fleshed
24 out and, if they are shown to be equivalent, I would take

1 that very seriously.

2 DR. ELASHOFF: As to safety, the AmBisome appears
3 to be at least as safe or safer than amphotericin B in terms
4 of what was measured in this study. Something that was
5 mentioned in terms of the design of the study and also
6 information that were given in terms of demonstrated
7 antifungal activity of AmBisome, what I saw were studies in
8 which some percent of patients were cured or whatever, but
9 none of them contained an internal control.

10 So, presumably, using that data to conclude that
11 they have demonstrated antifungal activity requires implicit
12 reference to an historical control which I, personally, am
13 not familiar with. So I wouldn't say that the data that
14 have been presented here demonstrate antifungal activity
15 from a statistical point of view.

16 Second, in terms of the success outcome that they
17 use in this study, AmBisome appears to be equivalent to
18 amphotericin B in terms of being within a plus or minus
19 10 percent confidence interval. Again, however, there is no
20 internal proof that amphotericin B is effective in this
21 population.

22 So it appears to be, in terms of this study,
23 equivalent to amphotericin B but whether either one is
24 effective, I don't think, has been proven by the data that

1 have been shown.

2 DR. EL-SADR: We are being asked today to comment
3 on an indication for this drug in treatment of febrile
4 neutropenia patients. So, in my own mind, I am
5 differentiating between that and treatment of fungal
6 infections.

7 I think the data presented here convince me that
8 AmBisome is similar to amphotericin B in safety and
9 effectiveness. I will stop there.

10 DR. LIPSKY: I would agree that it appears that
11 AmBisome may be more safe than amphotericin B in these
12 patients and it certainly appears to be equally efficacious
13 as amphotericin. I am a bit reassured that in the presumed
14 infections, there were, in the data presented, five deaths
15 in each group with an equal number of patients. That,
16 perhaps, gives some degree of comfort.

17 I think the way the question is phrased, or the
18 question is phrased, may be inappropriate because all we can
19 really do is to compare this to a gold standard. One might
20 say, "Gee; 50 percent rate. Is that something that you
21 believe is effective?" But I think, though, in this
22 situation what we have is compare to the gold standard.

23 DR. FEINBERG: I agree with most of the preceding
24 speakers. I guess I would be comfortable saying that this

1 liposomal formulation of amphotericin is at least as safe as
2 amphotericin B. It certainly appears to be safer in terms
3 of the acute infusion-related toxicity.

4 Just on the basis of clinical experience, I feel
5 less convinced about the nephrotoxicity, in that
6 artificially defined increases in creatinine, are
7 artificially defined increases in creatinine. When you
8 treat a patient with a life-threatening fungal infection,
9 you don't let creatinine stand in your way.

10 So, to me, this is something of a straw man. You
11 don't just stop giving people amphotericin because their
12 creatinine goes up a little bit or even a fair amount. So
13 that, to me, is less convincing.

14 But I think the infusion-related toxicities look
15 better than the amphotericin B. As far as effectiveness
16 goes, I am agreement with the preceding speakers. I think,
17 given this composite endpoint, given that the composite
18 endpoint included the proven and presumed cases, it would be
19 fair in my mind to say that this is within that confidence
20 interval roughly equivalent to amphotericin B.

21 I agree with Brian that those small numbers of
22 patients who had the disease of interest at entry are very
23 valuable patients and it is a shame that they are a small
24 number and that we don't have a complete set of information

1 about them.

2 DR. MATHEWS: I agree with the consensus opinion.

3 DR. DIAZ: I agree that AmBisome is at least as
4 safe and, perhaps, safer than amphotericin. Certainly, the
5 data that has been presented would suggest that it is as
6 effective as amphotericin B. But, and perhaps this is
7 jumping a little bit to Question 2, but I would like to,
8 since we are being asked for an indication for pediatric
9 patients and, in the pivotal trial, there are much smaller
10 numbers of pediatric patients, in particular, with wider
11 confidence intervals in terms of success, could we have a
12 little bit of information about the presumed fungal
13 infections in the pediatric, broken out into the pediatric
14 group, if that exists?

