

1 collected sufficient data on interactions to
2 provide specific guidance to the prescribing
3 physician, and that these are, thus, manageable.

4 Overall, we think voriconazole addresses
5 an important medical need that is currently not
6 met. Thank you for your attention.

7 DR. GULICK: Thanks, Dr. Baildon and Drs.
8 Patterson and Boucher. At this point I would like
9 to open it up to the committee members to ask
10 questions of the sponsor. Again, I would suggest
11 to people that we stick to questions of information
12 and clarification, and we will take up more of the
13 discussion in the afternoon. Dr. Wood, you are
14 jumping right in.

15 **Questions from the Committee**

16 DR. WOOD: I have several questions
17 regarding safety. Since visual disturbances are
18 most common and were observed not only in clinical
19 trials but also in animal studies, I want to know
20 was there any examination of whether or not it was
21 associated with C-max concentrations of
22 voriconazole or AUC levels in terms of any
23 correlation with specific drug levels that would
24 correlate with visual disturbances.

25 DR. BAILDON: Let me address your first

1 part with C-max. C-max is about one hour after
2 infusion. The onset of the visual disturbance is
3 somewhat earlier; it is about half an hour and then
4 it disappears within each event. Each individual
5 event disappears after about another 30 minutes.
6 So, the time course is not quite identical.

7 In our overall analysis of the correlation
8 between plasma concentrations and adverse events
9 there is a correlation between visual adverse
10 events and plasma concentrations, this being
11 somewhat more frequent at the higher end of
12 exposure but it is also present at the lower end of
13 exposure. It is between about 20 and 25 percent.

14 DR. WOOD: Regarding the visual
15 disturbances as well, most of the time they were
16 reversible within 14 days of discontinuation of
17 treatment. I am curious, the 38 patients whom you
18 have been able to monitor for over a year, whether
19 or not there were changes in their vision over
20 time, or if things remained stable or if they had
21 any chronic visual problems associated with chronic
22 administration.

23 DR. BAILDON: Let me just clarify that our
24 electrophysiology study addressed reversibility of
25 the underlying electroretinogram changes, the

1 underlying electrophysiological phenomena. What we
2 observe in patients, as I showed you, is that the
3 frequency of reports is highest in the first week.

4 DR. WOOD: Right.

5 DR. BAILDON: A number of patients
6 continue to report these events throughout
7 treatment but, actually, many patients do not
8 report them anymore after one, two, three weeks.
9 So, if I were to show you a curve showing time to
10 last treatment, that looks very similar to the one
11 of the first. So, it is somewhat difficult to say
12 what happens in these patients, the 38 patients
13 treated out for over a year. We have not received
14 any reports of significant alterations as adverse
15 event reports that we would pinpoint to the visual
16 disturbance as such.

17 DR. WOOD: A couple of other questions
18 regarding the cardiac deaths as well as the
19 anaphylactoid reactions. Were drug levels examined
20 at all in those patients, or were you able to
21 obtain drug levels? The reason I am curious is
22 because in the FDA handout, on page 27, one of the
23 things that I was quite impressed by is when you
24 look at the mean AUC for females compared to males,
25 whether it is with single dosing or with multiple

1 dosing, the AUCs for females are almost twice --
2 excuse me, much more than twice; seven times more
3 for young healthy males in terms of multiple
4 dosing, at least twice as much for single dosing,
5 and very similar -- five times as much for single
6 dosing in young health females and then nine times
7 as much almost in terms of chronic dosing. And,
8 the cardiac death and the anaphylactoid reactions
9 were in females.

10 DR. BAILDON: Can I address your
11 pharmacokinetic question first? If I could have PK
12 backup slide number 83?

13 [Slide]

14 This shows the data that you refer to
15 around the difference in exposure observed in Phase
16 I volunteers by sex and also by age where we see
17 what you highlighted, the higher exposure seen in
18 the female population. And, there was also among
19 males a shift in the Phase I population.

20 [Slide]

21 As I mentioned, we have collected over
22 3000 samples in over 1000 patients, and this
23 replicates that same analysis using our database
24 from the clinical trials. What you can see there
25 is that variability that we saw in the males, young

1 versus older patients, and versus the females we
2 don't observe that anymore. So, given all the
3 other factors influencing the variability on
4 exposure, we cannot decipher that same difference
5 in the patient population. That led us to the
6 conclusion we don't dose adjust.

