

1 DR. GULICK: Please come to the mike.

2 DR. MCMASTER: I missed the question.

3 DR. YOGEV: Data about teratogenicity.

4 DR. MCMASTER: Right.

5 DR. YOGEV: Should this drug be prevented
6 from women who are suspected to be pregnant?

7 DR. MCMASTER: Well, yes, there is
8 teratogenicity. In fact, we have cleft palates in
9 some animals that were treated, and there are a
10 number of other findings which were not unexpected,
11 this being an azole. This would be a Class C drug
12 and so pregnant women would be cautioned against
13 using this.

14 DR. GULICK: Dr. Hamilton?

15 DR. HAMILTON: I am sorry, I may have
16 missed this but I was obsessing about something
17 else while Dr. Stanley was obsessing about the
18 visual thing. Could you tell me the number of
19 people who have been followed the longest on
20 voriconazole, and what the length of that follow-up
21 is with credible ophthalmologic examinations, both
22 physiologic and objective?

23 DR. CHAMBERS: The one study that you
24 heard is the only kind of sophisticated visual
25 function testing.

1 DR. HAMILTON: That is how many people?

2 DR. CHAMBERS: I don't have the number in
3 front of me. It is not a large group.

4 DR. GULICK: Could we just clarify? What
5 you said was that a group hasn't been followed with
6 the diagnostic testing through 28 days, but the
7 question was how many people have been followed
8 clinically?

9 DR. HAMILTON: Including with some attempt
10 to assess --

11 DR. CHAMBERS: Yes, with sufficient
12 testing to be able to tell, and it is only that one
13 trial. Straight visual acuity testing, as was
14 presented, was not done in a sufficient form to
15 necessarily pick up small changes. A lot of the
16 discussions that have gone on during the trials
17 have been are these patients well enough to be able
18 to get to facilities to do the testing you would
19 like to see have done, and have the baseline
20 information earlier on to be able to tell if the
21 changes that you see, are they due to drug product
22 or due to something else. But to go back to answer
23 your question, we essentially have good testing on
24 28 days of dosing.

25 DR. GULICK: Other questions from the

1 committee? Go ahead.

2 DR. HAMILTON: Dr. Tiernan, I don't think
3 I understood well enough to ask the question that I
4 want to ask from slide number nine that you
5 presented.

6 DR. GULICK: Was that in the first set or
7 the second set?

8 DR. HAMILTON: First, study 307-602,
9 additional efficacy analyses.

10 DR. TIERNAN: Yes, that was to corroborate
11 the initial results that we had.

12 DR. GULICK: Can you speak up? I am
13 sorry, we can barely hear you.

14 [Slide]

15 DR. TIERNAN: This was just to corroborate
16 the initial results that we had in 307-602, and
17 these were just attempts to perform a more
18 conservative analysis.

19 DR. HAMILTON: Using what parameters? I
20 mean, what were the assumptions for these more
21 conservative analyses?

22 DR. TIERNAN: The first one was that the
23 DRC was allowed to upgrade investigator assessment.
24 So, we did an analysis that did not allow the DRC
25 to upgrade the assessment of the patients and we

1 penalized for that. So, that is the most
2 conservative analysis that we could have done in
3 that situation.

4 Then, in the second one if the
5 voriconazole patients switched to other licensed
6 antifungal therapy we actually penalized them for
7 that. We considered them failures. So, we felt
8 that was a very conservative approach. Then we
9 looked at four weeks after the end of the primary
10 endpoint, which was 16 weeks, to make sure that
11 there wasn't a problem with relapses.

12 DR. HAMILTON: I see. Thank you.

13 DR. GULICK: Other questions for the
14 agency from the committee? I have two short ones.
15 We have heard twice that two patients with
16 persistent fever actually didn't have persistent
17 fever. Can you explain that?

18 DR. POWERS: The way this works is that in
19 the case report form the investigators are allowed
20 to check off why the patient discontinued. So, in
21 two cases an investigator checked off fever. When
22 you go back and you look through the logs there is
23 no fever. So, it was inadvertently checked off on
24 the case report form.

25 DR. GULICK: Okay. My second question

1 was, if I understood you correctly talking about
2 the lower bound for non-inferiority, did you say
3 that the minus 15 percent picked for the
4 itraconazole study actually wasn't prospectively
5 chosen?

6 DR. POWERS: No, it was prospectively
7 defined. I guess what I am trying to say is if you
8 look at these three trials, the MSG32 trial to test
9 Ambisome versus amphotericin B deoxycholate, there
10 was discussion about what the lower bound should
11 be. There was discussion about what the lower
12 bound should be for this trial. For the
13 itraconazole trial there was no discussion. The
14 protocol came in that way and that is the way it
15 stayed, and there was no active discussion about
16 what it should be.

17 DR. GULICK: So, it was arbitrarily
18 selected and not really focused on?

19 DR. POWERS: I could actually show slide
20 40. Let's see how long it takes us to pull this
21 one up.

22 [Slide]

23 This is actually a comparison across these
24 three trials. Again, I want to caution people
25 about making comparisons across these because there

1 are a lot of differences between these trials as
2 far as demographics and other issues about the
3 trials.

4 In the Ambisome versus amphotericin B
5 deoxycholate trial, the top one which is MSG32, we
6 can see that this trial had a prespecified lower
7 bound of minus 10, and we see 50 percent response
8 rates -- about a similar number of patients that
9 there are in this trial, but they meet their lower
10 bound. They come out to be minus 6.8 percent.

11 The itraconazole trial had a prespecified
12 lower bound of minus 15. You can see the
13 differences here in the cure rates, but they met
14 their delta of minus 1 percent of the lower bound,
15 with an upper bound of 20 percent. Again, the
16 caveat went into the label for this drug that there
17 were more discontinuations due to lack of efficacy
18 in the itraconazole arm and more discontinuations
19 due to toxicity in the amphotericin B deoxycholate
20 arm.

21 Then we get down here and we look at this
22 trial, 603, and here we have again almost 400
23 patients. The reason why there are fewer patients
24 in the itraconazole study is because it was
25 designed with a lower bound of minus 15 which

1 allows you to set a sample size that is smaller.
2 But you can see here that even though we use a
3 prespecified lower bound of minus 10, in either the
4 raw or stratified analyses it does not go above
5 minus 10.

6 DR. GULICK: Thanks. Any further
7 questions from the committee for the agency?

8 [No response]

9 I have about 12:45 and we will break for
10 lunch for an hour. So, we will reconvene at 1:45,
11 right on the dot.

12 [Whereupon, at 12:45 p.m., the
13 proceedings were recessed, to be
14 resumed at 2:00 p.m.]

AFTERNOON PROCEEDINGS

1
2 DR. GULICK: There is no one who has
3 officially asked to speak at the open public
4 hearing, who made that known ahead of time. Is
5 there anyone who would like to speak that didn't
6 sign up ahead of time? Seeing none, we will close
7 the open public hearing and we are now four minutes
8 ahead of the agenda.

9 [Laughter]

10 As one point of clarification, there was a
11 lot of discussion towards the end of the last
12 session about the ophthalmologic findings. I would
13 like the sponsor, who has offered to present us a
14 couple of clarifying slides, to start off with that
15 and then we will proceed to the charge to the
16 committee.

17 DR. BAILDON: Thank you very much. I just
18 do want to share the clinical data we have.

19 [Slide]

20 This is the slide on the acuity changes
21 observed from baseline to follow-up in our
22 esophageal candidiasis study, where we could
23 investigate visual effects a little better than in
24 some of our other studies. The median treatment
25 duration in this study was close to two weeks,

1 which is a similar duration you would see in an
2 empirical therapy study and as I have shown you
3 before, there were no changes in acuity between
4 groups.

5 [Slide]

6 This shows the same population and the
7 investigation we did here is contrast sensitivity
8 testing. So, this is testing contrast sensitivity
9 and, again, we see no difference in changes from
10 baseline to end of therapy between fluconazole and
11 voriconazole.

12 [Slide]

13 We have then done the same test for color
14 vision where we look at color vision changes and,
15 again, we see no differences between the two
16 groups.

17 [Slide]

18 This is mostly an HIV-infected population
19 and we also looked at abnormal fundoscopy at end of
20 therapy, about two-week therapy with either
21 fluconazole or voriconazole and, again, there is no
22 immediate apparent difference between in the two
23 groups.

24 [Slide]

25 As Dr. Chambers quite rightly highlighted,

1 we don't have very much good data on long follow-up
2 and I want to highlight that we are committed to a
3 long-term safety study, ocular safety study in
4 patients where we are recruiting patients with
5 Paracoccidioides infections who require at least
6 six-month therapy and who are also ambulatory. Of
7 the 42 patients targeted, we have recruited 26
8 patients and 4 have completed our protocol. That
9 is an ongoing protocol where we are doing more
10 extensive visual testing, along the lines suggested
11 by Dr. Chambers, and actually in the break we
12 agreed on a few extra measures that should be part
13 of that to provide the detail that we discussed
14 earlier. So, we hope that this study will then
15 provide at least 6-month data. Patients are
16 treated for at least 6 months and then longer. If
17 necessary, they can go on longer, and they will
18 undergo this extensive visual testing at baseline
19 and then at the last follow-up. That was all I
20 wanted to add.

21 DR. GULICK: Thanks for that
22 clarification. Are there additional questions just
23 to follow-up on these specific points? Dr. Wood?

24 DR. WOOD: Is there any plan to try and
25 capture ocular toxicity, or at least assessment of

1 ocular toxicity in pediatric patients?

2 DR. BAILDON: Well, I discussed these 38
3 patients who were treated for more than one year.
4 We actually saw a lower reporting frequency of
5 visual adverse events than in the overall
6 population.

7 DR. WOOD: And those were all pediatric
8 patients?

9 DR. BAILDON: They were not all pediatric
10 but a good part of that population is actually
11 pediatric patients. Dr. Boucher highlighted that
12 early on in the program we have seen very good
13 efficacy in central nervous system disease, and we
14 allowed compassionate treatment of children, in
15 particular if they had failed other agents and
16 fatality is around 100 percent in that, of CNS
17 disease. So, these children, treated for a long
18 time, are actually more young children. The
19 problem we have there is that the lower frequency
20 of reports partly is due because they don't report
21 it after a long time anymore but young children
22 don't report it anyway.

23 I think Dr. Thomas Walsh, in one of our
24 studies, had a child who said it was pretty cool
25 when she experienced this, but it is a bit more

1 difficult to test that and we have not done any
2 visual real testing on the children.

3 DR. GULICK: Thanks again. Dr. Goldberger
4 will now review the charge to the committee.

5 **Charge to the Committee**

6 DR. GOLDBERGER: Thank you.

7 [Slide]

8 Question number one, is there sufficient
9 information to support that voriconazole is safe
10 and effective for the treatment of invasive
11 aspergillosis? If not, what additional information
12 would be needed to support this indication?

13 Unless the committee has any questions, we
14 felt that this was a pretty straightforward
15 question.

16 [Slide]

17 Question number two, is there sufficient
18 information to support that voriconazole is safe
19 and effective for empiric antifungal therapy in
20 febrile neutropenic patients? If not, what
21 additional information would be needed to support
22 this indication?

23 I would make a couple of comments about
24 this. One is that unlike a separate question on
25 study design for aspergillosis studies, for future

1 aspergillosis studies, we didn't include a separate
2 question for study design for empiric therapy, I
3 think in part because we expected that during the
4 discussion there would be some comments about
5 endpoints and other issues which would be helpful.
6 Although, certainly, if the committee later on
7 wishes to talk more about study design in this
8 area, that would be fine.

9 The second thing is there was quite a bit
10 of data presented this morning about analyses of
11 how different subgroups perform, different
12 components of the overall endpoint in empiric
13 therapy performed. Should the committee have an
14 interest in thinking about this indication rather
15 than simply yes or no but, rather, attempting to
16 define a group for whom the drug might be
17 indicated, or should the committee want to provide
18 some specific advice about caveats that should be
19 included in any indication, that would be fine.

20 What we would obviously like though is
21 advice that is sufficiently specific so that it can
22 be included in product labeling and be useful and
23 comprehensible for treating physicians. So, in
24 other words, a lot of data was presented and either
25 the sponsor or ourselves can review some of these

1 analyses. But should you wish to do that, and we
2 are in no way recommending that you do but a lot of
3 time was spent discussing this, we would like
4 advice, and sufficiently specific, so that it could
5 be helpful ultimately in allowing physicians to
6 make appropriate decisions in how to use the drug.

7 [Slide]

8 Question number three, what additional
9 Phase IV studies would you recommend? Obviously,
10 one thing here we are certainly interested in to a
11 large degree but by no means exclusively is any
12 additional advice you have about drug interaction
13 studies. Obviously, a fair amount was presented
14 about drug interactions. The company certainly has
15 made a substantial effort. There are still some
16 unresolved questions so that specific advice about
17 this would be most welcome, as well as any other
18 advice about Phase IV studies.

19 [Slide]

20 Finally, what additional advice does the
21 committee have regarding the design of future
22 studies needed in the development of therapeutic
23 agents for the initial therapy, and therapy of
24 patients refractory or intolerant to other
25 antifungal therapies, in patients with pulmonary

1 and/or disseminated aspergillosis?

2 We thought that we would ask this question
3 again, in part because this was a question we asked
4 last January when another product came before the
5 advisory committee for an aspergillosis claim,
6 although a somewhat different claim than this one,
7 i.e., limited to salvage therapy. And if, based on
8 the data you have seen today, you have any other
9 observations in this area they, again, would be
10 most welcome. In addition, should you have any
11 other comments regarding design of trials for
12 empiric therapy, they also would be most welcome.
13 That is basically it unless there are questions.

14 **Committee Discussion and Vote**

15 DR. GULICK: Thank you. Just to inform
16 the committee, I think the way I would like to do
17 this is to take the questions one by one. We will
18 start with some general discussion and then at the
19 conclusion of the discussion we will take a formal
20 vote among the voting members of the committee; the
21 same for question number two. Questions number
22 three and four are really additional advice from
23 the committee. We won't be taking formal votes on
24 those particular questions. So, let's start with
25 question number one.

1 Is there sufficient information to support
2 that voriconazole is safe and effective for the
3 treatment of invasive aspergillosis? Dr. Wood,
4 would you like to start?

5 DR. WOOD: I think the answer is yes. The
6 data is pretty straightforward and I don't have any
7 issues or concerns about invasive aspergillosis.

8 DR. GULICK: Dr. Mathews?

9 DR. MATHEWS: I agree.

10 DR. GULICK: Dr. Hamilton?

11 DR. HAMILTON: I basically agree as well,
12 I would just like to make a few comments, however.
13 Probably not everyone has overlooked the very
14 important facts that we are dealing with both very
15 serious underlying diseases and consequent very
16 serious infections. So, we have to view any
17 decisions we make in light of that. This is not a
18 trivial circumstance by any means. I think that is
19 important both in terms of the assessment of the
20 urgency of new treatment options and in the
21 assessment of whatever safety considerations there
22 may be and in light of what our current therapeutic
23 options are which are, in my view, imperfect, at
24 best, as will this one be. We are not talking here
25 about a therapeutic intervention that is going to

1 solve disseminated aspergillosis. We hope it has
2 some substantial impact but it is not going to
3 eliminate that problem. So, we hope others will be
4 searching for even newer and more effective and
5 potentially less toxic interventions as well.