15 I would just like to see where the peds patients
16 fall in that category. I am a little bit reassured by the
17 mortality rates that the FDA presented for the presumed
18 groups, but I would just like to see the numbers if they are
19 there.

20 DR. BUELL: Based on the investigator's
21 designation, there were four in children in AmBisome, four
22 presumed, and there were two in children on amphotericin B
23 that were designated presumed.

24 DR. DIAZ: And the mortality of those?

1 DR. BUELL: What is the question? I'm sorry.

2 DR. DIAZ: You said there were four in the
3 AmBisome and two in the amphotericin group.

4 DR. BUELL: That were given the designation of
5 presumed infections.

6 DR. DIAZ: What about their outcome?

7 DR. BUELL: I can't do that right here, to trace
8 their outcome. Those in the presumed category in general
9 had a better outcome than those in the proven. I could look
10 for these specific patients to find out.

11 DR. DIAZ: That's okay.

12 DR. ELASHOFF: Was that both presumed and proven,
13 or just presumed.

14 DR. BUELL: No; I am just giving the presumed.

15 DR. ELASHOFF: The proven was.

16 DR. BUELL: We have a slide if we can put it up
17 that is proven by age, I believe. Slide 70.

18 [Slide.]

19 This is the breakdown of the treatment-emergent
20 investigator-designated proven. That was the 16 versus 32,
21 by age. You can see two in AmBisome, no deaths, three in
22 amphotericin B, two deaths. This is the intermediate-age
23 population of the predominant population in the study and
24 then this is the elderly.

1 DR. HAMMER: I agree with my colleagues. Just a
2 couple of brief comments. First, it appears to me that this
3 was a rigorously done study that was attempted to be
4 designed with the best advice at the time and was designed
5 as an equivalent study and, I think, achieved its goals with
6 the data generally, except for the one point that has been
7 raised about the presumed infections, fairly clear.

8 My own sort of appreciation of the data is that I
9 think for adults, that AmBisome is safer with respect to
10 particularly nephrotoxicity and infusion-related reactions.
11 Dr. Feinberg's point about the clinical significance of the
12 creatinine is well taken but, certainly, statistically that
13 is proven and the infusion-related reactions also
14 substantiate that.

15 With regard to efficacy, it certainly is
16 equivalent, it was shown, I think, fairly clearly to the
17 gold standard of amphotericin B. So I would say it is at
18 least comparable and there were some hints in some areas
19 that there may be some superiority when you get to the
20 proven fungal infections, a very important aspect.

21 I think, although those numbers are small and it
22 is a subgroup, it is a very important part of the study
23 because, although we are debating what the presumptive
24 infections mean, the proven infections are really key, from

1 an infectious disease perspective, in sort of detailing what
2 this drug may be doing.

3 So I think there were important hints there but,
4 as far as how the study was designed in achieving its goals
5 as an equivalent study and is it safe and effective as
6 empirical therapy in febrile neutropenic patients, my own
7 feeling is that the data from this single study substantiate
8 that.

9 That is the final point. It is a very well run
10 study. It is a single study, however. We know how
11 difficult these studies are in this patient population.

12 If there are no further comments, then I think we
13 should, for the record, vote on the first question. The
14 voting members of the committee are Drs. El-Sadr, Lipsky,
15 Feinberg, Mathews, Diaz, Wong and Elashoff.

16 So I will just put this to a vote. Sometimes, we
17 separate safety and efficacy. Is there a desire to separate
18 those two questions, or can we just vote on the combined
19 question. So; is AmBisome safe and effective for use as
20 empirical therapy for febrile neutropenic patients. All
21 individuals who feel that that answer to that question is
22 yes, please raise your hand.

23 [Show of hands.]

24 DR. ELASHOFF: If it were safe and equivalent, I

1 would say yes. I have a little trouble with safe and
2 effective.