7 Now I will turn to your question around
8 the anaphylactoid reactions. These were events
9 that occurred right at onset of infusion. So, we
10 checked blood levels and we could confirm that the
11 volunteers received what we thought they should
12 have had, which was the solubilizing agent in one
13 volunteer and voriconazole I.V. in the three
14 others. But the exposure was extremely minimal.
15 This was a very, very small amount. So, I don't
16 think it is related there.

17 In that one death I described in the
18 empirical therapy study, which was in a Canadian
19 patient, that was after the end of the first
20 infusion at a time when we would expect C-max but
21 we do not have plasma samples. We are fortunate to
22 have Dr. Jeremy Ruskin here and maybe we can raise
23 that later. It was a patient who had suffered
24 significant cardiac damage in the time prior to
25 infusion, probably related to idarubicin therapy.

1 So, it is somewhat difficult to assess but we
2 cannot exclude the relationship.

3 DR. WOOD: In the 26 deaths that were
4 associated with hepatic transamination elevation,
5 we went through four in detail. I found it very
6 interesting that one of the four deaths was
7 associated with an undiagnosed history of an
8 individual being at risk for cirrhosis. Did you go
9 back to the remaining 22 patients and see whether
10 or not any of those 22 patients had conditions such
11 as a history of alcohol abuse or chronic hepatitis
12 B or C that would predispose them for maybe having
13 undiagnosed cirrhosis?

14 DR. BAILDON: We did not find anything
15 that would contribute to an explanation beyond the
16 very brief data I have given you. The first
17 patient I highlighted stands out actually because
18 that patient had a higher exposure. It would be
19 only a very, very few percent of our patients who
20 have exposure beyond 10 mcg/mL. The exposure in
21 that patient was 13 mcg/mL and that is explained by
22 the hepatic impairment. The other patients, where
23 we have plasma samples, actually have exposure
24 around 6 mcg/mL which is well within the range we
25 would observe. So, I don't think that would add

1 anything. I do not have any more specific detail.
2 I think we could get the narrative if you want to
3 review the patient. We have a narrative
4 description of it, but there is nothing that stands
5 out.

6 DR. WOOD: All right. My last question
7 relates to the poor metabolizers and the alleles in
8 the CYP2C19. In your study you noted that it was
9 probably in approximately two percent of
10 Caucasians. I am curious whether or not anyone
11 from your pharmacology team can comment on what the
12 incidence of poor metabolizers may be in other
13 ethnic groups.

14 DR. BAILDON: If I could have PK backup
15 slide 81, I can actually show you the data that
16 have been published to date on this issue.

17 [Slide]

18 As you can see, what I talked about is the
19 Caucasian population, and that is the majority of
20 our patients. Two percent are poor metabolizers
21 and 73 percent extensive. This is about the same
22 distribution seen in black populations where there
23 is a difference, and Asian populations where 15-20
24 percent are poor metabolizers. We have not
25 analyzed that in our Phase III studies but what we

1 have done is analyzed again plasma samples, as I
2 showed you, in our Phase III population, subdivided
3 by race, as a surrogate for the genotype.

4 [Slide]

5 This shows you the results of that
6 analysis. I highlighted that the majority is
7 Caucasian, 861. This is the distribution observed
8 here. This is the 25th percentile and 75th
9 percentile, with the median as a line in the box,
10 here. If you look at the Asian population, it is
11 somewhat higher. The median is shifted somewhat
12 higher, which would reflect this up to 20 percent
13 incidence of poor metabolizers. However, it is
14 still contained within the range of exposures we
15 observed overall and that is why we concluded that
16 we don't need to dose adjust. Does that answer
17 you?

18 DR. GULICK: Dr. Hamilton and then Dr.
19 Morrison.

20 DR. HAMILTON: Given the recognized
21 difficulty of distinguishing the contribution of
22 one pathogen from another, your focus on invasive
23 Aspergillus and the common coo-existence of several
24 pathogens at the same time -- could you elaborate a
25 little bit on what efforts were made to distinguish

1 invasive aspergillosis as a sole pathogen from
2 others? What diagnostic techniques were employed
3 to make a definitive diagnosis, just in general; I
4 am not talking about in detail? And, this is not
5 to question the acumen of the expert clinical panel
6 but it would just be useful for me to know what
7 those elements were.

8 DR. BOUCHER: Certainly, I would be happy
9 to address that. In our major comparative studies,
10 the global comparative aspergillosis study and the
11 empirical study that we described, we used modified
12 MSG EORTC criteria which have been developed
13 specifically to aid in the diagnosis which, as Dr.
14 Patterson mentioned, is difficult in this setting.