6 As to that broad array of diseases that we
7 have left out of the analysis for today, because I
8 am sure there had to be just a whole lot of other
9 serious problems that were encountered that have
10 not been focused on today, some of which fall into
11 an infectious category, I would guess that the
12 sponsor probably has substantial information about
13 that population of illnesses, and I would hope they
14 have plans to pursue a formal analysis of those to
15 see whether their drug or potentially others might
16 have interventions that would help. It is a pretty
17 desperate population, I would say. So, I would
18 encourage rapid assessment of that.

19 Although there remain some issues of
20 safety here, again in the context of the problem is
21 we are dealing with, I, for one at least, am
22 willing to deal with the uncertainty of absolute
23 safety of this drug to proceed, but I strongly
24 recommend that the sponsor pursue what avenues
25 should be pursued in light of what has been said

1 about the visual changes, etc. I vote yes.

2 DR. GULICK: Just to clarify, we are not
3 taking a formal vote yet, but appreciate people's
4 opinions. Dr. Schapiro?

5 DR. SCHAPIRO: I would also agree
6 definitely that the answer to the first question is
7 definitely yes. I think to stress a little bit
8 what additional studies would be done, I think
9 that, again as we have discussed in the past,
10 looking at the benefit/risk ratio for the different
11 indications, I think it is an easy answer for us
12 for invasive aspergillosis. Based on what Dr.
13 Hamilton said now, that is definitely a situation
14 where with what we have now I think it is
15 definitely justified to approve the drug and give
16 it to patients.

17 As we maybe slide down to less
18 life-threatening, urgent conditions --

19 DR. GULICK: Can I suggest that you hold
20 -- finish your thought.

21 DR. SCHAPIRO: Just one point. I think
22 that that should not stop us. The fact that we
23 consider it safe for one indication -- safety is
24 relative, and it is relative to the urgency. So,
25 although I think that for that indication we

1 definitely have seen data, it is not a matter if
2 the drug is safe or not safe. I think for that
3 indication for that serious infection, yes, it is
4 safe.

5 DR. GULICK: Thanks. Other committee
6 members wish to ring in her? Dr. Wong?

7 DR. WONG: Sure, I mean I guess I want to
8 begin by saying that I really want to congratulate
9 Pfizer for putting this together. I had my doubts
10 before I saw the data that we saw here today that
11 anyone was going to be able to show us such
12 powerful data as a mortality difference between a
13 standard therapy and a new therapy for
14 aspergillosis, and I am delighted to see that and I
15 think you are really to be congratulated. So, the
16 answer to the question is, yes, it is safe and,
17 yes, it is effective.

18 DR. GULICK: Dr. Englund?

19 DR. ENGLUND: I agree, yes; yes.

20 DR. GULICK: It sounds like we are
21 reaching some consensus here. Others want to make
22 a statement? Dr. Morrison?

23 DR. MORRISON: I agree with what has
24 previously been stated. The one question I have is
25 does any caveat need to go into the package insert

1 or information regarding this compound with regard
2 to the non-fumigatus Aspergillus species? The fact
3 that the response rate in these may not be as good,
4 but we really don't know that for sure because the
5 patient numbers are small.

6 DR. GULICK: Barring further comments,
7 clearly the consensus of the committee is we are
8 delighted to see a randomized study for this
9 particular disease. As Dr. Wong mentioned, the
10 results are quite impressive in terms of
11 demonstrating a survival benefit. As others
12 pointed out, assessing a risk/benefit ratio in this
13 particular population is extremely important -- a
14 very compromised group; a disease that is quite
15 severe, and the current treatment options are
16 suboptimal.

17 So, the consensus seems to be that we find
18 the drug safe and effective. I would like to take
19 a formal vote so each voting committee member can
20 go on record as stating what they believe. So the
21 question again, is there sufficient information to
22 support that voriconazole is safe and effective for
23 the treatment of invasive aspergillosis? Dr.
24 Rodvold, we will start with you.

25 DR. RODVOLD: I vote yes, and I again

1 endorse that this is a great study.

2 DR. GULICK: Dr. Wood?

3 DR. WOOD: Unequivocally yes.

4 DR. GULICK: Dr. Mathews?

5 DR. MATHEWS: Yes.

6 DR. HAMILTON: Yes.

7 DR. YOGEV: Yes, but just at the bottom,
8 if yes, what additional studies?

9 DR. GULICK: We can come back to that.

10 DR. YOGEV: If you are going to come back
11 to it, I will talk about it later but I think it is
12 important to realize that this is a devastating
13 disease. There was breakthrough on the dose which
14 was recommended and it is not about 50 percent, and
15 I would encourage the company to go with a higher
16 dose compared to this dose to show that although in
17 an animal model there is something that suggested
18 the same rate of reduction in the amount of the
19 fungus, we might get an additional benefit without
20 increasing the risk.

21 DR. GULICK: So, can I suggest that we
22 come back to this point when we talk about Phase IV
23 commitments and further studies that need to be
24 done? Is that okay? We still need to record your
25 vote though, Dr. Yogev.

1 DR. YOGEV: I said yes.

2 DR. ENGLUND: Yes.

3 DR. SCHAPIRO: Yes.

4 DR. WONG: Yes.

5 DR. DEGRUTTOLA: Yes.

6 DR. GULICK: And the chair votes yes.

7 That is unanimous, ten votes yes; no votes no. So,
8 with your permission, Dr. Yogev, we won't answer
9 the second part of that question.

10 Let's move to question number two, which
11 should generate some discussion. Is there
12 sufficient information to support that voriconazole
13 is safe and effective for empiric antifungal
14 therapy in febrile neutropenic patients? There are
15 a number of issues to consider in answering this
16 question. Dr. Schapiro is going to start.

17 DR. SCHAPIRO: I think it is a difficult
18 question to answer. I think we saw a very nice
19 presentation from the sponsor. I think the
20 analysis done by the agency was very helpful,
21 especially for us who are less schooled in the
22 statistics. I think it is very clear that this is
23 a complex question and it is not one necessarily
24 that has a yes/no with the statistics.

25 Going back to the issue of risk/benefit, I

1 think that there are definitely a lot of open
2 questions with the toxicity. They have been well
3 addressed and well discussed. I think there is
4 still concern regarding the visual disturbance. I
5 think that we have no data. The patients who died
6 in the study were not investigated with
7 histopathology from the retina of those patients,
8 which might have given us some insight, and I think
9 that there is not a lot of data, not any long-term
10 data and that is concerning.

11 I think that for the hepatic toxicity it
12 is a pity we weren't able to delineate some markers
13 that would help us identify the high risk patients.
14 Although rates of Child's A or B cirrhosis are
15 conditions which would have a dose reduction, as I
16 think was brought out earlier, many patients that
17 you see, you don't know that. You have some
18 clinical markers but we weren't given any
19 guidelines that a clinical can use and often we
20 don't have time to make a diagnosis of cirrhosis.
21 So, that is of limited help.

22 Of course, therapeutic drug monitoring --
23 there was some data in the background that in some
24 of the early studies it looked like there were
25 thresholds at 5, maybe 0.5-5 but, of course, in the

1 analysis that the company did it didn't pan out. I
2 think maybe in the future if more work does define
3 some good clinical markers and maybe a drug level,
4 I think that would greatly help us reduce some of
5 the concerns with the toxicity. It may also allow
6 us to increase the doses if we were able to monitor
7 how high they are going. So, I think that is also
8 of concern when we look at that.

9 I am pretty much convinced that that is an
10 alternative therapy. I don't know if we have
11 wording where we can say that, you know, we would
12 use it if Ambisome was contraindicated, if there is
13 that type of wording that can be put in. That was
14 sort of my feeling from this.

15 I am also not convinced -- the summary
16 statement that this drug is better tolerated than
17 Ambisome, I wasn't convinced by the data we saw
18 that it is a more tolerated drug. I thought maybe
19 there is data going both ways. But with what we
20 have seen now, the current drug looks a little bit
21 better.

22 DR. GULICK: Dr. Wood and then Dr. Yogev.

23 DR. WOOD: Why don't you go ahead?

24 DR. GULICK: Okay, Dr. Yogev first.

25 DR. YOGEV: My answer will be definitely

1 no. I think all the complexity is part of the
2 issue, but as the data were presented it is not.
3 If I take the Aspergillus out I have even more
4 concerns. For some bizarre reason, this drug did
5 less good in Candida than one would expect. This
6 is a population where 1/20 really need it, and some
7 people say it is higher. With all the toxicity you
8 mentioned, I think this drug should wait for much
9 better data to convince me.

10 Now, if you tell me there is Aspergillus,
11 we already answered that in number one. But if you
12 don't know, is it empiric, my answer is no.

13 DR. GULICK: Others want to make comments?
14 We will take one at a time, Dr. Rodvold and then
15 Dr. Wong.

16 DR. RODVOLD: Well, I guess one of the
17 caveats that struck me was that there was a
18 category of high risk patients that did better.
19 They had bone marrow transplant people and another
20 group there, and I just wondered if language is
21 needed for alternative therapy for them. When you
22 take them away from there and you get into some of
23 the others, the moderate risk group and things like
24 that, then the data, you know, goes swinging the
25 other way. So, the high risk group was something

1 that either needs discussion or whether or not that
2 can be incorporated into a label underneath this
3 indication.

4 DR. GULICK: Dr. Wong?

5 DR. WONG: I guess if I had to give a yes
6 or no answer, have they demonstrated the efficacy
7 of this drug for empiric therapy, I would say not
8 yet. But I want to make a couple of comments to
9 put our interpretation of these results in the
10 context of what we have seen earlier.

11 I wasn't on this committee back in '94 or
12 '95 when it was decided that these sorts of studies
13 should be analyzed using this composite endpoint
14 that has now been used three times in a row. But I
15 was here the first time we heard data like this
16 when we looked at Ambisome versus Fungizone. I
17 believe I commented at the time that I thought that
18 using an endpoint like that was really going to
19 hurt people down the line because it mixes too many
20 things. It combines efficacy and toxicity, which I
21 think is clearly a big mistake. It also gives the
22 local investigators preconceived ideas about
23 whether or not a drug is going to work, who is not
24 blinded. It gives that person the opportunity to
25 really determine the outcome in an individual

1 patient by withdrawing his patient from that study
2 drug. It makes efficacy assessment in a study like
3 this almost impossible. That is what I thought a
4 few years ago when we saw the Ambisome versus
5 Fungizone results and I think that is precisely
6 what has happened here.

7 I think the study, as designed, was
8 negative, but I also believe that this drug is
9 probably going to be found to be useful as empiric
10 antifungal therapy for neutropenia patients with
11 persistent fever once we get past the idea that we
12 should be trying to make up a fuzzy endpoint to get
13 around the problem of insufficient power, and start
14 counting what we really care about, which is how
15 many people develop fungal diseases and how many
16 people don't die during the course of their
17 antifungal prophylaxis. When we do that my guess
18 is that this will be just as good as anything else.

19 DR. GULICK: Other thoughts? Dr.
20 Morrison?

21 DR. MORRISON: Just a brief addition to
22 Dr. Schapiro's comments. I likewise have a little
23 bit of difficulty trying to determine who has
24 hepatic impairment because I don't know the Child's
25 classification right off the top of my head. I

1 wonder whether within the sponsor's database of
2 those patients if there is any way they can go back
3 -- maybe they have already done this -- and look at
4 the actual transaminases, the bilirubin levels, and
5 try to determine if there might be some more
6 discrete laboratory cut-offs that could be used for
7 knowing when you need to have the dose.

8 DR. GULICK: Dr. Hamilton?

9 DR. HAMILTON: I guess I have a version of
10 Dr. Wong's opinion about this. In this population
11 I don't think we do all that well with anything
12 really, which is very discouraging for those who
13 take care of these patients. And, progress in that
14 regard comes in nanometers, it seems like. So, I
15 am actually not that impressed with any
16 deficiencies that have been identified in the
17 voriconazole approach to the neutropenia host. I
18 think they are about the same. I mean, you can do
19 the statistics if you want to but I don't see that
20 there is a whole lot of difference.

21 With that background, my expectations are
22 not incredibly high. I can tell you that if that
23 drug is available and I am on the unit and my
24 hospital administrators are asking why it costs me
25 so much to treat all these patients with liposomal

1 amphotericin, among the first questions I am going
2 to ask is how much does this stuff cost. Now, I
3 don't know how much this is going to cost. I am
4 sure nobody is going to tell me --

5 [Laughter]

6 -- but I think cost will become an issue
7 here in terms of the practicality when this becomes
8 available, which I have no doubt it will be with it
9 is today, tomorrow or six months from now.

10 DR. GULICK: Dr. Englund?

11 DR. ENGLUND: Well, I agree that we need
12 something in our bone marrow transplant patients,
13 and I would focus on those. I would agree that we
14 have better data on the more severely
15 immunosuppressed than we have on the moderately
16 immunosuppressed. We need something, and we need
17 something so we don't have to suffer through this
18 amphotericin liposomal, and then what do you do?

19 I am concerned about the indiscriminate
20 use of it and, as a pediatrician, I am concerned
21 that there is no data that I have seen on retinal
22 changes in kids over time, and those kids are going
23 to get things a long time. You have some patients
24 and I would like to see that before I would
25 recommend using an empiric therapy in children with

1 developing eyes. I don't know that much about
2 their eyes but when we treat these kids we are
3 treating them for a cure. You know, they are
4 getting a bone marrow transplant for a cure and
5 they are going to be living a long time, and we
6 want to make sure that we are not doing any harm.
7 So, I would be very concerned about empiric therapy
8 in children.

9 However, for the adults I really like the
10 idea of having an alternative, as a clinical, and
11 if, in fact, we are going to do that I think we
12 need more resistance data. So my two things are
13 safety data in kids, and I would like resistance
14 data. What are you going to do? You have got to
15 be telling me a little more when we are treating
16 people with voriconazole for esophageal
17 candidiasis. What is happening two months down the
18 road? Are we then, again, knocking out all our
19 azoles so that I don't have any other therapy to
20 give to them? Maybe there is not enough resistance
21 data out there but I haven't seen anything and I
22 have experience with patients that have not
23 responded and you don't have much left after that.

24 DR. GULICK: Something that is clearly
25 influencing the committee is the non-inferior study

1 where the lower boundary for the 95 percent
2 confidence interval and minus 10 was crossed. I
3 wonder if we would like to comment on that in
4 particular since that has come up several times
5 today, about how appropriate the cut-off is. That
6 is based upon recommendations from committee
7 meetings from 1995 and '95. Dr. Mathews?

8 DR. MATHEWS: Well, you know, I think that
9 is a clinical judgment but there is a way to kind
10 of translate it into other terms that clinicians
11 might understand. It would be the number of
12 patients you would need to treat to observe a
13 benefit for a single patient. If you look at the
14 point estimate for the empiric therapy indication,
15 if you compare the response rates of the
16 voriconazole group to the amphotericin group, it is
17 16 patients who would be treated with voriconazole
18 for one patient who would die that wouldn't have
19 died if they had gotten amphotericin. In the
20 Aspergillus study, where there was a benefit shown
21 for voriconazole, it is five patients treated for
22 every life saved by voriconazole.

23 You know, I am as troubled, as everybody
24 else is, about why there is a clear-cut positive,
25 unequivocal response in the people with definite

1 disease and I would say a negative response, based
2 on the prespecified criteria, in the empiric
3 therapy group. But one thing we have to remember
4 that I think was talked about in the FDA background
5 is that in non-inferiority trials any
6 misclassification in outcome assessment is going to
7 tend to make the drugs look more similar. And,
8 despite the fact that the expert review panels were
9 blinded, there had to be some misclassification.
10 So, that is going to tend to attenuate the
11 differences between groups. I think it is a very
12 different setting than if this was set up as a
13 superiority trial.