3 DR. HAMMER: We can note the modification.

4 DR. EL-SADR: I think maybe change it, similar in
5 safety and effectiveness?

6 DR. HAMMER: Put a footnote that a couple of
7 members--

8 DR. WONG: I would be willing to say it is safe
9 and effective.

10 DR. HAMMER: Yes; I am willing to say it. That is
11 why I think it is a footnote.

12 DR. WONG: I would not support changing it to safe
13 and equivalent.

14 DR. HAMMER: That is why we are saying, for the
15 members who want it, equivalent will be a footnote.

16 DR. MURRAY: From a regulatory perspective,
17 effective is equivalent to a gold standard, something that
18 is recognized as a gold standard. So effective would be
19 equivalence to a gold standard. We think it is the same
20 thing.

21 DR. GOLDBERGER: I think that, basically, here, in
22 this case, we deliberately did not go into detail about
23 asking you to specifically compare it to amphotericin. That
24 could have been a leading question, knowing that you might

1 get into it anyway, partly because we recognized that we did
2 not present the full range of data that exists in this
3 product.

4 I gave you a sense, earlier on, of what the FDA
5 review thought about the treatment of fungal disease but,
6 certainly, it was not presented in the detail that one might
7 normally expect and, therefore, it is somewhat unfair to
8 make comparisons in the absence of that type of detail.

9 We gave you, I hope, a little background and asked
10 the company to present so you would have some sense of what
11 we think, but, basically, effective takes into account
12 obviously the way the clinical trial was done. And, as was
13 pointed out, if amphotericin B is considered the gold
14 standard, which I think most people would agree with,
15 regardless of whether it carries that indication, you are
16 certainly free, then, to use the term "effective" by stating
17 that it was as good as amphotericin B even if there are some
18 regulatory issues we might have to work through.

19 DR. HAMMER: Is there anyone who votes no?

20 [No response.]

21 DR. HAMMER: So, for the record, it is a unanimous
22 vote.

23 Now we get into the other discussion issues. The
24 second point for discussion is, "Please comment on the

1 discordant results for proven and presumed fungal infections
2 in Study 002."

3 DR. DIAZ: I think that discordant results are the
4 results that have given us the most pause in thinking in
5 terms of trying to sort those patients out and figure out
6 what was going on with them, in particular, because, as
7 someone stated earlier, this is empiric therapy for presumed
8 fungal infections.

9 Those are patients who, by physician standards or
10 the person taking care of them felt that the patient most
11 likely had a fungal infection although it was not proven.

12 I am again, as I said, more reassured by the data
13 that was presented in terms of looking more carefully at
14 mortality rates amongst those groups with proven and
15 presumed and would agree that if the presumed patients had
16 fungal infections or just were not proven, that one would
17 expect their mortality, also, to be higher than it was.

18 However, I think there are lots of things we don't
19 know about those patients that may have just put them into a
20 presumed category. We don't know how many tests were done,
21 what types of tests, if there was any uniformity across the
22 study in terms of how they were diagnosed or how diagnoses
23 were looked for in these particular patients.

24 So it may be just an incidental result that they

1 happen to end up in the AmBisome group albeit there were
2 fairly small numbers of them. But, certainly, the results
3 were discordant. I would like to know a little bit more
4 about where those particular--we don't know much about those
5 particular patients, in particular, where they were in their
6 therapy, what kinds of patients they were and, perhaps, were
7 they patients where, for one reason or another, they were
8 looked at more carefully or were put in a higher-risk
9 category by the physician taking care of them.

10 DR. MATHEWS: I don't really have any much
11 confidence in interpreting those discordant results. I
12 don't know of any biological reason why that difference
13 should have been observed. It is basically the same drug, a
14 different delivery system.

15 We asked some questions about when in the course
16 of the treatment these infections emerged. There didn't
17 appear to be marked differences. In terms of dosage
18 equivalency that had been--I think that is another issue
19 that could have been probed where the cumulative doses at
20 the time of the infection's diagnosis equivalent.

21 I think, more importantly, there are these issues
22 that relate to diagnostic intensity and I think that, as
23 excellent as the study was conducted, it sounds to me like I
24 think there is room for improvement in terms of

1 documentation of what procedures were done when a given
2 clinical scenario unfolded, comparable number of blood
3 cultures.

4 If you do a bronchoscopy, were there comparable
5 numbers of biopsies and so on and so forth, none of which
6 you may have great control over in that sycoption, but at
7 least to be able to document that key parameter.

8 Also, the issue of the blinding, I think there is
9 no question in my mind that the blinding was effective in
10 terms of the actual drug itself, in terms of the way it is
11 packaged. But I think that the reviews by the independent
12 investigator and by the Agency, all of those reviews are
13 only conditionally independent because they are conditional
14 on the source documents.

15 What gets into those documents is prespecified but
16 what is left out is often at the discretion of the
17 indication filling out the forms. So, for all those
18 reasons, I would not place great emphasis on the meaning of
19 those observed differences.

20 DR. FEINBERG: I share Chris' opinion on this. I
21 don't know what this means. It seems soft. It is
22 discordant. It is always troubling when data don't line up
23 nicely but it is hard to understand in on a biologic basis.
24 It is not only the same drug on a mg/kg basis. It was more

1 of the same drug.

2 That these results should move in opposite
3 directions makes not a great deal of sense to me. I think
4 the only reassuring thing in terms of what we talked about
5 in terms of our response to Question 1 is that it is
6 reassuring that the liposomal formulation had a better track
7 record at least for the proven infections and from an
8 infectious disease standpoint. There is data you can sort
9 of sink your teeth into, that people actually had a
10 diagnosis.

11 I don't know what to make of it. I don't know how
12 much it is worth belaboring.

13 DR. LIPSKY: I am not going to belabor it.

14 DR. EL-SADR: I think it is very important for
15 this sponsor and for other sponsors who are doing similar
16 studies to continue to use this endpoint and collect the
17 presumed events because I think with this patient
18 population, a lot of the events will be presumed knowing
19 that they are very sick and often invasive procedures are
20 difficult and unlikely, or can be difficult to be done.

21 So I think it is a good idea to collect them and
22 it would be interesting to see if this holds up with other
23 liposomal products as well. I know that the data that Dr.
24 Buell gave us on that mean time-to-diagnosis, I think it was

1 both for proven and presumed, correct? Seven days and 11
2 days?

3 I am just curious whether the mean time-to-
4 diagnosis for the presumed events was also similar or not
5 but that might be something--

6 DR. BUELL: The data that I gave you was for the
7 proven category as specified by the investigators. If we
8 use the strict criteria, 6 in each group were really
9 presumed. My feeling is that we need to relook at that
10 because if it was based on a urine or stool, as some of the
11 presumeds were, it could be diagnosed and picked up earlier.

12 I would just like to make one comment. It was a
13 double-blinded study and I think you have to keep that in
14 mind when you ask questions about the diagnostic intensity
15 because they would be approaching these patients equally
16 presumably because it is double-blinded.

17 DR. EL-SADR: That is the nature of these clinical
18 trials and it is very hard to strictly tell people what to
19 do diagnostically. I think this is real life. So, again, I
20 think it remains to be just seen in other studies of this
21 product and maybe of other liposomal products.

22 DR. ELASHOFF: I certainly have no biological
23 expertise. The only thing that was implied about something
24 is that if the liposomal formulation affects X-ray findings.

1 However, it sounds like the criteria for presuming an
2 infection were not detailed or consistently applied nor were
3 the criteria for what you are supposed to do whether it is
4 proven or not if it is presumed doesn't sound as if they
5 were detailed or consistently applied.

6 Therefore, I don't think you can make much of the
7 division into proven versus presumed.

8 DR. WONG: I guess I have a little bit of a
9 different take on this issue. When I read the briefing
10 document, I was struck, as I am sure everyone was, by the
11 apparently pronounced difference in proportion of patients
12 who developed proven infection during treatment.

13 Then I was really very surprised that the results
14 for presumed infections were exactly in the opposite
15 direction and apparently compensatory. I thought a lot
16 about how that might happen. The reason was that this trial
17 raises the possibility that we actually may have a superior
18 drug to the one that we have all been using for many years.