14 With regard to the issue of the composite
15 endpoint, you know, I understand Dr. Wong's point
16 on that and we have debates about composite
17 endpoints here and elsewhere, but the fact is, at
18 least as I understand the history of this, that one
19 of the motivations for the composite endpoint is
20 that the ascertainment of definite infections is
21 incomplete, at best. So, there is a significant
22 proportion of patients enrolled in these studies
23 for whom the outcome would be unclear because
24 definitive diagnosis wasn't made.

25 So, the composite endpoint, with all its

1 faults, I think is a serious attempt that would
2 seem to work well in two other trials that we saw
3 presentations of their data here, and I don't think
4 the rule should be changed to rely on post hoc
5 analyses of efficacy in this setting.

6 DR. GULICK: Dr. Wong?

7 DR. WONG: I guess I disagree, Chris, with
8 that last point. We were both here for the
9 Ambisome presentation. My impression of the data
10 that was presented when the Ambisome versus
11 Fungizone study was presented was that on the basis
12 of the composite endpoint the two treatments gave
13 similar results. But the number of breakthrough
14 fungal infections that occurred with Fungizone was
15 higher than occurred with Ambisome. Here again
16 today, we have seen a comparative study in which I
17 believe the composite endpoint basically gave us
18 misleading results.

19 Now, they can't be ignored because that
20 was the criterion that was set out in the protocol
21 and you can't change the protocol after the results
22 are analyzed. But I believe that the results that
23 we see today based on that composite endpoint are
24 actually misleading because what we really want to
25 know in a study such as this is how many patients

1 developed fungal infections and how many patients
2 are alive at the end of the treatment. In this
3 study the answer to those two questions was the
4 same number, and the answer in the Ambisome versus
5 Fungizone study was that the Ambisome was better.

6 So, I think in both cases trying to craft
7 a multi-component endpoint that takes into account
8 safety, efficacy and investigator bias in an
9 unblinded study is really the wrong way to go. I
10 am afraid that if the agency feels committed to
11 using a study design like this the same thing is
12 going to happen over and over again until, you
13 know, the third or fourth time this happens and
14 people just throw up their hands and say let's
15 start counting what we really care about, which is
16 fungal infections and deaths.

17 So, I think we can't apply that post hoc
18 to this study and say that we really got a positive
19 result when the result was negative, but the next
20 study I think should be designed very differently
21 from this one and should really be designed to show
22 what we care about most rather than surrogates such
23 as, you know, fever or whether or not the
24 investigator felt comfortable enough to continue
25 the study drug. I mean, when an investigator says

1 no, I want to switch, that doesn't mean the drug
2 has failed. That means that the investigator's
3 comfort level has been reached. That may or may
4 not have any relationship with whether or not the
5 drug is working. So, in an unblinded studies I
6 don't think that should ever be allowed to be an
7 efficacy endpoint. But -- well, that is all I have
8 to say.

9 DR. GULICK: Dr. Wood?

10 DR. WOOD: While I think the overall
11 answer to question number two is no because of the
12 combined endpoints that we talked about, I would
13 like to concur with Dr. Englund in the sense that
14 when we look at high risk patients who are at great
15 risk for Aspergillus and breakthrough infections,
16 there definitely was an advantage with voriconazole
17 and I think I would like to make that available to
18 patients for whom we really don't have anything
19 good. I don't think that that component of the
20 data, in terms of that subset analysis which was
21 consistent both when done by the sponsor as well as
22 by the FDA, should be ignored since our ultimate
23 goal is to try and make available efficacious as
24 well as safe treatments for people who need them,
25 particularly if our treatment options are very

1 limited.

2 DR. GULICK: One thing that we have only
3 touched on tangentially today is how much the
4 standard of care in this particular field has
5 changed even since '94 and '95, and some of the
6 points in the background section were that
7 fluconazole prophylaxis is used quite routinely
8 today; also that growth factors often reduce the
9 time of absolute neutropenia in patients.
10 Actually, we saw some data to show that that was
11 true of the study, that the time that patients
12 spent with absolute neutropenia was much shorter
13 than in prior studies.

14 I wonder if we could call on our expert
15 consultants in the field maybe just to make some
16 comments about that. Dr. Rodvold?

17 DR. RODVOLD: Well, I don't know if I am
18 expert on that one. But those are all true, I
19 mean, every one of those points. When I read this
20 document before this meeting I found that that is
21 what was throwing me a little bit in how to
22 interpret the study. These days, you even treat
23 people more on an outpatient basis that are less
24 severe, and trying to keep them out. Then, when
25 they do come in you are pushing them out faster.

1 So, all those factors come up.

2 I think that tells you that you almost
3 have to come back and re-look at this negative 10
4 percent on the bottom because there are new factors
5 even since this decision was made. So, I would
6 think that the agency is probably going to have to
7 come back and maybe readdress that whole document
8 again a little bit to account for that, or at least
9 give opinions on that because I think it is
10 influencing the outcome to these type of studies.

11 I agree with what was said by Dr. Wong,
12 that you could run into this time after time in
13 future studies. So, despite that it is not that
14 old a document, it almost needs to be updated
15 already.

16 DR. GULICK: Dr. Morrison or Dr. Wong,
17 anything more to say about the changing standard of
18 care?

19 DR. MORRISON: I think the points you make
20 are good and I think one certainly needs to keep
21 these aspects in mind, specifically not only did
22 the receive antifungal prophylaxis but the type of
23 antifungal prophylaxis and the issue of whether
24 growth factors were used or not. Those two facets
25 need to be built into and considered for future

1 trials. I don't know how easy it will be to
2 backtrack in this study to look at those aspects.
3 I think it will be difficult.

4 DR. GULICK: Dr. DeGruttola?

5 DR. DEGRUTTOLA: I have a comment going
6 back to your question about is 10 percent the right
7 criterion for non-inferiority, and I think that
8 question is obviously related to the issue of
9 endpoint, what is chosen and how rare or frequent
10 the endpoint will be. I agree with Dr. Wong's
11 comments about the need to distinguish between
12 safety and efficacy endpoints.

13 My concern about using an absolute 10
14 percent for your definition of non-inferiority is
15 that it has different meaning depending on what the
16 response rate is. If the response rate is 30
17 percent for the control drug, as in this case, then
18 what you need to exclude is 20 percent. In that
19 case you would be talking about one arm having 50
20 percent more success than the other arm. So, that
21 is quite a considerable difference in relative
22 terms. Whereas, if you are at about a 50 percent
23 response rate, then the 10 percent rule would
24 require greater than 40 percent, which is, in
25 relative terms, less important.

1 So, I think that rather than using
2 consistent 10 percent rule across the board,
3 regardless of what the endpoint is or what the
4 response rate is expected to be, to have a rule
5 that is either in relative terms or at least takes
6 into account not only what the expected response
7 rate will be but what you do if it actually turns
8 out to be less than you expected. I mean, you
9 know, if you had 15 percent response then,
10 obviously, five percent could not be considered
11 equivalent. So, I think that the whole issue of
12 endpoint -- how it is going to be, and then
13 deciding what non-inferiority means and what is
14 appropriate will need more consideration.

15 DR. GULICK: Dr. Schapiro?

16 DR. SCHAPIRO: Going back to your question
17 regarding the changes in prophylaxis, the duration
18 I think was remarkable. It was far shorter, and
19 the fact that patients are being given prophylaxis.
20 I think what it does impact, of course, is what
21 degree of safety are we looking for. Going back to
22 what Dr. Yogev and Dr. Mathews mentioned, how many
23 patients are actually needing to be treated and how
24 many are we treating that actually don't need it?
25 I think it pushes us to be more careful. I think

1 that was also in the directive of the agency. We
2 will be more cautious regarding interactions and
3 toxicities and I think that will push us to looking
4 for a higher degree of safety and more knowledge of
5 interactions before we would use a drug.

6 DR. GULICK: Maybe we can consider some of
7 the questions that Dr. Goldberger elaborated on.
8 Would the committee be in favor of defining certain
9 subgroups, based on the data that we have seen
10 today, that might be appropriate for this
11 particular indication? Did the data support that?
12 Or, would people be in favor of breaking things
13 down? Dr. Mathews?

14 DR. MATHEWS: You know, a number of people
15 have taken note of the observation that in the high
16 risk group there seemed to be a benefit but, again,
17 you know, that is a post hoc analysis although it
18 was a stratification variable, if I am correct in
19 my memory. I would have to ask what is the
20 biological plausibility of that observation. For
21 that reason, I would have problems saying that it
22 wasn't -- we couldn't say that it was effective
23 overall according to the primary endpoint analysis
24 but then make a statement that it was effective in
25 a high risk group. I mean, why wasn't it effective

1 in the moderate risk group, unless it was a problem
2 of ascertainment -- under-ascertainment of outcomes
3 tending to attenuate that? I don't know.

4 DR. GULICK: Dr. DeGruttola?

5 DR. DEGRUTTOLA: I don't know if I am
6 allowed to ask a question of either the agency or
7 the sponsor about whether there was ever a formal
8 test of whether the category of high or moderate
9 risk -- if there was an interaction between that
10 and the randomized therapy on the outcome.
11 Obviously, in one case the lower confidence bound
12 excludes 10 and in another case it doesn't, but
13 that doesn't imply that there is actually an
14 interaction. I mean, these estimates and
15 confidence intervals are going to bounce around a
16 little bit by chance. So, the question is was
17 there a formal test for interaction between high
18 and moderate risk and the randomized therapy?

19 DR. POWERS: We didn't do such an
20 analysis. I don't know if the sponsor did or not.

21 DR. BAILDON: We did that; we are checking
22 for the results. The point was made about the
23 biologic plausibility. I would just like to
24 highlight that the period at risk at time of
25 neutropenia varied greatly between the patients who

1 were in the high risk category and the patients who
2 were in the moderate risk category. That is
3 something we have. There was quite a big
4 difference and one of the points that is well known
5 is that there is a good correlation between
6 patients remaining neutropenic and their increasing
7 risk of a fungal breakthrough infection as they
8 remain neutropenic. As soon as you go out towards
9 ten days or longer, then the risk of having a
10 fungal infection goes up considerably. So, I would
11 say that there is some biologic plausibility for
12 that difference in treatment effect, which would be
13 higher in the group of patients who are at higher
14 risk of fungal infection, be it occult or open or
15 documented.

16 DR. GULICK: Thank you. Just let us know
17 and we can display the data. Dr. Englund?

18 DR. ENGLUND: I just think that the
19 difference reflects the fact that we aren't
20 diagnosing true cases, and when we combine safety
21 and efficacy we are seeing something because in the
22 moderate risk group the true incidence of
23 aspergillosis is really quite low and, therefore,
24 to approve a drug for a population in which it is
25 quite low and I don't have all the data I want

1 would make me uncomfortable. Now, breaking up the
2 group into two groups statistically, I leave that
3 -- I would like other people's opinions.

4 DR. GULICK: Dr. Wong?

5 DR. WONG: I guess I would look at it in a
6 little bit different way. I don't think I would
7 try to break the groups up, especially since that
8 wasn't specified before. But I found that the
9 FDA's slide number 21, breakthrough infections
10 sensitivity analysis, where voriconazole and
11 liposomal amphotericin B were compared more
12 breakthrough infections plus protocol-specified
13 failures in the voriconazole group, if someone
14 switched for so-called effective, giving equivalent
15 results tells me that these are almost surely
16 equivalent therapies. And, I am very sorry that
17 the study wasn't designed to ask this question
18 rather than the question that it was designed to
19 ask, which I think was really muddled and
20 confusing. Because this is what I would really
21 want to know and here they came out the same. So,
22 I don't think I would try to massage it by subgroup
23 analysis. I think that the question was the wrong
24 question and the data actually to answer what I
25 wanted to know is here.

1 DR. GULICK: Another question that Dr.
2 Goldberger asked us to consider was whether
3 approval for this indication might be appropriate
4 with some caveats. Maybe the committee could
5 entertain that approach also -- or not. Do people
6 have thoughts about that? Dr. Englund?

7 DR. ENGLUND: I just want to say that I
8 don't think there is enough pediatric data to
9 approve it with caveats. So, for the children at
10 least -- not for treatment but for empiric therapy
11 without data, some data at least on the eye
12 findings -- I think that shouldn't be a caveat; we
13 shouldn't do it.

14 DR. GULICK: Dr. Morrison?

15 DR. MORRISON: Do we know how many people
16 with calculated or actual creatinine clearances of
17 50 or less got oral drug out of these studies?

18 DR. GULICK: Either the agency or the
19 sponsor, could you help us with that question?

20 DR. BAILDON: Could you give us just a
21 minute?

22 DR. GULICK: Sure.

23 DR. RODVOLD: One of the problems, to
24 support what I think she is asking is that of
25 making dosage adjustments on creatinine clearance,

1 not creatinine. I know they used some creatinine
2 as a cut-off here but creatinine clearance is a
3 little bit better because you account for age and
4 you account for gender, which are factors in this
5 drug's disposition at times. So, I guess
6 creatinine clearance comes back to be a player for
7 me to think through who should be either on or off,
8 or dose adjustment of the drug.

9 DR. GULICK: Dr. Hamilton?

10 DR. HAMILTON: While they are looking for
11 this additional information, maybe Dr. Goldberger
12 could maybe expand a little on what the breadth of
13 the caveats might be. Are we talking about caveats
14 that just take the form of verbiage in the package
15 insert, or are we talking about requirement for
16 additional analyses, additional data? What?

17 DR. GOLDBERGER: To answer the second part
18 of your question first, if you don't think there
19 should be an approval now, the kind of things we
20 would be interested in are specific recommendations
21 about additional studies, additional data,
22 additional analyses, etc.

23 When I spoke about caveats in the
24 labeling, caveats can include -- and there are
25 always issues with these, one caveat can include --

1 and I think someone on the committee has already
2 suggested this, recommending the product when, for
3 instance, other products cannot be used, or
4 refractory or intolerant to other approved
5 products. There is such a thing as a second-line
6 indication, and that is one possibility.
7 Obviously, one issue here is that is not really how
8 the drug, of course, was studied. It was studied
9 as initial therapy and, therefore, one would have
10 to believe that there was sufficient -- on balance,
11 looking at all the data -- sufficient biological
12 plausibility.

13 Another caveat gets down to sort of what I
14 also talked about, about subgroups. That is, is
15 there a group for whom the product could be
16 recommended and, therefore, obviously other groups
17 which could be specified for whom the product might
18 be recommended? In other words, a little more
19 specificity instead of simply saying this drug is
20 approved for empiric therapy, this drug is approved
21 in such-and-such. In other patient groups, you
22 know, the drug was not shown to be effective.
23 Issues like that.

24 Now, the reason I would even bring this up
25 is that so much data was presented this morning

1 about the different subgroup analyses, and all,
2 that I think it is an inevitable question that
3 people would ask, and such things can be done. The
4 last concern about them, obviously, is what many
5 people on the committee have already talked about,
6 not all of these analyses were obviously clearly
7 prespecified. Some were prespecified in terms of
8 stratification; others were prespecified perhaps as
9 secondary analyses, etc., and that raises some
10 concerns as well.