19 That, obviously, is a very exciting prospect. We
20 don't do very well with patients with invasive fungal
21 diseases who are neutropenic and if we have something that
22 is better, we should all know that.

23 Unfortunately, I think I have decided that this is
24 not the case. I would propose that the most likely

1 explanation in my mind for the discordant results--that is,
2 better results with AmBisome than with amphotericin B for
3 proven infections and worse results for presumed infections--
4 -is that the AmBisome administration may actually have
5 influenced the ability to prove infections, the total number
6 of which were probably of relatively equal number.

7 We saw from the presentation from the sponsor that
8 the minimal inhibitory concentrations of AmBisome and
9 amphotericin B in culture were roughly similar but we also
10 saw that the blood concentrations in animals and also in
11 humans, given the doses that were equivalent to those given
12 in this study, were substantially higher in the patients who
13 received AmBisome than in those who received amphotericin B.

14 So one interpretation of the data would be that it
15 is more difficult to culture out organisms that are,
16 nevertheless, present in the presence of higher blood
17 concentrations of the drug of interest. I think that might
18 explain the difference. Obviously, we can't answer that
19 question.

20 Does the same apply to bronchoalveolar lavage
21 fluid? Again, we don't know, but that would be a
22 possibility. So I think we are really left with two
23 hypotheses, one of which is extremely exciting and would be
24 nice if it were true, and that is that AmBisome is really

1 superior to amphotericin B in this situation.

2 The second is if the two drugs are equivalent and
3 that AmBisome had a different effect on diagnostic accuracy
4 of standard culturing than did amphotericin B. I am afraid
5 I suspect that the second may be more likely, but it is
6 still an open question.

7 DR. KAM: If I could have some clarification. We
8 were told that patients could enroll a second time after the
9 waiting-out period. Were any of the presumed cases then
10 later confirmed to be proven cases? Does the sponsor have
11 that kind of data? In other words, could a patient have
12 gotten on to the study as an AmBisome patient and had
13 presumed infection and then the same patient down the line a
14 month, or whatever, later been proven to have a fungal
15 infection but ended up on the amphotericin arm?

16 Would that have been a possible scenario?

17 DR. BUELL: I think there were not enough patients
18 reentered. Only 62 patients reentered, so I don't think we
19 have enough of a sampling to draw conclusions about an
20 outcome like that.

21 DR. ELASHOFF: And it was stated that they were
22 not included, the second time around was not included in the
23 data we saw.

24 DR. KAM: Not included in the analyses. Okay. I

1 just wanted to clarify that for my own understanding. But I
2 think that, in terms of the discordant results, I know that
3 the presumed infections offer us a mixed collection of
4 clinical scenarios. However, I think, in terms of looking
5 at the bottom-line mortality, they still actually had a
6 fairly significant clinical outcome.

7 So, in my opinion, I think they have to be
8 combined despite the discordance. I think I agree with all
9 the comments that have been said by my predecessors.

10 DR. HAMMER: I would agree. I don't have much to
11 add. We are basically being asked to firmly grip sand here
12 with this discussion point. Since we don't have enough
13 information, as Chris and others have mentioned, you really
14 have to go through the charts if you want us to really
15 wrestle with what these presumed fungal infections may be.

16 Is it biologically meaningful? Again, I don't
17 think we know whether this is a fluke or biologically
18 significant. I think what Brian said and what Jim said
19 earlier about whether diagnostic ability is being curtailed
20 because of the activity of AmBisome and so you get sort of
21 partial syndromes rather than full-blown syndromes that you
22 can diagnose is, perhaps, the one hypothesis you can put
23 forward.