11 In the end, of course, what we are asking
12 you to do is to look at the totality of information
13 that is available, recognizing that the drug did
14 not meet the agreed upon primary endpoint, but that
15 there are other pieces of information that suggest
16 the drug could potentially be useful using all that
17 information as well as what you have heard about
18 the safety profile, giving us a recommendation
19 basically about what you think in this situation.
20 I mean, there are ways to craft wording in the
21 labeling or defining indications but we would ask
22 you to be, you know, as specific as possible
23 because we would have to turn a recommendation into
24 labeling that would be useful to clinicians so they
25 would understand what we were trying to say and

1 could use the product accordingly.

2 DR. GULICK: Have you found the
3 information that you were looking for?

4 DR. BAILDON: Thank you.

5 [Slide]

6 Now, this denotes creatinine shifts. If
7 you look on the left side, we have classified
8 patients by calculated creatinine clearance, and
9 the bottom group would be those patients who were
10 considered with a severe renal impairment at
11 baseline with a calculated creatinine clearance of
12 less than 30 mL/minute. Then we looked at what the
13 baseline creatinine was and how they did they
14 shift, did the maximum creatinine during study
15 increase significantly, by the categories moving to
16 the right there. That is our total NDA pooled
17 population so this is the voriconazole-treated
18 population looking at creatinine shifts.

19 [Slide]

20 Another way to look at it, this analyzes
21 creatinine levels, median change in creatinine over
22 time for the two groups, voriconazole and Ambisome,
23 in the empirical therapy study. As you can see
24 there, voriconazole is an absolutely flat line.
25 There is no influence on voriconazole and there

1 were patients with preexisting renal impairment in
2 that study, and with Ambisome you see the shift
3 that you would expect.

4 DR. GULICK: Thank you. Dr. Wood and then
5 Dr. Yogev.

6 DR. WOOD: In reviewing the trial design
7 analysis, it was stratified by risk of fungal
8 infections. So, I don't know exactly how that risk
9 was defined but that was done prospectively before
10 the trial was conducted and analyzed. So, I think
11 the issues that we are seeing in terms of a benefit
12 in terms of breakthrough infections in high risk
13 individuals versus moderate risk individuals is
14 legitimate because there was the stratification
15 according to risk prospectively as part of the
16 trial design.

17 The other question, and I don't believe
18 this data was presented but I would be very
19 interested in seeing it in terms of in the empiric
20 trial what were the outcomes of voriconazole versus
21 Ambisome in patients who had ANCs less than 100?
22 So, that would clearly be a very high risk for
23 invasive disease. Then, those with prolonged ANC
24 durations of greater than 10 days, if there was any
25 difference there.

1 DR. BAILDON: Sure. Do you mind if we --

2 DR. GULICK: No, no, please go ahead and
3 respond.

4 DR. BOUCHER: I will try to answer the
5 duration of neutropenia question first, and just to
6 clarify, the prespecified risk strata specified
7 that high risk patients were patients with
8 allogeneic transplantation as well as relapsed
9 leukemia. I just wanted to clarify, in our
10 comparison of our other studies this morning that
11 Dr. Powers presented the important point I think in
12 comparing the recent paper published on
13 itraconazole was that that study did not include
14 allogeneic transplantation at all in the study.
15 So, another point about the design of our trial was
16 that patients had to have an ANC below 250 for 24
17 hours prior to randomization. So, these were
18 profoundly neutropenic patients.

19 [Slide]

20 I just want to clarify again about the
21 duration of neutropenia because, again, it has been
22 a little confusing in a way when we discussed it.
23 We know in our patients the median duration of
24 neutropenia prior to randomized, which you see in
25 the top row, during therapy and then in total.

1 What we know is that in the high risk patients the
2 median duration of neutropenia was 17-18 days
3 compared to 12-13 days.

4 [Slide]

5 If we could go back to slide 10 and we go
6 back to our breakthrough infections looking at
7 them, as Dr. Powers also presented, according to
8 risk, we have nearly 10 percent emergence of
9 invasive fungal infections in this high risk group,
10 which many would agree is an unacceptably high rate
11 of emerging fungal infections given the mortality,
12 as Dr. Patterson shared with us this morning in
13 this setting. Does that help with the neutropenia?

14 DR. WOOD: It does.

15 DR. BAILDON: I want to come back to the
16 other question that was asked previously about the
17 statistical analysis between the two groups. If we
18 do logistic analysis on a two-factor interaction
19 model of treatment and risk, that does not turn out
20 to be significant, a significant difference.

21 DR. GULICK: Dr. Yogev?

22 DR. YOGEV: I think that looking for
23 language, as you said, I would consider it as
24 preliminary data, at best, in the high risk group,
25 and if you look at the breakdown of what type of

1 fungus Aspergillus makes the difference and, you
2 know, from personal experience in patients who have
3 bone marrow transplants, we see a little bit more
4 Aspergillus than Candida and I think it would be
5 just fair to put in the preliminary data to suggest
6 that if no other therapy is available voriconazole
7 should be, but I would discourage at the same time
8 using it in others because there are no data to
9 support it. That, by the way, would cut also the
10 number of patients by almost 60, 70 percent, those
11 who are going to be exposed to the drug who are in
12 other categories. So, look at a balance in
13 between.

14 DR. GULICK: Dr. Wong?

15 DR. WONG: Maybe I can propose some
16 wording. I mean, as I look at these data
17 voriconazole was equally as effective as liposomal
18 amphotericin B in preventing breakthrough fungal
19 infections and death in febrile neutropenic
20 patients. Although that wasn't the
21 protocol-specified primary endpoint, in my opinion
22 that is the most important question. So, I think I
23 could support an approval with working like that.

24 DR. GULICK: Dr. Yogev?

25 DR. YOGEV: We are saying the same thing,

1 just if you take the high risk out from that
2 statement it won't be accurate. On the other hand,
3 if you take the high risk what you are saying is
4 right just for the high risk group. That is where
5 we need it. That is where I think it would be
6 unfair not to, but in the moderate you increase
7 toxicity just by the numbers and you don't get
8 really any difference, or even worse if you do the
9 calculation -- it is even worse.

10 DR. GULICK: Dr. Hamilton?

11 DR. HAMILTON: Isn't the distinction here
12 between high risk and moderate risk somewhat
13 artificial? I mean, bone marrow transplant
14 recipients and people who relapse with leukemia --
15 isn't that what you said?

16 DR. ENGLUND: I think there is a huge
17 difference actually in multiple diseases --

18 DR. HAMILTON: I don't disagree with that.
19 I am saying there are some people who likely fall
20 into those very high risk individuals who have been
21 excluded because they didn't happen to have that
22 disease. I mean, there must be a range --

23 DR. ENGLUND: I am sure there is an
24 overlapping range but when you look at just all the
25 other diseases from, you know, CMV to RSV, bone

1 marrow transplant is still the worst.

2 DR. HAMILTON: I don't disagree with that,
3 but what I am trying to do is homogenize the rules
4 here so that you can, you know, pick out those
5 people who truly are and if all the bone marrow
6 transplant patients fall it, great. They probably
7 will.

8 DR. ENGLUND: I think we do have to be a
9 little careful to make it somewhat simple; you
10 can't ever --

11 DR. HAMILTON: I am asking the question
12 can we do that in a way that is other than just
13 disease category.

14 DR. YOGEV: But that is all the data you
15 have.

16 DR. HAMILTON: Oh, I don't think so --

17 DR. YOGEV: I mean from what we have here.
18 The way the high risk was defined, there is a
19 difference where voriconazole has a place. In the
20 other it doesn't. So, to take what we have, that
21 is why I would use it as the preliminary data
22 suggest and not that it is an indication.

23 DR. GULICK: One more comment?

24 DR. ENGLUND: I just think this would be a
25 perfect way of introducing a Phase IV study in this

1 patient population to get bigger number and safety
2 and toxicity, a Phase IV study post-approval in
3 bone marrow transplant patients, with ocular and
4 ophthalmology follow-up, to really assess it, and I
5 would say that that should be a condition because I
6 really think you need to see what is going to be
7 evolving over time as you treat these patients. I
8 mean, what are we going to be seeing once we put
9 large numbers of patients, bone marrow patients on
10 this therapy?

11 DR. GULICK: Dr. DeGruttola, last comment?

12 DR. DEGRUTTOLA: I just wanted to
13 reiterate the point that if any information from
14 this study is used as a justification that the
15 language should state that it is post hoc analyses
16 of a completed study and that they weren't primary
17 results because the post hoc analyses are never
18 going to carry the weight, obviously, of the
19 protocol-defined analyses, and I would hope that
20 that would be communicated in perfect wording to
21 physicians.

22 DR. GULICK: Dr. Goldberger?

23 DR. GOLDBERGER: We can certainly --

24 DR. GULICK: Can you speak up?

25 DR. GOLDBERGER: We can certainly put a

sgg

1 statement like that in labeling. Keep in mind that
2 basically it would still, from the practical point
3 of view of promoting it, etc., it would obviously
4 still be approved for that indication. We could
5 include it in some detail in the clinical study
6 section, however, that would be part of the
7 labeling.

8 The other issue is that I just want to
9 make sure this impression is correct, the great
10 bulk of the discussion over the last few minutes in
11 this area has concentrated on interpretation of the
12 efficacy results. I just want to make sure that on
13 balance people, therefore, are reasonably
14 comfortable with the safety profile with regard to
15 potential approval for this indication. We haven't
16 talked a whole lot about it. We have talked a lot
17 about the safety profile, but is this primarily an
18 issue of efficacy? Or, how much does the safety
19 also play a role? It would just be helpful for us
20 to hear a little bit about that.

21 DR. GULICK: Yes, thanks for helping us
22 focus on that. So, let's consider safety for this
23 indication. Dr. Mathews?

24 DR. MATHEWS: Well, in addition to the
25 unresolved issues regarding the ocular toxicity, I

1 think that there is insufficient knowledge of drug
2 interactions, that we have already talked about
3 earlier, which creates uncertainty in my own mind
4 about the potential toxicity on both sides of the
5 equation, both in terms of efficacy of the levels
6 of voriconazole achieved in the presence of
7 inducers, for example, and also what would happen
8 to the levels of the other drugs which have not
9 been studied either in two-way or, preferably, in
10 three-way interactions. So, I think the toxicity
11 issue is an important part in my own
12 decision-making about this.

13 DR. GULICK: Dr. Wong?

14 DR. WONG: I think with respect to the eye
15 disease what we have seen so far and what has been
16 proposed so far is really not enough, especially
17 with respect to long-term consequences. The
18 patients who have already received voriconazole,
19 even in the course of the clinical trial, could be
20 called back for new eye examinations so that you
21 can answer the question are there remote effects
22 after stopping therapy. And, it seems to me that a
23 study, presumably conducted in South America, of 42
24 subjects treated long term is just not enough to
25 satisfy the question are there going to be

1 important eye complications with extended use of
2 this drug. So, those studies I think need to be
3 expanded both in breadth and also in time.

4 DR. GULICK: Dr. Schapiro?

5 DR. SCHAPIRO: Just to refocus on the
6 question, I think safety is very important here. I
7 think probably my major consideration is the fact
8 that I am more comfortable with Ambisome than I am
9 with what we have seen for this drug, and even if I
10 am convinced that they are similar, I still think
11 that we have unanswered questions and I have
12 difficulty defining the patients that are high risk
13 for toxicity and, therefore, I still would have a
14 problem with toxicity.

15 DR. GULICK: Dr. Yogev?

16 DR. YOGEV: I thought that is why I am
17 going to narrow it to the high risk. That is
18 Aspergillus. That is where your Ambisome is going
19 to fail. For me, I have problems in this disease
20 situation. I agree we need to pursue it and it has
21 to be part of what you do, but to suggest that
22 because of that in such a life-saving procedure to
23 wait for more -- that is why I would like to say it
24 is preliminary data because, to be honest with you,
25 I saw more patients than I would like to failing on

1 Ambisome and this one is telling me you have
2 another percent, or whatever, better. So, for me,
3 yes, side effects are important but that is why I
4 would agree not to do it in other populations.

5 DR. GULICK: Dr. Wood?

6 DR. WOOD: I concur with Ram's statement
7 because in the end patients who are dead of
8 Aspergillus don't have to worry about their
9 eyesight, and I think that is a major issue and
10 concern, that we have significant failures with
11 Ambisome and I think there is some data that is
12 significant, that is not debatable, that patients
13 at very high risk for invasive aspergillosis do
14 appear to have a benefit from having voriconazole,
15 and I would like to be able to make that benefit
16 available to patients, with the understanding that
17 the ocular studies and the toxicity monitoring in
18 terms of the breadth, duration and the populations,
19 kids and adults, needs to be done.

20 DR. GULICK: Dr. Schapiro?

21 DR. SCHAPIRO: A brief response, Dr.
22 Yogev. If this were the study design to look at
23 that, I think we could answer the question. We
24 still have in mind what percent of patients in the
25 high risk group actually did have the Aspergillus

1 infection. That would have to be the analysis.
2 And, if we would really call that group
3 Aspergillus, not neutropenic patients. I think
4 that would focus it. I think if we did have a
5 group and we found that there is a very high attack
6 rate of Aspergillus in the population -- I think we
7 saw very convincing results for Aspergillus that is
8 a biologic plausibility and I think that would be a
9 good indication. The question is, is that so? I
10 mean, if those patients are impending Aspergillus,
11 that is a good indication.

12 DR. GULICK: Is this a response because
13 other are waiting?

14 DR. YOGEV: Yes, unfortunately, it is a
15 response. Don't throw away the baby with the
16 water. Look at what happened to the Ambisome.
17 This is a progression that was randomly assigned
18 and still you have a huge amount of Aspergillus
19 breakthrough, 13 I think versus 4. And, we know
20 from other data in bone marrow transplants with
21 Aspergillus, we are getting more and more of them
22 and, interestingly enough, in the recurrent
23 leukemia which I don't understand, but those are
24 effects that you have higher with this specific
25 fungus.

1 DR. GULICK: Dr. Rodvold?

2 DR. RODVOLD: I agree. I think once you
3 put the high risk into it you are willing to take
4 safety a little bit with you, but with that, I
5 think the slide that the FDA presented about
6 additional issues regarding the ocular issues of
7 the rechallenge people, people that have underlying
8 eye diseases, what we don't know is what are risk
9 factors or what characteristics you would want to
10 be careful with. You are totally in the blind, so
11 to speak, on the eyes and so that is the issue in
12 all of these populations but even more here, going
13 on to identify those people -- and this drug is
14 going to be repeated a bunch of times and you are
15 going to have, like it or not, other antifungals on
16 board. I mean, I have already seen that in my own
17 institution with the last compound you approved.
18 They are doubling up on it for not necessarily good
19 reasons, and that is going to happen with this one
20 as well in the wrong patients. So, we need to know
21 what patients we don't use it in, or we do
22 something else and that is not in here as far as I
23 am concerned.

24 DR. GULICK: Let's see if I can draw some
25 consensus in what we said. The committee was

1 challenged by question two. Let's state that up
2 front. But, first of all, it is important that we
3 did affirm with question one that we feel this drug
4 has proven efficacy in other fungal infections,
5 particularly aspergillosis, and we saw some
6 information about Candida that was part of the
7 1994, '95 recommendations for an appropriate agent
8 for febrile neutropenia -- the empiric treatment
9 was that it did demonstrate activity against those
10 two organisms. So, we did agree with that.

11 With regard to safety issues, the points
12 that were made were that the risk/benefit ratio in
13 this particular population is somewhat different
14 from those who have proven or highly suspected
15 aspergillosis, and we talked about that. A fact
16 that several people mentioned was that many
17 patients who don't have fungal infections at all
18 will receive a drug given for empiric treatment of
19 fungal infection. Therefore, the safety issues are
20 clearly important and maybe somewhat different in
21 terms of the risk/benefit analysis in this
22 population.

23 I think the committee feels that we would
24 like to see more safety information; that there was
25 perhaps not enough safety information, particularly

1 with regard to the visual changes, and that we
2 truly want to see additional data. Also, on
3 drug-drug interactions some information is
4 available but a lot of information is not
5 available. So, those did concern, I think, the
6 committee in general about the safety of using this
7 drug in this clinical setting.

8 Perhaps even more thorny was the efficacy
9 issue, and I think the fact that the 603 study did
10 have a negative result strongly influenced the
11 committee, with many caveats. Looking with 20/20
12 hindsight, we are frustrated by the design of this
13 study, in retrospect. The fact that the minus 10
14 percent lower limit of the confidence interval was
15 chosen based on previous recommendations, as Dr.
16 DeGruttola pointed out, a different response rate
17 might have dictated a different number there. In
18 actuality, the response rate that was predicted for
19 this study was more on the order of 50 percent and
20 it was seen to be more on the order of 30 percent.

21 And, we were frustrated with the composite
22 endpoint that was recommended by the previous
23 committee. Mixing elements of safety and activity
24 into one endpoint makes it difficult --
25 "misleading" was a word that Dr. Wong used in

1 trying to really associate what are the activities
2 of the individual agent.

3 We struggled with an analysis of the
4 secondary endpoints and the subset analyses. We
5 saw some interesting signals that this drug may
6 have more benefit in the high risk group; may be
7 efficacious in terms of breakthrough fungal
8 infections; mortality, but there were also concerns
9 that many of these were not prospective analyses
10 but post hoc assessments of the same data and that
11 the study really wasn't designed to look at those
12 questions.

13 We mentioned changing standard of care in
14 this particular population. It is more of an
15 outpatient disease; fluconazole is routinely used
16 as prophylaxis, and the use of growth factors and
17 the decreased time of neutropenia, which strongly
18 influenced one of the parts of the composite
19 endpoint for this particular study.

20 We considered labeling and subgroups that
21 might benefit from this therapy, and there was
22 general disagreement, some people citing the fact
23 that most of these were small retrospective
24 analyses of the data, not prospectively designed;
25 others saying that really those are the endpoints

1 that we should be looking at. So, there was some
2 disagreement about that.

3 Also, thinking about caveats that one
4 might use, for example, one that was suggested was
5 using the drug if the first-line agents in a
6 patient who is refractory were intolerant to that.
7 There was some support for that. On the other
8 hand, as people pointed out, this particular study
9 would not support that indication in that it was an
10 initial treatment study. There were many calls for
11 additional studies that might help us sort this
12 question out.

13 With that very clear response of the
14 committee --

15 [Laughter]

16 -- we do need to take a formal vote on
17 this question. So, again, is there sufficient
18 information to support that voriconazole is safe
19 and effective for empiric antifungal therapy in
20 febrile neutropenic patients? Again, we will start
21 with you, Dr. Rodvold.

22 DR. RODVOLD: I have to answer the
23 question this way without a caveat, right? Is that
24 what you are saying?

25 DR. GULICK: Yes, we have to say yes or no

1 basically to this question and then we may make
2 give some other considerations.

3 DR. RODVOLD: I would say no.

4 DR. GULICK: Dr. Wood?

5 DR. WOOD: It hurts to say no.

6 DR. GULICK: Dr. Mathews?

7 DR. MATHEWS: No.

8 DR. GULICK: Dr. Hamilton?

9 DR. HAMILTON: Yes.

10 DR. GULICK: Dr. Yógev?

11 DR. YOGEV: No, but... we will talk about
12 that.

13 DR. GULICK: Dr. Englund?

14 DR. ENGLUND: No, but...

15 DR. GULICK: Dr. Schapiro?

16 DR. SCHAPIRO: No.

17 DR. GULICK: Dr. Wong?

18 DR. WONG: Yes.

19 DR. GULICK: Dr. DeGruttola?

20 DR. DEGRUTTOLA: No.

21 DR. GULICK: I would also vote no. So,
22 for those keeping score, there were two yes votes
23 and eight no and two "no, but" votes. We are going
24 to combine those into no.

25 Given that result, we really need to

1 consider the second part of this question, which is
2 if we do not feel that there is sufficient
3 information, what additional information would be
4 needed to support this indication? Dr. Schapiro?

5 DR. SCHAPIRO: Going back to the little
6 discussion we had in this corner, the box as
7 defined, it is a very high rate. The total number
8 of patients was 141 and it was 13. In the other
9 group it was 2/143. So, I would agree that for
10 that group the risk/benefit does justify it. So,
11 we can discuss this as a caveat or as a study, but
12 I think a study for that group, from this analysis,
13 would suggest we would have results which would
14 very much justify that indication.

15 DR. GULICK: So just to clarify, you are
16 talking about the high risk subgroup?

17 DR. SCHAPIRO: Yes, the high risk.

18 DR. RODVOLD: That is what I agree with
19 too. I brought that up originally, the high risk
20 group, as well as Dr. Wong's comment about the
21 other endpoints. When you throw those two in and
22 that population, my vote goes swinging 360 the
23 other way, to yes. So, that is where you get to
24 can you language this, or do you go pursue another
25 study to beef this up?

1 DR. GULICK: I look to Dr. Goldberger. Do
2 you want us to consider formal wording for another
3 indication here or would just our advice be
4 sufficient?

5 DR. GOLDBERGER: Actually, I think you
6 have worded that so well as to make it very easy to
7 answer. I think the latter part, more your advice
8 about whether we should at least consider the
9 possibility of an indication, perhaps more
10 restrictive or more limited than simply saying it
11 is indicated for febrile neutropenia. I don't
12 think you have to necessarily provide us with the
13 exact wording, rather, the sense of what the
14 committee thinks would be sufficient.

15 DR. GULICK: So, I would suggest that our
16 vote, particularly the "no, buts" should show that
17 the committee was conflicted about this with regard
18 to some of the things that we said. So, we are not
19 going to take another vote. That eases the tension
20 a little.

21 DR. YOGEV: I think the problem is in the
22 question and not in our answers and we are defined,
23 unfortunately, by the question and that is why at
24 least some of us, me especially, said no, because
25 of everything that we discussed before. But if the

1 question would have been "if not" and "if yes" I
2 would say no to the majority but yes to this one.
3 And I would discourage asking the company for
4 another study. I agree with all the faults that
5 this study had. It was designed like that but I am
6 familiar with many things which we are doing in
7 practice by ad hoc analyses that have become more
8 and more acceptable. I don't want to mention here
9 the meta-analysis that many of us are working by,
10 which is even worse this one.

11 So, I would encourage the agency to change
12 maybe the question a bit or to accept this
13 variation, and I would be more than happy to
14 suggest to the chair yes to vote on this high risk
15 group because I think it is so important; we need
16 to care about the patient.

17 DR. GULICK: I would suggest that the
18 agency will benefit from hearing opinions. Our
19 votes are recommendations. They are not binding.
20 So, I think what you just said and what others have
21 said is getting the message across without having
22 to come up with wording and take another vote,
23 which may not really be our responsibility, unless
24 you think differently.

25 DR. GOLDBERGER: No, I think that you

1 don't have to certainly provide exact wording. We
2 have already gotten just from the discussion, I
3 think, a reasonable amount of advice about some of
4 the possibilities that people have raised, and it
5 is a matter now of thinking about that. So, I
6 think from that perspective we are okay.

7 The one thing that perhaps is not entirely
8 clear, and members may want to comment -- I don't
9 know if it is necessary to have a formal vote or
10 not -- how strong the desire is that we would
11 attempt to fashion some sort of more limited
12 indication with what information is available now
13 versus the idea of asking for some additional data
14 and deferring that decision about a limited
15 indication, or a more straightforward indication,
16 until the additional data is available. That is
17 actually the one remaining issue. We have
18 certainly gotten sufficient suggestions about what
19 a limited indication might be. On balance, does
20 the committee prefer that approach or getting some
21 more information and then making a decision at that
22 point.

23 DR. GULICK: Just so I understand, we have
24 taken a vote and said the information that we have
25 today we didn't feel demonstrated the proposed

1 indication as stated.

2 DR. GOLDBERGER: Right.

3 DR. GULICK: Possibilities are that a
4 limited indication be recommended from the data we
5 have today, or another indication might be made
6 based on data --

7 DR. GOLDBERGER: Well, in other words,
8 basically what we would then be thinking is, rather
9 than another indication, that you would recommend
10 some additional studies, the primary purpose of
11 which would be to support the indication that is up
12 there. In other words, there is a belief among at
13 least some members of the committee that based on
14 what we know about the drug it ought to be
15 effective in this indication and that perhaps, for
16 instance, the wrong endpoint was selected and,
17 logically following from that is the idea that a
18 study utilizing a different endpoint might end up
19 being a better test of the drug. That, of course,
20 is a substantial investment by the sponsor. So, it
21 is helpful to get advice as to how useful that
22 would be, for instance, as one type of information.

23 DR. GULICK: Again just so I am clear on
24 what you want us to do --

25 DR. GOLDBERGER: What we would like to

1 know, in other words, you voted basically that
2 there is not sufficient data to support the
3 indication of empiric antifungal therapy of febrile
4 neutropenic patients. Two committee members voted
5 "yes, but" which is could. We might include that
6 as an option in subsequent voting --

7 DR. GULICK: It was actually "no, but" --

8 DR. GOLDBERGER: Now the question is
9 whether or not or how actively we should pursue
10 some sort of more restricted or limited indication
11 based on what we have now. Keep in mind there is
12 one basic rule that I do want to emphasize. We
13 cannot put something about this study in product
14 labeling unless, in essence, we are giving some
15 type of indication. I do want to make that very
16 clear. We cannot put a description of a study in
17 the labeling but not say that it is indicated. De
18 facto, if it is in the label it should be
19 considered an indication. So we can, of course, be
20 specific about the indication and say for high risk
21 patients or as an alternative in certain situations
22 and the describe the study, and that is fine. We
23 can't just put this in for people to have access to
24 and say nothing about an indication. That is the
25 one option that we cannot do.

1 DR. GULICK: It sounds like what you would
2 like us to consider is, is there a more limited
3 indication that the committee would support.

4 DR. GOLDBERGER: Should we attempt to do
5 that with the sponsor, or should we work on
6 defining what type of additional information could
7 be used to support the indication that is up there
8 right now?

9 DR. GULICK: So, two topics we want to
10 discuss -- is there a limited indication with the
11 data we have and that we have seen today, or is
12 there more data that we would suggest to support
13 the indication in the question.

14 DR. WOOD: Do the questions have to be
15 "or" or can it be an "and" and an "and?"

16 DR. GOLDBERGER: You can basically state
17 you would like to see a limited indication now but
18 you also really would like to see some additional
19 data which, of course, might support a broader
20 indication later on. That is perfectly all right.

21 DR. GULICK: Let's consider them
22 separately. So, let's consider do we feel that
23 there is enough information here to propose a
24 limited indication based on the data we have seen
25 today, and what would that limited indication be.

1 Dr. Schapiro?

2 DR. SCHAPIRO: For the question of an
3 indication for patients with bone marrow
4 transplant, I would say that I would agree to that
5 limited indication and would not require a study.

6 DR. ENGLUND: Bone marrow and relapsed
7 leukemia, the two that they had in the study.

8 DR. SCHAPIRO: For those two indications I
9 do not think we need another study. I think we
10 should approve that limited indication. That would
11 be my feeling.

12 DR. GULICK: Others have thoughts?

13 DR. RODVOLD: I agree with that part. To
14 broaden that you would need more data to be able to
15 come to labeling like this. So, the immediate is
16 to include high risk, put language in for that, and
17 move that indication in without necessarily more
18 data. Then, if the sponsor and agency wants that
19 to be broader than the high risk group, then you
20 will have to pursue whatever it takes to get that.

21 DR. GULICK: So, again, I really would
22 like to consider one at a time. So, we are still
23 considering is there a limited indication that we
24 would feel comfortable approving, or recommending
25 approval today based on what we have seen?

1 DR. WOOD: I would feel comfortable
2 recommending approval for a limited indication in
3 high risk patients, as defined prospectively, being
4 those patients undergoing allogeneic bone marrow
5 transplant and relapsed leukemia. I believe there
6 is sufficient data there.

7 DR. GULICK: Dr. DeGruttola?

8 DR. DEGRUTTOLA: I don't have any comment
9 about recommending one way or another but I do
10 think it is important to remember the analysis that
11 the sponsor just presented saying they didn't see
12 an interaction between the level of risk and the
13 randomized treatment. So, while there may be a
14 suggestion of a difference between the voriconazole
15 and the control drug among the high risk patients,
16 it wasn't demonstrated that, in fact, there was any
17 difference between the low and high risk groups.
18 So, I think people would have to be relying on
19 their other medical knowledge which, obviously,
20 people are for making this consideration. Even as
21 a post hoc analysis there is not strong evidence,
22 as I understood, for an effect of risk on the
23 treatment difference.

24 DR. GULICK: Dr. Yogev, if you have some
25 questions, it would help everybody to ask them.

1 DR. YOGEV: Can you repeat it? Maybe I
2 missed it because I thought when you do the high
3 risk by itself there is a benefit.

4 DR. DEGRUTTOLA: Well, there is no
5 evidence of an interaction -- there may be a point
6 estimate. The point estimate may be a little bit
7 better favoring voriconazole for the high risk and
8 a little bit worse favoring amphotericin for the
9 low risk -- the point estimates, but when a formal
10 test was done, as I understand it, to see whether
11 level of risk had an effect on that treatment
12 difference, it did not. In other words, the
13 question is was one better and the other worse by
14 chance, or was there a real proven statistical
15 difference between the two? And, as I understand
16 it, there a trend there that things look better in
17 the high risk group but it isn't demonstrated that
18 risk interacts with the randomized treatment. So,
19 I think in order to support the notion that there
20 should be an indication in the high risk group, I
21 think people should bring whatever other medical
22 knowledge they may have that tends to strengthen
23 the data by itself but, as a statistician, is not
24 strong enough to support.

25 DR. WONG: I really agree with that. I

1 personally believe that trying to split the
2 population is the wrong approach. I think that the
3 sponsor's data has demonstrated to my satisfaction
4 that breakthrough fungal infections and deaths are
5 prevented by voriconazole as well as they were
6 prevented by the liposomal amphotericin B in the
7 study we saw today, and I wouldn't try to break out
8 subgroups.

9 DR. GULICK: Did the agency want to speak
10 to Dr. DeGruttola's point?

11 DR. POWERS: I am translating. Our
12 statisticians say they agree completely with Dr.
13 DeGruttola's remark.

14 DR. GULICK: So just to clarify again,
15 although there was a trend towards an improvement
16 in the higher risk subgroup, statistically there
17 was no difference between the two groups.

18 DR. POWERS: The other point I would like
19 to make again is that even though patients were
20 stratified this way, when you divide it into high
21 risk and low risk and then look at the results in
22 those, that is still a secondary analysis. It is
23 not prespecified ahead of time.

24 DR. GULICK: Would we like to also
25 consider safety given that we are talking about

1 particular groups? Dr. Englund?