24 But I still think that is really just a hypothesis

1 and so many things are going on here, particularly since the
2 clusters and the pulmonary aspect of things where we know
3 how much interpretation and difficulties go on in thinking
4 about chest X-rays in this difficult group of patients. I
5 don't think it is really easy to say

6 The mortality group, in the presumed situation,
7 however, is reassuring in that sense. So I am not given
8 pause there. I think, overall, for the interpretation of
9 the study, you have to lump them together. That is what was
10 prespecified in the protocol and so at least gives you a
11 sense that it is equivalent if you combine everything,
12 again, harking back to what we said with the first question.

13 It is the proven fungal infections where there
14 seems to be clearly an advantage in this analysis to
15 AmBisome is really what I think one wrestles with. This
16 brings up the point, in any clinical trial, when you start
17 looking at presumptive diagnoses, it becomes extremely
18 difficult.

19 I think what point No. 2 really tells us is to try
20 to think hard about future trials. In this patient
21 population, you cannot ignore presumptive syndromes, again,
22 because of the clinical difficult in going after diagnoses
23 aggressively, but prespecifying them as best you can,
24 perhaps separating them up front.

1 Instead of lumping them with proven infections,
2 perhaps having a protocol-driven real-time contact with the
3 principle investigators--I don't know if that happened here,
4 and it is very difficult in this patient population, but
5 maybe there are ways to separate this group out for future
6 studies if, in fact, those are done, to learn something from
7 this discordance.

8 I think it remains an issue that we will not be
9 able to solve unless there are more data that can be
10 extracted from the database and the original source
11 materials that have been raised by other members of the
12 committee.

13 Point No. 3, the last point, for discussion which
14 this naturally leads into is, "Please comment on design
15 issues for future trials with particular attention to the
16 endpoint or endpoints which should be given emphasis."
17 Maybe I will start with Virginia.

18 DR. KAM: I think that when empiric-therapy trials
19 are begun and the duration that patients have been placed on
20 antibacterial coverage before starting antifungal coverage,
21 appears to be shortened. When I think Dr. Pizzo did his
22 initial studies on the febrile neutropenic patient and
23 showed the utility of amphotericin, he waited about seven
24 days prior to starting antifungal therapy.

1 During that period of, if you will, evaluation,
2 there were about 30 percent of patients who developed fungal
3 infections, proven, probable or presumed. Now that I see
4 that we are moving empiric therapy closer and closer to
5 three and four days, it may impact on our ability to
6 diagnose fungal infections and then becomes a finer line
7 between prophylactic use and empiric therapy for a targeted
8 fungal infection.

9 So I think that, obviously, prior to starting
10 newer trials, the period where you are going to allow the
11 antibacterials to do their job before starting antifungals
12 needs to be defined.

13 The second thing is that right now I think it is
14 fairly clear and evident on the presentation this morning
15 and others that the endpoint should be fungal infections.
16 As we have seen between the proven and the presumed
17 infections seen in the two arms of the study total about 14
18 percent of each group of patients and not the 30 percent
19 that was initially reported in the trials that are probably
20 now 30 years old.

21 So I think fungal endpoints are to be the primary
22 endpoint. I think, as even Dr. Walsh has commented, fever
23 alone during this period may not be an adequate assessment.
24 And then, thirdly, because there had been such a discordant

1 result in Question No. 2 about making a firm diagnosis, I
2 think having, in the design of the study, to go aggressively
3 after tissue biopsy and/or autopsy should be pursued.

4 In this manner, I think we define exactly what
5 these nebulous presumed infections may be and, perhaps,
6 provide some education as to some changing trends in the
7 types of fungal infections that we are now seeing in the era
8 of very broad-spectrum antibiotics, use of growth factors,
9 et cetera, and immune modulators.

10 DR. WONG: I have a few suggestions. One is that
11 I don't think, in considering studies of this type and
12 clinical indications of this type, we will be able to avoid
13 using these reasonably complex composite clinical endpoints.
14 But I would advise that they be refined in a couple of ways.
15 One is that I think that the toxicity parameters do not
16 belong in the efficacy endpoints. They really should be
17 separated out.

18 If we run into a very toxic drug, it could really
19 confound things. Second, I think, although it is necessary
20 to use these composite clinical endpoints that have some
21 components that almost surely are soft, every effort should
22 be made to analyze rigorously the minority of patients who
23 really give us the opportunity to ask the question, is the
24 drug an effective antifungal agent.