2 DR. ENGLUND? I would just like to amplify
3 Dr. Schapiro's statements of the whole thing, which
4 is risk/benefit. We don't have, to my mind, great
5 long-term safety data and so by limiting it to the
6 people who have the chance to benefit the most
7 because they are at the highest risk of having
8 serious consequences not based -- well, based on
9 the data from the study and based on general
10 epidemiology, I would vote yes for partial
11 approval.

12 DR. GULICK: Others? Dr. Schapiro?

13 DR. SCHAPIRO: Victor, just my take on
14 this, if we didn't have any logical explanation why
15 this would happen you would say the statistics are
16 not saying that this is so. But we say that this
17 is a group where we expect more Aspergillus and we
18 think this is a drug which is better for
19 Aspergillus and, therefore, we are not surprised
20 that these results are the results, that would be
21 the kind of reasoning and not that the statistics
22 are telling you that you have identified a
23 subgroup.

24 DR. DEGRUTTOLA: Exactly. In other words,
25 what you could say is these results are consistent

1 with the way I would expect it to go given my
2 medical knowledge, but you can't say that they
3 support or really show that result.

4 DR. GULICK: Dr. Goldberger, do you
5 recommend we take a formal vote on the limited
6 indication of have you heard enough?

7 DR. GOLDBERGER: I think, personally, I
8 guess I have heard enough.

9 [Laughter]

10 Let me just say this, I recognize how
11 painful this has been for the committee members but
12 I will tell you that it greatly facilitates the
13 subsequent discussions we will have with the
14 sponsor on this issue. Although Pfizer is
15 certainly pleasant to work with, labeling
16 negotiations, by their nature, tend not to be very
17 pleasant and having this type of interaction is
18 very helpful in just thinking of a framework for
19 our discussions with them, and it will save both us
20 and them I think a lot of time. So, it was
21 actually quite useful to do it now since the issue
22 would have undoubtedly come up in subsequent
23 labeling negotiations, which is why we wanted to
24 get your input now.

25 DR. GULICK: So, short of a vote, maybe

1 again I can just try to say what we felt as a
2 group. There is a difference of opinion here. I
3 think people are responding to the fact that the
4 high risk group perhaps is in the most need of
5 therapies and that we have seen at least a signal
6 that there is a demonstration of activity here, and
7 that the risk/benefit in a group that you can
8 define as high risk clearly is different from other
9 groups that may have received the therapy in the
10 overall study.

11 Along with that is the biological
12 plausibility that we would like to see the drug
13 work in this group that needs it the most.
14 However, we have been reminded that the
15 statistically analyses don't clearly show a
16 difference between these groups, and we have been
17 reminded that the analyses that we did see were
18 actually retrospective; they were secondary
19 analyses, not primary analyses.

20 We need to come back to what additional
21 data we would recommend in support of a primary
22 indication. Things that people have said so far --
23 with regard to safety, we would like to see longer
24 term description of the visual changes; that we
25 would like to see more drug interaction

1 information. In terms of efficacy, people have
2 suggested that looking at fungal breakthroughs
3 alone, perhaps in a second study and/or confining a
4 second study to a subpopulation which would be more
5 at high risk, are options that have been brought up
6 in the discussion. There may be others. Other
7 suggestions? Dr. Hamilton?

8 DR. HAMILTON: I would think the sponsors
9 possibly could look at their data to see if they
10 could define who actually constitutes high risk
11 patients. This would be, obviously, a
12 retrospective analysis but could address concerns
13 that I expressed relative to the use of disease
14 classifications as opposed to biologic measurements
15 that have some objectivity to them.

16 DR. GULICK: And I think you also made the
17 important point before that there is a large amount
18 of data available now that could be looked at or
19 could be follow-up on, and then another way to
20 approach this is to come up with a completely new
21 study, and that both approaches may have their
22 benefits here.

23 DR. WONG: One idea that comes to my mind
24 from the Aspergillus study is that you have this
25 outside expert panel that reviews cases in a

1 blinded way, but for this study the efficacy of
2 treatment was not assessed in a blinded way. Am I
3 correct there?

4 DR. BOUCHER: There was a blinded data
5 review committee in the empirical therapy study
6 that both assessed diagnosis of infection and
7 certainty of infection, as well as outcome at the
8 end of therapy.

9 DR. GULICK: Just to be clear, they were
10 blinded as to therapy.

11 DR. BOUCHER: Yes, yes.

12 DR. GULICK: Other thoughts?

13 DR. RODVOLD: The sponsor has done a lot
14 of pharmacology work and I compliment them for it.
15 In fact, it is amazing how much they have done.
16 But in this area, and it is not often thought of in
17 the labeling, but drug interactions with cancer
18 drugs is still out there. There are a lot of
19 protein binding issues; there are CYP issues. So,
20 with or not that is influencing the disposition of
21 this drug, I don't know. I know they showed
22 average concentrations and average value across a
23 lot of populations, but maybe just going back and
24 tweaking out these transplant patients, leukemics
25 in other populations that will be in this audience

1 to make sure that the dosage they are using is the
2 right dose based on the pharmacology in this
3 audience because they are complex patients. Other
4 drugs have been characterized with different PK
5 issues, and just to make sure we haven't overlooked
6 that. If they have already done it, that is great
7 but I want to ask to make sure they know the PK in
8 the audience of these neutropenic patients and
9 different types of neutropenic patients, and then
10 also is there any influence of drug-drug
11 interactions from anti-cancer drugs which is often
12 not studied and is only studied with basically
13 specific groups. St. Jude's, for example, has done
14 it with some of the kids. So, I would recommend
15 some of those caveats down the line.

16 DR. GULICK: I think people are getting
17 tired here. Let's move to the next question, which
18 actually segways nicely onto this question, what
19 additional Phase IV studies would you recommend?
20 Dr. Wong?

21 DR. WONG: With respect to aspergillosis,
22 I think that the data are very clear that
23 voriconazole worked, but what we don't know is
24 whether voriconazole is as good as, not as good as
25 or better than several alternative drugs and I

1 think that those studies should definitely be done.
2 I would recommend that voriconazole be compared to
3 liposomal amphotericin B and capsosungin in the
4 same sort of clinical study design that was shown
5 here today.

6 DR. GULICK: Dr. Morrison?

7 DR. MORRISON: At least in the setting of
8 aspergillosis, clearly, the cure rates aren't as
9 high as we would like although they are better than
10 what we have previously seen. And, I think that
11 raises the issue of looking at combinations of
12 therapies in future trials, possibly either
13 combinations of antifungal drugs but also one could
14 consider combinations of these drugs with agents
15 such as growth factors.

16 DR. GULICK: Let me mention some of the
17 other things that have come up earlier today in
18 terms of Phase IV things. In terms of safety,
19 again, we wanted to see longer term safety on
20 visual changes. I guess there is very little human
21 histology data. Clearly, it is difficult to get
22 such data.

23 We wanted to see information on QTc,
24 prolongation of QTc interval at higher
25 concentrations of the drug. We would like to see

1 more description on the anaphylactoid reaction that
2 came up. Other patient populations that we have
3 suggested over the course of the day -- clearly,
4 pediatrics are very important, particularly with
5 regard to visual changes. Several people mentioned
6 those with preexisting eye disease or specifically
7 retinal disease; those with hepatic insufficiency
8 and/or renal insufficiency, and there was a plea
9 that those insufficiencies be defined in terms that
10 clinicians know how to use in particular.

11 Drug-drug interactions that we have
12 mentioned over the course of the day, specifically
13 the HIV non-nucleoside reverse transcriptase
14 inhibitors Efavirenz and Nevirapine and, as was
15 mentioned earlier today, ritonavir as being, of the
16 protease inhibitors, the most potent one that
17 interferes with CYP3A4. Nelfinavir should probably
18 also be added to that list.

19 Let's see, we requested earlier today
20 information on activity of voriconazole against
21 other fungi that we didn't really consider today or
22 that we saw limited data on. There was a plea for
23 more resistance data. Then, most recently,
24 comparative data, as Dr. Wong suggested, of
25 voriconazole against some of the other agents that

1 are used commonly, liposomal amphotericin B and
2 capsosfungin being two examples. And, as Dr.
3 Morrison reminded us, combination therapy of the
4 antifungal agents would be an appropriate place to
5 go from here.

6 Others to add to that list? Dr. Yogev?

7 DR. YOGEV: Well, when you say pediatrics,
8 I just want to make sure the company is not feeling
9 comfortable with up to six months candidiasis in
10 the newborn, and after that kids sick less than six
11 months -- so, I hope both the agency and the
12 company will work on less than six months in
13 pediatrics.

14 I noticed when I read this very thin
15 yellow book that in vitro data shows, which is
16 surprising, that cryptococcus is very sensitive to
17 this specific material and might be in many
18 populations, especially in AIDS patients if not in
19 the United States and other places, a good one.
20 Then also histo and blastomycosis, again, we are
21 starting to see more and more of them and it will
22 be very important to look into that.

23 DR. SCHAPIRO: A very minor issue,
24 actually, nelfinavir is important to study. If I
25 am not mistaken, of all the protease inhibitors, it

1 utilizes 2C9 and not 3A4. So, actually although we
2 are sort of fixated on this drug we should actually
3 go from nelfinavir maybe for throughout others.
4 So, it is a little bit different than our classic
5 3A4.

6 DR. GULICK: That is right and that is why
7 I threw it in there. Dr. Hamilton?

8 DR. HAMILTON: Implicit in one of your
9 suggestions, Dr. Gulick, is that the activity
10 against other fungi be explored as well. This
11 points out I think one of the major difficulties of
12 the kinds of studies that we just reviewed, that
13 is, knowing exactly what is going in people who are
14 febrile and neutropenic. If we knew at that moment
15 X person has Candida or Y person has Fusarium and Z
16 person has crypto we would be a long ways ahead.
17 Now, it occurs to me that in the course of this
18 study a substantial amount of specimens must have
19 been collected, and I don't know what happens to
20 specimens in these circumstances but I know what
21 happens to them in circumstances in which I have
22 been involved. They sit in my freezer forever and
23 nothing gets done with them unless I do something.
24 But there are people out there who might want to
25 actually utilize those specimens in a productive

1 way to help identify diagnostic techniques that
2 would be very useful in the acute stage of these
3 infections. That would be very helpful I think in
4 focusing therapy. So, I would encourage general
5 collaboration with your ideas.

6 DR. GULICK: Thanks. Dr. Wood?

7 DR. WOOD: I would just like to reinforce
8 a comment that Jonathan had made earlier this
9 afternoon regarding trying to take advantage of
10 autopsy specimens for any histopathologic
11 examination of eye findings because these were huge
12 studies with a huge number of patients, many of
13 whom died and many of whom underwent autopsy. So,
14 just being able to get the retinal autopsy findings
15 of everyone who was exposed to voriconazole would
16 get us some information fairly quickly and rapidly
17 that we really feel is lacking regarding human
18 toxicity in the ocular findings.

19 DR. GULICK: Let's move to our last
20 question. This really follows up, as Dr.
21 Goldberger mentioned, on several previous meetings.
22 What additional advice does the committee have
23 regarding the design of future studies needed in
24 the development of therapeutic agents for the
25 initial therapy, and therapy of patients refractory

1 or intolerant to other antifungal therapies, in
2 patients with pulmonary and/or disseminated
3 aspergillosis?

4 Although we have talked a lot about it, we
5 may want to expand that to the empiric febrile
6 neutropenic patient population also. Dr. Wong?

7 DR. WONG: At the last meeting that we had
8 to discuss an aspergillosis application I think I
9 said that I didn't want to see another presentation
10 that depended on historical controls, and I am
11 delighted to see that today we didn't have to
12 depend on an analysis of historical controls. I
13 hope that the agency has now had demonstrated to it
14 that a proper controlled trial for aspergillosis
15 can be done, and this should be expected in the
16 future. Indications that companies get based on
17 analysis of historical controls alone I think
18 should no longer be allowed.

19 The second plea that I would make is to
20 put a stake into the idea of this composite
21 endpoint that incorporates both efficacy and
22 toxicity in the same measure. They should be
23 analyzed separately and I don't think that there is
24 any reason not to do that.

25 DR. GULICK: Dr. DeGruttola, maybe you

1 could comment on the use of non-inferiority studies
2 in general and what limits might be suggested.

3 DR. DEGRUTTOLA: Well, as I believe it was
4 Dr. Hamilton who said -- my memory may be incorrect
5 -- that the definition of non-inferiority has to be
6 a clinical definition. It is really I think the
7 clinicians that need to say what they consider
8 non-inferiority in a particular setting. But I
9 think that we need to keep in mind that if you are
10 using absolute differences it does matter where you
11 are in terms of the expected response, and that
12 relative differences may be more useful to consider
13 just because you don't have to have as specific an
14 idea of what the response will be.

15 DR. GULICK: Would others support the
16 continued use of non-inferiority studies in this
17 setting, as was recommended in '94, '95 by the
18 expert committee?

19 DR. WOOD: I would prefer that the
20 committee or that the FDA consider the
21 modifications that Victor had suggested earlier
22 this afternoon in terms of taking into account the
23 relative response rates when looking at
24 inferiority.

25 DR. GULICK: One of the things we were

1 asked to consider is initial treatment versus
2 refractory treatment, and that has come up several
3 times today. Do people have comments? If we
4 focused on refractory patients in terms of study
5 design itself, clearly a group that is in need of
6 therapies? Good idea?

7 DR. ENGLUND: Sure.

8 DR. GULICK: Okay. It is like pulling
9 teeth at this hour!

10 DR. YOGEV: let me give you one tooth --

11 DR. GULICK: Thank you.

12 DR. YOGEV: I think one of the problems of
13 this specific study and many that I see is because
14 we expect to have difficulty enrolling patients we
15 shy away from trying to define groups in different
16 studies, or stratify as this is called. We are
17 terrified by the N, and this is the best example,
18 if they would be prospectively done, the data we
19 had today that we are struggling with so much,
20 would probably be completely different. And, what
21 always bothers me in studies coming both from
22 industry of even multiple sites from the NIH is
23 that we are opening it too much without realizing
24 where it is going to end. So, I think a better way
25 to define it -- for example, the way the question

1 was put over here, I think it has already put us in
2 trouble because it is only pulmonary and
3 disseminated in one center and it should be
4 different because it is a different disease. That
5 goes to one of your suggestions, "or refractory to
6 therapy." But those have to be defined up front,
7 and the N has to be defined better. It anyhow
8 takes a long time and we need to make sure can we
9 do it or not. I don't think we spend time in
10 devising the protocol and how it would work. So I
11 would encourage to write the protocol in a
12 different way and we will then go into those issues
13 in a more specific population prospectively.

14 DR. GULICK: Do people have other
15 comments? We struggled a lot earlier with subgroup
16 analyses and retrospective versus prospective looks
17 at the data. Do people have other comments about
18 that issue in particular? Dr. DeGruttola?

19 DR. DEGRUTTOLA: No, I think actually that
20 the sponsor did a very good job of specifying what
21 were prospectively defined analyses and what were
22 retrospectively analyses and subgroup analyses, and
23 I think the important thing is just keeping in mind
24 those distinctions when you review data.

25 I think one other issue actually that I

1 would comment on is that if you are doing subgroup
2 analyses, I believe it is useful to do formal tests
3 of interaction rather than say, oh, there was a
4 significant effect in one group and there wasn't a
5 significant effect in another group. We have to
6 raise the issue of was there adjustment for
7 multiple testing; how were these categories
8 defined; and so on. I think if you do formal tests
9 for interaction they can be useful in this setting
10 as well, as we saw in this case.