1 In this study, I guess there were a total of 22
2 patients who were found, subsequent to enrollment, to have
3 had infection at the time of enrollment. I would have liked
4 to have seen those patients really analyzed in detail so
5 that one could answer the question, did the drug work at all
6 and, if so, which one was better.

7 So I think that that should be incorporated and it
8 is going to be the case that it is a minority of patients,
9 oftentimes a small minority. But even a few patients can
10 answer some important questions.

11 Second, I think that in analyzing, other than for
12 the primary endpoint, especially for the problem of emerging
13 infections, very careful attention has to be paid to the
14 possibility that a treatment, itself, may influence the
15 ability to diagnose the diseases of interest.

16 I don't know the answer of how to deal with that
17 except that I believe that that is what we have seen here
18 today. Lastly, I think that one should take great efforts
19 to exclude bias introduced by differences in mortality or
20 autopsy rates and that people who have proven infection,
21 because they died and had autopsies, should be separated out
22 so that we could see who moved from the presumed group to
23 the proven group because they died as opposed to they were
24 proven during life at the same time as everybody else.

1 DR. ELASHOFF: I agree that I would like to see as
2 much as possible, in terms of the actual impact on
3 infections since it is pretty easy to show something
4 equivalent to something else if there is really no disease
5 taking place. I would like to comment that if we are going
6 to try and look at those who have existing infections when
7 the study starts or emergent infections that the power
8 issues are probably going to require perhaps even larger
9 studies than the one that was done here.

10 I would also like to see, to the extent possible,
11 really detailed criteria and instructions for how you get to
12 have a presumed infection and how you get from there to a
13 proven one. I think that especially when side-effect
14 profile looks somewhat different, the question of the extent
15 to which the investigator might pursue things more if they
16 think they are one drug or the other brings up not just
17 trying to do the double blind as well as you can from a
18 logistic point of view but trying to find out what kinds of
19 guessing is going on and how much that has been influenced
20 by other things like the side-effect profile.

21 DR. EL-SADR: I think the composite endpoint that
22 was picked for study actually in some ways was the very
23 rigorous one because it required the patients to be
24 categorized as a success if they had really satisfied many,

1 many different criteria.

2 I think probably I believe that the issue of the
3 major primary endpoint would be the emergent, proven and
4 presumed fungal infections. I think that key--that is what
5 we are trying to do with these treatments and survival. I
6 would hope that survival would also be a bit longer-term
7 survival, maybe four weeks post-study-drug and follow-up
8 period.

9 DR. LIPSKY: I think that one key issue that
10 perhaps this drug was a little different, but, for
11 scientific rigor, it would be nice that we have absolute
12 surety in efficacy in known infections prior to jumping into
13 empiric use.

14 I understand that the drug has been out for ten
15 years and a colleague from London came to give testimony to
16 that fact. But it would just seem that detailed data should
17 be presented so you know that, certainly, there is not an
18 increased risk to the situation, et cetera.

19 That being said, looking at an individual
20 situation of empirical therapy, obviously have enough
21 documented cases. That has been discussed I guess at at
22 least two workshops, so it need not go into that in detail.
23 But if one is, then, going to make assumptions about
24 presumed infection, then there should be absolutely rigorous

1 criteria for what that would be.

2 I understand yes that, hopefully, by a
3 prospective, randomized, double-blind controlled trial that
4 whatever fog is in one arm would hope be in the other. But
5 I think that we can do better than that.

6 Then, just one final comment that if, indeed,
7 there was, in this trial, some obscurity because of the
8 therapy, it would most likely be because the therapy was
9 better than the gold standard.

10 DR. GOLDBERGER: I largely agree with the other
11 speakers that the composite endpoint could be refined,
12 future protocols could tighten up on how evaluation ought to
13 proceed and that there should be longer follow up. I would
14 like to just focus on what should be the primary endpoint.

15 I actually think that the primary endpoint should
16 really be focused on the fungal infection. The composite
17 endpoint adds information and is useful. I don't think it
18 should be abandoned. I think it should be refined. But, in
19 my mind, I think it would be best used as a supportive
20 endpoint or secondary endpoint rather than being the other
21 way around.

22 DR. MATHEWS: This, I think, was an excellent
23 trial, very well done. I find that the composite endpoint,
24 its major flaw I think is in not prespecifying the criteria

1 for presumptive diagnosis. It might have been helpful--many
2 trials, I know, have endpoint committees that, in real time,
3 review endpoints by a group of investigators.

4 That might be helpful in the future to review
5 presumptive and proven endpoints.

6 The last comment is that while doing a randomized
7 double-blinded trial should theoretically protect from bias
8 in diagnostic ascertainment, there are numerous examples in
9 clinical-trial history where, because of the point Dr.
10 Elashoff made about different toxicity profiles, and so on,
11 it is not sufficient guarantee that there isn't some subtle
12 loss of blinding.

13 If you were to have presented us data where the
14 opposite findings were observed, where there were more
15 proven infections in the AmBisome group than in the
16 amphotericin group, we would be doing quite a dance to
17 explain it and approve the drug.

18 So I think it is worth the effort in future trials
19 to have some measures of diagnostic intensity building into
20 the protocol so you can document what was done in one and
21 the other and at least be able to talk other than in an
22 anecdotal way about those sorts of issues.

23 DR. DIAZ: I would basically reiterate that. I
24 think having a composite endpoint was useful but we really

1 have to focus upon emergent fungal infections and, likewise,
2 the presumed fungal infections and having some kind of
3 rigorous protocol in terms of trying to control for the
4 types of activities that go about in terms of trying to make
5 diagnoses would be useful and, also, having more
6 information, perhaps even on a real-time basis, about the
7 patients and where they sit currently in terms of their
8 immunosuppression would help, perhaps, sort out some of
9 these problems in the end result.

10 DR. HAMMER: I think all of the points have been
11 well made by my colleagues. Personally, I don't think you
12 can get away from a combined endpoint in these studies in
13 part for the practical issues of samples sizes, et cetera,
14 but also that that reflects the clinical situation in which
15 these drugs are used.

16 However, things can be refined as has been
17 reflected, certainly survival issues and the proven emergent
18 fungal infections. As therapies improve and as approaches
19 improve, one way to sort of tackle that is to enrich the
20 patient population for the high-risk patient so that you, in
21 fact, try to insure that you are able to see sufficient
22 numbers of proven fungal infections to see a difference,
23 perhaps, or at least equivalence with two different
24 treatments.

1 I think the point about you have to include
2 presumptive infections but that you need to try to
3 prespecify that and rigorously define them as best you can
4 in the situation is well taken.

5 Lastly, I would agree with Brian that the
6 composite endpoint may be necessary here and appropriate but
7 that safety issues should be separated. I think it is not
8 difficult at all for either clinicians or reviewers to
9 separate those issues and, in fact, we generally try to do
10 that.

11 So I think, basically, the way this study was
12 approached was excellent. It can be refined if future
13 studies, in fact, are going to take this a step forward.

14 I don't have anything else to add. Mark, is there
15 anything else that the committee needs to address?

16 DR. GOLDBERGER: No. I think, actually, in spite
17 of the fact that there was a lot of vagueness in Question
18 No. 2, in particular, you have provided advice that will be
19 useful to us. I think the sense I got from the comments is
20 that few people are willing to place a great deal of weight
21 on the presumed endpoint in this particular clinical trial,
22 but I think you gave good guidance about how one might
23 approach the program for future trial.

24 I think that that, certainly, is a reasonable

1 approach so I think we are satisfied with that.

2 DR. HAMMER: Thank you.

3 I would like to personally, and for the committee
4 members, thank Fujisawa and the presentation this morning
5 and the representatives of the agency.

6 This meeting is adjourned. Thank you.

7 [Whereupon, at 12:35 p.m., the proceedings were
8 adjourned.]