11 DR. GULICK: One part of the composite
12 endpoint for the study we looked at was fever in
13 relationship to the time of neutropenia. As we
14 pointed out earlier, the time of neutropenia is
15 shortening in general. Do people have comments
16 about that particular endpoint? Dr. Wong?

17 DR. WONG: I think the trouble here is
18 that how long someone is febrile is not really the
19 question. So, the study should be designed to ask
20 the most relevant question that matters, which in
21 this case is how many patients developed
22 breakthrough fungal infections and how many
23 patients died. How many days of fever is really
24 much less important, I mean an order of magnitude
25 less important and I am afraid what drove the

1 results in this study, which was a shame.

2 DR. GULICK: Further comments or issues?
3 To Dr. Goldberger and the agency, have we done what
4 you want us to do? Do you need anything else from
5 us?

6 DR. GOLDBERGER: No, I think that is fine.
7 I was trying to think of maybe three or four other
8 questions --

9 [Laughter]

10 DR. WONG: Each with five sub points!

11 DR. GOLDBERGER: Yes! No, we thank you.
12 I think this discussion was very helpful. Your
13 comments about febrile neutropenia in particular
14 were very helpful, both in terms of thinking about
15 it with regard to this product and thinking about
16 the broader issues of study design, etc.

17 DR. GULICK: Great! So, I would like to
18 thank the members of the committee, particularly
19 the ones who are the long-term survivors and lasted
20 to the end of the two days. I appreciate that.
21 Thanks to the sponsor for your presentations and
22 for the follow-up clarifications, and to the agency
23 for organizing the day, and the audience out there
24 somewhere. Thanks very much.

25 [Whereupon, at 3:55 p.m., the proceedings

1 . were adjourned.]

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C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



ALICE TOIGO

Lawyer's Notes

0

0.007 148:11
0.01 148:10
0.1 36:15; 121:7; 166:19, 23; 173:17
0.37 174:22
0.4 56:7; 172:20
0.417 155:16
0.5 24:20
0.5-5 223:25
0.554 155:15
0.6 56:6; 134:13
0.89 56:7
0.9 176:17; 179:9; 183:19

1

1 24:19; 36:16; 42:23; 51:18; 97:8; 120:1, 1; 128:1; 206:14
1.08 61:15
1.2 179:2
1.25 24:21
1.4 74:10; 176:4
1.5 89:3
1.5-fold 29:1
1.7 172:10
1.8 178:12
1.9 174:17; 183:8
1/20 225:6
10 26:6; 60:13; 65:10, 11; 68:7, 19; 73:6; 74:25; 108:20; 119:10; 141:23, 23; 142:14, 23; 154:5; 162:3, 24; 164:6; 166:7; 167:2; 170:11; 183:21; 186:8; 187:4; 206:7; 207:3, 5; 231:2; 237:3; 238:6, 13, 23; 239:2; 241:12; 249:24; 251:5, 8; 263:13
10-14 123:11
10.6 68:6
100 17:13; 30:2; 140:23; 163:15; 188:24; 211:16; 249:21
1000 29:22, 24; 106:22
1003 151:12; 157:6
101 137:16
102 133:18
11 32:19; 47:14; 51:20; 52:1; 55:9; 168:4, 5
11-fold 33:11
11.6 166:23
11.7 183:7
112 153:25
11:35 147:12
12 31:11; 37:17, 20; 41:7; 42:11, 19; 43:9, 11, 14, 16, 23, 24; 44:9; 45:16; 49:21; 50:9, 17, 23; 51:2, 17, 24;

52:2, 5, 12, 18; 53:4, 14; 54:5, 23; 56:19; 57:6; 66:21; 68:18; 78:3; 81:12; 88:13; 124:14; 130:12; 139:23; 140:14; 141:16; 152:11; 153:7; 159:5; 166:19; 182:5; 188:21, 22; 190:13; 199:2, 6, 6
12-13 251:3
12-month 86:17
12-week 133:25
12.1 173:17
12.4 172:14
12.7 181:4
12/22 180:10
1200 81:22
12:45 207:9, 12
12A-30 7:2
13 16:1; 50:22; 56:2; 57:8; 60:12, 13; 69:13; 72:21; 108:21; 175:1; 260:19; 267:8
13.1 183:19
133 47:25; 51:8; 151:22
14 42:24; 71:16; 88:3; 104:16; 119:2, 6, 12; 125:12; 128:17; 132:17; 141:24; 189:4
14/22 180:7
141 267:8
144 47:24; 50:1; 151:22
1493 77:7
15 60:18, 20; 61:16; 137:7, 9; 142:14; 143:2; 162:6, 11; 205:3; 206:12, 25; 239:9
15-20 109:23
15.2 172:20
150-1004 188:19
16 153:13; 169:5; 204:10; 231:17
16/27 60:4
17 99:6
17-18 251:2
172-year 77:22
18 6:21; 7:11; 67:16; 80:12; 169:5; 175:15
18-65 190:14
18.6 193:5
19 32:16; 71:2; 89:14; 90:24; 115:13
194 47:18
1955 19:23
1956 161:5
197 96:18
1970s 160:5
1982 160:7
1989 160:12
199 47:7
1991 19:21
1994 160:19; 161:1; 166:11; 262:7
1995 160:19; 231:7

1997 39:23; 163:4
1:45 207:10

2

2 37:17; 85:3; 148:9
2.1 173:23; 177:10
2.2 176:9
2.5 32:11; 115:12; 116:5, 12; 146:25
2.5-fold 28:25
2.7 177:13
2.8 52:21; 176:11
2/143 267:9
2/5 180:10
20 41:6; 45:21; 48:21; 54:1, 11; 95:10; 104:13; 110:12; 148:20; 152:18; 160:12; 170:15; 185:7; 206:15; 238:18
20/20 263:11
20/21 175:6
200 29:2, 15; 37:21; 38:1; 42:20; 87:12; 135:21; 142:16
2000 13:22; 22:20; 40:4; 146:19
208(b)(3 6:21
208)(a 7:11
2090 77:11
21 7:3; 48:15; 69:1; 74:7; 134:4; 137:8; 174:3; 243:9
21-266 149:9
21-267 149:10
21.2 52:20; 53:2
21.8 55:7
212 24:12
22 50:15; 66:18; 71:13; 75:20; 108:9, 10
22.43 62:10
23 71:2; 134:3; 173:8
23.7 68:12; 166:14
23/92 58:16
24 25:24; 65:1; 69:6; 72:19; 182:24; 188:9; 196:16; 197:1; 198:21; 250:16
24-month 86:7; 197:3; 198:1, 3
25 41:8; 48:14, 18; 58:16; 70:4; 104:13; 155:14
25-28 133:7
25-35 83:4
250 64:25; 250:16
256 63:10
257 91:15
25th 84:19; 110:8
26 62:14; 82:9; 89:14; 108:3; 135:15, 23; 210:7
26/50 58:12
27 48:20; 105:22; 188:22
276 41:11
277 48:2

28 15:23; 70:22; 84:12; 127:21; 182:7; 189:3, 21; 202:6, 24
29 84:24
29.8 124:4
2:00 207:13
2:1 155:5
2C19 28:11, 12; 194:7, 9
2C9 28:11; 194:7, 9; 287:1

3

3 37:20; 87:11, 22; 139:5, 12, 13; 140:16; 141:16; 191:5
3.1 173:21; 174:19; 176:20
3.2 61:14
3.3 173:24; 178:10
3.5 118:11
30 73:8; 79:6; 83:23; 94:25; 104:5; 172:24; 175:13; 238:16; 248:12; 263:20
30.1 68:13; 166:15
300 29:2; 38:3; 84:11; 87:12, 23; 88:5; 132:4; 137:1; 142:16; 188:21
3000 29:24; 77:3; 106:22
304 150:13, 25; 151:9, 13; 153:23; 154:12, 22; 155:1, 10, 13, 24; 156:8, 14; 157:8
305 190:24
307 39:24; 49:17; 53:8
307-602 190:24; 191:4; 203:8, 16
307/602 150:13, 25; 151:1; 154:8; 157:9, 10
31 68:3; 173:1
31.6 52:19; 152:13
31.7 55:13
31.9 55:13
32 166:9; 173:5; 182:2; 183:12
32.5 180:25
323 91:22
33 127:25; 182:13
33.6 152:17
34 91:6; 148:8
35 60:3; 81:11
35.9 183:1
355(n)(4 7:4
36 62:11; 72:4; 182:14, 17
36-year 148:18
36.5 181:1
360 267:22
365 32:17
368 41:10
37 15:19; 45:22; 154:19
38 71:24; 104:17; 105:12; 147:18, 19; 211:2

38.5 124:3
39 16:3
392 47:9, 14
3:55 294:25
3A4 28:12; 34:19; 35:23; 194:7, 10, 11, 14, 15; 287:1, 5

4

4 31:12; 37:25; 38:3; 42:18; 47:9; 87:12; 88:5; 96:24; 136:8, 11, 25; 138:21; 139:5, 12, 14, 24; 140:14; 148:22; 181:2; 190:13; 210:8; 260:19
4.1 179:3
4.5 68:4
4.6 179:6
4.7 176:22; 181:5
4.8 72:9
4.9 183:4
40 16:8; 18:4; 31:17; 91:2; 139:21, 23; 205:20; 238:24
40.8 183:3
400 29:7, 12; 33:24; 37:17; 87:13; 137:5; 188:21; 206:22
41 70:22; 93:16
415 66:24
42 51:4; 210:7; 257:23
421 66:19
422 66:24
426 63:10
428 66:19
43 84:25; 159:5
44 90:14; 134:2
443 77:16
45-year 46:9
470 96:23
476 58:23
48 64:16; 71:24; 181:13
48-80 159:17
480 96:25
49 14:4
49.1 154:16

5

5 33:24; 87:13, 14; 136:10, 15; 137:4, 9; 139:9; 174:18; 223:25
5-component 166:1
5.2 176:19
5.3 178:25
5.4 72:10
5.5 179:8
5.9 177:9
5/13 124:2
5/14 87:16
5/38 147:24

50 13:23; 41:3; 47:20, 21;
57:17, 23; 58:3, 14; 61:19;
67:11, 15; 73:9;
5, 18; 124:6; 133:23;
137:17, 25; 140:5; 155:10;
159:10; 166:8; 188:7;
198:20; 206:7; 221:14;
238:19, 22; 244:17;
263:19
50-year 95:2
50.1 183:13
500 78:2; 97:2
51 62:10
52 58:12; 71:7; 133:23;
155:13
52.8 52:16; 152:12
53.5 55:6
54 154:2
546 23:19
56 52:7; 130:2
56.2 183:14
57 51:23
58 13:24; 56:1; 154:1;
181:23, 23; 182:16
59 14:7
595 15:17

6

6 29:7; 37:17; 87:10, 21;
96:24; 108:24; 119:4;
130:14; 210:16
6-month 210:15
6.1 68:16; 166:17; 173:15;
183:17
6.5 174:22
6.6 178:9
6.8 206:10
6.9 177:12
6/21 136:9; 137:8
6/8 175:5
60 49:3; 91:23; 120:23;
169:6; 170:4; 252:10
60-100-fold 23:21
60-some 140:17
60.3 154:17
602 39:24; 46:10; 49:16;
53:7
603 145:23; 150:16;
157:22; 164:4; 165:5;
166:14; 181:12, 20;
182:21; 190:24; 206:22;
263:9
53:9; 185:24
60:9
63 49:3
64-year 90:21
64.7 124:5
68-year 148:7

7

7 87:15; 164:11; 167:25;
168:6
7-43 145:10
7.8 172:17, 18
70 124:17; 182:10; 252:10
70-some 123:5
71 55:24
73 64:5; 109:21; 182:9
75 117:15
75th 110:8
76th 84:20
77 50:9; 55:9; 128:9;
135:22; 136:3
786 65:12; 67:3

8

8 72:12; 138:22; 170:4;
188:8; 190:13
8.4 178:12
80 59:24; 65:8; 117:19;
118:6; 120:24
80-day 117:22, 25
81 109:15
83 106:12
837 67:2
84 44:5, 17; 49:22; 50:4;
51:5, 10; 52:8; 55:20, 21;
56:2, 5, 13; 57:9; 80:4, 9;
124:22; 153:10, 18
85 47:19
861 110:7
866 65:12
87 14:2; 23:20; 59:22
871 66:17

9

9 16:13
9.2 74:10; 175:17; 176:6
9.6 152:16
9.9 178:7
90 14:9; 41:5; 60:14;
116:3
91 67:21
92 45:23; 155:11
94 226:11; 236:5; 290:17
95 47:8; 52:22; 53:8, 18;
55:14; 56:6; 61:12, 14;
68:5, 17; 73:4; 142:24;
152:14, 20; 162:1; 166:11,
18, 22, 25; 167:6, 14, 22;
168:2; 171:13; 172:12, 18;
174:11; 175:19, 20; 183:6,
18; 226:12; 231:1, 7;
236:5; 262:7; 290:17
96 27:11; 40:16; 64:22
98.3 61:12
99 171:13; 174:9, 20;

175:20; 177:11; 178:11;
179:11; 181:3

A

a-wave 84:16, 17
abated 94:7; 98:15; 99:1
Abbott 4:22; 7:24
ability 42:10
ABLC 17:23
able 27:6; 44:4; 67:22;
86:13; 104:18; 105:20;
116:5; 129:7; 135:21;
140:8; 157:15; 159:12;
162:17; 202:12, 17, 20;
219:11; 223:12; 224:6;
259:15; 274:14; 288:14
abnormal 75:18; 82:8,
14; 83:2; 89:3; 127:15;
144:10, 11; 209:19
abnormalities 119:19;
128:1, 2; 191:24; 196:3;
199:7
abnormality 88:12, 22;
89:5; 92:12; 119:20;
121:16; 136:23; 144:21;
197:16, 19, 20
abortia 60:6
about--l 4:14
above 37:8, 10; 50:11;
207:4
absence 34:23; 65:23;
68:10; 78:14
absolute 54:11; 56:2;
57:8; 64:25; 97:2; 163:15;
217:22; 236:9, 12; 238:13;
290:10
absolutely 248:24
absorb 93:24
absorbed 27:10
absorption 35:13
abuse 90:18; 108:11
accept 147:4; 269:12
acceptable 21:18;
102:3; 269:8
accepted 17:8; 141:6
access 272:23
accidental 137:20
accordance 6:21; 7:3
according 30:5; 31:4;
41:7, 13; 48:9, 12; 49:5;
53:14; 65:16, 23; 67:7, 9;
73:25; 74:22; 118:21;
122:12, 14; 124:8; 171:4;
172:7; 240:23; 249:15;
251:7
accordingly 248:1
account 136:12; 150:7;
234:7; 237:8; 239:6;
245:3, 4; 290:22
accounting 30:9
accumulate 147:2
accumulates 32:9
accurate 253:2

achieve 33:25; 37:5
achieved 23:6; 24:23;
48:5; 67:4; 188:5; 257:6
acknowledge 149:14
across 20:9; 24:17;
30:17; 38:4; 60:2, 19; 83:3;
89:13; 93:5; 97:23; 100:1;
111:16; 116:16; 118:18,
24; 119:16, 21; 129:24;
130:13; 134:13; 155:23;
205:23, 25; 239:2; 269:21;
282:22
act 154:24
Acting 5:24; 7:25
action 10:23; 84:4; 96:9
active 20:20; 23:3;
164:17; 205:15
actively 272:9
activities 87:1; 99:10;
264:1
activity 12:8; 24:10;
25:13; 84:18; 85:8; 262:9;
263:23; 280:6; 285:20;
287:9
acts 34:6
actual 49:24; 128:3, 10;
159:7; 169:24; 177:23;
199:21; 228:4; 244:16
actuality 263:18
actually 9:6; 12:17;
30:19; 35:21; 58:18;
79:19; 96:25; 98:25;
105:7; 108:17, 23; 109:15;
116:2; 117:4, 14, 17;
118:6; 119:1, 3, 8; 121:13;
125:18; 126:13; 127:5;
129:9; 131:7; 134:11, 25;
137:3, 5; 139:16; 140:5, 6,
11; 141:20; 142:12;
143:24; 147:21; 157:11;
161:16; 163:8; 168:8;
169:21; 171:21; 174:7;
176:25; 179:17, 20; 181:8;
182:3, 4; 184:7; 186:2;
187:11; 198:2, 4, 6; 204:6,
16; 205:4, 19, 23; 210:11;
211:4, 10, 18; 228:15;
233:24; 236:10; 239:7, 23,
24; 241:13; 243:24;
253:17; 259:25; 268:5;
270:17; 272:7; 279:21;
280:18; 281:10; 283:18;
286:24; 287:1, 2, 25;
292:19, 25
acuity 85:16; 86:2; 128:4,
11, 15, 19; 129:8; 202:13;
208:20; 209:3
acumen 111:5
acute 21:2; 38:24; 39:12,
17; 40:12, 20, 23; 41:21;
42:3; 46:9, 19; 57:13; 76:3,
9; 90:13; 91:16; 95:4;
100:1; 102:5; 142:2; 288:2
acutely 29:18; 142:3
ad 269:7
add 108:25; 120:8;
121:10; 139:20; 210:20;
286:6

added 89:25; 285:18
addition 7:20; 22:13;
67:22; 153:13; 157:12;
215:10; 227:21; 256:24
additional 64:24; 66:21;
98:21; 100:21; 152:24;
156:17; 189:7; 195:19;
203:9; 210:22; 212:11, 21;
214:8, 12, 20; 215:22;
218:8; 221:8, 19; 245:11,
16, 16, 21, 21, 22; 261:6;
263:2; 265:11; 267:3;
270:13, 16; 271:10; 273:6,
18; 280:20; 283:19;
288:22
address 8:10; 56:10;
79:1; 98:1; 103:25;
106:10; 111:9; 116:23;
118:8; 121:24; 123:19;
129:13; 144:23; 145:19;
160:2; 173:12; 194:1;
281:12
addressed 16:19;
104:24; 223:3
addresses 6:9; 22:5;
102:2; 103:4
addressing 27:5; 52:11;
56:11
adequate 11:8, 9; 33:25;
152:7; 154:5
adequately 155:21;
169:3; 171:17
adjourned 295:1
adjective 15:4
adjust 107:6; 110:16;
132:7; 171:10; 179:12
adjusted 52:21; 55:14;
68:8; 146:6, 12
adjusting 132:3
adjustment 30:21; 31:4;
32:25; 35:6, 19; 245:8;
293:6
adjustments 34:13, 15;
179:13; 244:25
administered 19:20;
98:5, 16, 17
administration 33:13;
104:22
administrators 228:24
adult 139:5, 25
adults 139:13, 14;
140:16; 230:9; 259:19
advance 145:16
advanced 16:10; 18:5;
61:18
advantage 153:20;
186:12, 13, 16; 235:16;
288:9
adverse 75:19; 78:16, 21;
81:6, 9, 10, 11, 15, 24;
82:6, 15, 23; 83:16; 87:5;
94:23; 100:9; 101:3, 11;
104:8, 9; 105:14; 147:20;
191:1, 5, 24; 192:2, 7;
211:5
advice 195:18; 213:18,
21; 214:4, 12, 16, 18, 20;

215:22; 268:3, 7; 270:3;
271:21; 288:22
advise 115:10
Advisory 4:5; 8:25; 9:3;
149:21; 150:21; 163:4;
195:18; 215:5
afebrile 180:13; 181:13;
182:24
affect 11:11; 192:20;
199:16
affected 34:18
affiliation 8:17
affinity 194:8
affirm 262:3
afraid 234:10; 293:25
afternoon 103:13; 208:1;
288:9; 290:22
again 11:14; 16:6, 13;
18:12, 24; 31:1; 32:11;
40:21; 43:10, 13; 51:12,
21; 52:25; 54:10; 57:19;
68:16; 74:15; 75:2; 81:24;
85:6, 9; 86:1; 89:9; 93:12;
95:11; 98:22, 23; 99:4;
100:3; 103:10; 110:1;
113:7, 9; 119:20, 23;
120:2; 121:16; 128:19;
129:5, 6, 9; 133:25; 134:2;
143:14; 144:18; 161:21;
162:25; 164:3; 165:24;
166:2, 10, 21; 170:5, 9;
172:14; 173:14; 175:25;
181:25; 183:5, 19; 184:19;
185:10; 196:2; 205:24;
206:15, 22; 209:9, 15, 21;
212:3; 215:3, 9; 217:20;
218:9; 220:21, 25; 230:18;
233:15; 234:12; 237:8;
240:16; 250:20, 21;
265:17, 20; 271:23;
274:21; 277:14, 19; 280:1;
284:19; 286:20
against 20:12; 23:4, 5;
24:11; 26:22; 76:14; 97:7;
102:10; 201:12; 262:9;
285:20, 25; 287:10
age 31:4, 11; 48:9; 67:7;
106:16; 126:3; 139:23;
140:14; 182:4, 5; 189:13;
198:7, 7; 199:15, 17; 245:3
aged 115:19; 190:14
agency 7:13; 8:22;
147:16; 149:2; 199:12;
204:14; 207:7; 220:20;
234:10; 237:6; 242:1;
241:6; 244:18; 269:11, 18;
274:18; 277:9; 286:11;
289:13; 294:3, 22
agency's 7:1, 16
agenda 6:13; 8:5; 208:8
agent 12:3; 98:18;
107:12; 114:15; 115:11;
116:19; 122:7; 129:11;
147:1; 262:7; 264:2
agents 14:24; 17:18, 21;
19:13; 26:10; 36:8; 40:8;
59:18; 82:4; 93:6; 100:15;
101:21; 165:1; 211:15;

214:23; 265:5; 284:14;
285:25; 286:4; 288:24
aggressive 14:17; 19:11
ago 170:15; 227:4
agree 192:15; 199:14;
216:9, 11; 218:5; 219:19,
23; 229:11, 13; 237:11;
238:10; 251:10; 258:20;
259:4; 261:2; 262:10;
267:9, 18; 269:4; 274:4,
13; 276:25; 277:12
agreed 210:12; 247:14
agreement 9:14; 10:5,
20; 45:24; 150:2; 151:15;
191:16
ahead 116:25; 127:23;
197:23; 203:1; 208:4, 6, 8;
224:23; 250:2; 277:23;
287:16
aid 111:13
AIDS 61:18; 286:18
aim 20:8
aimed 37:7
al 120:19
Alan 163:6
albicans 23:19; 130:2, 6,
8; 148:9; 150:4
albino 198:5
ALBRECHT 5:24, 24
alcohol 90:18; 108:11
algorithm 88:19
alive 234:2
Alivisatos 149:17
alkaline 82:16; 191:22,
25
alkaloids 33:17
alleles 109:7
allocated 47:18
alogeneic 15:24; 46:11,
22; 48:19; 54:8; 57:2, 21;
65:18; 67:17; 74:4; 76:11;
91:5; 148:19; 250:8, 14;
275:4
allograft 120:20
allow 35:24; 44:14;
140:12; 152:2; 153:5;
156:22; 203:24; 224:5
allowed 18:7; 27:13;
38:2; 40:16; 119:14;
181:9; 182:6; 203:23;
204:19; 211:14; 235:6;
241:6; 289:18
allowing 42:7; 214:5
allows 21:22; 27:11;
44:10; 77:23; 207:1
almost 13:22; 106:1, 7;
140:23; 170:15; 206:22;
227:3; 237:2, 14; 243:15;
252:10
alone 15:25; 71:17;
281:3; 289:17
along 17:21; 24:3, 4;
53:18; 120:25; 176:14;
210:10; 280:11
ALT 87:16, 20, 21; 88:10,

22, 24; 119:18, 20; 120:1;
121:13, 16; 136:23;
137:11, 13, 14
alteration 144:25
alterations 101:12;
105:14
altered 188:13
Alternative 14:24;
224:10; 225:21; 230:10;
272:21; 283:25
alternatively 123:15
Although 13:13; 15:4;
18:3; 19:8; 122:22; 180:8;
183:15; 185:8; 213:6;
215:6; 217:19; 218:25;
221:16; 223:14; 240:17;
252:20; 277:15; 279:14;
284:9; 287:1; 289:4
ALTs 138:13
always 113:16; 174:11;
245:25; 291:21
amazing 282:15
Ambisome 165:6;
166:10, 16, 17; 172:18, 23;
173:1, 3, 7, 16, 23, 24;
174:2, 4, 16, 19; 175:2, 7,
16, 18; 176:7, 12, 19, 22;
177:7, 10, 11; 178:9, 11,
25; 179:2, 3, 6, 15, 24;
180:10; 181:1, 3, 22;
182:14, 15, 16, 17; 183:3,
5, 14, 17; 184:11; 185:6;
186:14, 24; 205:9; 206:4;
224:12, 17; 226:16; 227:4;
233:9, 10, 15; 234:4, 5;
248:22; 249:2, 21; 258:8,
18; 259:1, 11; 260:16
ambulatory 85:24; 210:6
America 257:23
American 160:6
Among 54:1; 73:19;
74:13; 82:10; 106:18;
112:5; 151:8; 192:1, 5, 8;
194:16; 215:20; 229:1;
271:12; 275:15
amongst 93:3
amount 107:15; 140:7;
214:13; 221:18; 260:18;
270:3; 281:17; 287:18
ampho 131:4, 6
amphotericin 14:24, 25;
15:3; 18:9, 10, 21, 22;
21:20; 26:10; 39:16;
41:19, 25; 42:5, 9, 22;
44:15; 47:19, 21, 25;
48:15, 21; 49:13; 51:9, 13,
15, 16, 18; 52:20; 54:6, 24;
55:7, 10, 12; 56:1, 15, 22;
63:21, 25; 64:1, 8; 66:20,
24; 68:3, 14; 69:2, 13, 20,
23; 70:4, 15, 22; 71:3, 7,
14; 72:5, 11, 12, 22; 74:7,
11, 14; 75:24; 80:3, 21, 23;
81:20; 82:3, 11; 88:16;
89:7, 16; 90:22; 93:4;
94:14; 101:18; 102:18, 25;
123:6, 8, 9, 12, 13, 18;
124:4, 6; 131:13, 13, 20;

134:3; 136:14; 142:5;
143:5, 6; 144:16, 22;
148:24; 151:3, 23; 152:4,
6, 13, 20; 153:16, 20;
157:25; 160:25; 161:3;
163:5; 164:17; 165:6, 17,
22; 166:10; 169:1; 170:1;
179:22; 192:3, 6; 193:22;
205:9; 206:4, 19; 229:1,
18; 231:16, 19; 243:11;
252:18; 276:8; 277:6;
284:3; 286:1
amplify 278:2
amplitude 84:16; 85:1, 6,
12
analyses 32:23; 118:6;
146:4; 152:25; 153:14;
158:11; 166:25; 170:23,
25; 171:3, 20; 186:11, 15,
22; 187:8; 203:9, 21;
207:4; 213:10; 214:1;
233:5; 245:16, 22; 247:1,
6, 9; 255:15, 17, 19; 264:4,
9, 24; 269:7; 280:15, 17,
19, 19; 292:16, 21, 22, 22;
293:2
Analysis 31:1; 40:3;
48:5; 53:1, 6, 20; 68:1, 15,
15; 73:5; 74:23; 95:25;
97:9; 101:5; 104:7;
106:23; 110:6; 114:10;
125:2, 9; 133:9; 143:19;
145:21, 22, 23; 146:10;
151:21; 153:5, 7, 24;
164:6; 166:20; 169:10, 16;
172:7, 16; 175:10, 22, 23,
25; 182:19, 23; 186:19;
199:2; 203:18, 24; 204:2;
217:7, 14; 222:20; 224:1;
235:20; 240:17, 23;
241:20; 243:10, 23; 249:7;
251:17, 18; 260:1; 262:21;
264:3; 267:12; 275:10, 21;
277:22; 281:12; 289:12,
17
analyze 84:4
analyzed 29:23; 32:20;
81:6; 96:17; 109:25;
110:1; 226:13; 233:22;
249:10; 289:23
analyzes 248:20
anaphylactoid 76:3;
98:2, 11, 22; 99:17, 20;
105:19; 106:8; 107:8;
190:16, 18; 285:1
ANC 249:23; 250:16
ANCs 249:21
and/or 195:7; 215:1;
281:3; 285:8; 289:2
Andy 145:18
anecdotally 129:17
anemia 90:22
animal 26:24; 63:4;
103:19; 196:12, 20; 198:9,
9; 200:5, 20; 221:17
animals 25:5, 22; 26:2, 4;
28:8; 196:23; 197:10;
198:17, 22; 199:10, 17;

200:9, 16, 17; 201:9
announcement 6:8
anoxide 93:23
answered 225:11
anti-cancer 283:11
antiarrhythmic 191:12
antibacterial 160:14
antibiotics 64:23; 93:8
antibody 159:14
antifungal 9:8, 22; 10:18;
12:3; 13:8; 14:21, 21;
18:17; 19:12; 25:4, 23;
36:8; 40:16; 42:6; 43:3, 19,
22; 44:25; 50:14, 16;
51:22, 24; 58:1; 59:18;
62:5, 14; 63:18; 65:24;
67:13; 68:10; 76:19;
81:21; 82:4; 100:15;
123:25; 124:8; 145:9;
149:24; 150:8, 17; 151:4;
152:8; 154:6; 155:3;
157:23; 158:4; 160:2, 13,
20; 164:13; 166:4; 168:16;
171:5; 176:14, 16; 204:6;
212:19; 214:25; 222:13;
227:10, 17; 237:22, 23;
265:19; 272:3; 284:13;
286:4; 289:1
antifungals 261:15
antigen 16:25; 159:13
antihistamines 192:20
Antiviral 4:5; 9:3
Antonio 12:14; 25:20
anymore 105:8; 107:2;
147:24; 211:21
apart 37:18
apiospermum 60:5
apparent 209:22
appear 119:25; 259:14
appearance 6:11, 19;
7:12
appears 19:12; 101:13;
172:10, 22; 194:12
applaud 157:14
applicant 9:6, 15, 19;
10:8; 155:18; 161:11;
164:18; 173:19; 190:4, 11,
16, 19; 192:15; 193:6, 15;
194:20; 195:14
applicant's 151:16
application 289:8
applied 112:4
apply 234:17
appreciate 12:1; 218:3;
294:20
approach 20:8; 116:24;
120:11; 121:5; 138:6;
204:8; 228:17; 244:5;
270:20; 277:2; 281:20
approaches 15:14;
19:13; 59:24; 181:21
approaching 14:9
appropriate 10:23; 21:9,
14; 76:18; 86:24; 102:19;
121:17; 132:3; 143:7;