15 For a definite diagnosis in both studies
16 and across our clinical program, including all the
17 patients that we shared, a definite diagnosis is
18 based on the recovery of the pathogen from a
19 normally sterile site or the recovery of the
20 pathogen by culture, say, from a bronchoalveolar
21 lavage in the lung with a concomitant
22 histopathologic confirmation. So, that would be
23 the criteria for a definite diagnosis.

24 Now, in terms of ruling out other
25 pathogens that might be mistaken for aspergillosis,

1 a particular concern might be Zygomycetes which are
2 not well covered with voriconazole. In that case,
3 culture diagnosis for confirmation was rigorously
4 applied and I can tell you that in the global
5 comparative aspergillosis study we had, among the
6 deaths not due to aspergillosis, one patient with
7 Zygomycetes in each treatment arm. So, those were
8 patients where a diagnosis was made of Zygomycetes.

9 In the empirical therapy study we shared
10 we had two breakthrough infections due to
11 Zygomycetes in the voriconazole arm. They were
12 diagnosed as the investigators were rigorously
13 pursuing confirmation.

14 In terms of the relevance of other
15 pathogens, say Candida when you are looking for
16 aspergillosis, our data review committee in the
17 global comparative aspergillosis study reviewed all
18 the available mycology, as well as the radiology
19 and the other evidence, and decided in their
20 decision of assessment of certainty of diagnosis
21 that this was definite or probable invasive
22 aspergillosis, and several of our patients had
23 isolates of Candida from bronchoalveolar lavages
24 and aspirates and sputum that were not considered
25 pathogenic.

1 DR. HAMILTON: How about viruses? I am
2 particularly interested in CMV, and seeing Bob
3 Rubin here, I suspect some serious consideration
4 has been given to the contribution that that might
5 have in these very seriously ill patients.

6 DR. BOUCHER: Certainly, and that was
7 again rigorously looked for. We had a few patients
8 with CMV pneumonitis, including transplant
9 patients, in our total population -- again,
10 pathologic and virologic diagnoses were sought.
11 Dr. Rubin, would you like to comment further? Dr.
12 Rubin was a member of the data review committee for
13 the global comparative aspergillosis study and has
14 been involved.

15 DR. RUBIN: Thank you. John, there was an
16 attempt. That is always the problem in these
17 complicated patients in terms of what else could be
18 going on. CMV was looked at seriously with both
19 viremia assessment and BAL assessment and
20 pathologically. It did not seem to be playing a
21 significant role, but if there were patients with
22 combined infections where there was definite or
23 probable evidence of Aspergillus they were carries
24 as Aspergillus and we were looking for an endpoint
25 on the Aspergillus.

1 In point of fact, that kind of prejudiced
2 -- and there were more of them in the voriconazole
3 as I remember -- that prejudiced because it meant
4 there had to be effective treatment not only of the
5 Aspergillus but of the other pathogens that were
6 there. And, we had an uncomfortable feeling that
7 there were deaths that were attributed to
8 Aspergillus that probably were another pathogen so
9 that the success may have been better but the
10 strength of the analysis was that we were all
11 blinded and had no idea which group we were
12 thinking about.

13 DR. GULICK: Dr. Morrison?

14 DR. MORRISON: I have two questions with
15 regard to the use of this agent in patients with
16 renal or hepatic impairment, and then also a brief
17 question with regard to aspergillosis.

18 First of all, in patients with hepatic
19 impairment you recommended that the maintenance
20 dose would be halved in these patients. How are
21 you planning on defining hepatic impairment? Are
22 you going to be using any specific LFT cut-off
23 numbers?

24 DR. BAILDON: No, this was, as in our
25 multiple dose study, defined as child pure B

1 cirrhosis so it would be the same recommendation.

2 We have not studied child pure C.

3 DR. MORRISON: Okay, because from a
4 clinical standpoint, when you are caring for these
5 patients sometimes it is helpful to have some more
6 discrete cut-off. So, you are not planning to do
7 that?

8 DR. BAILDON: No.

9 DR. MORRISON: My second question,
10 patients with renal impairment -- you would advise
11 that the oral formulation of the agent be used in
12 patients with creatinines greater than 2.5. In our
13 grey manual, on page 19, it said that in patients
14 who have creatinine clearances of less than or
15 equal to 50 only the oral formulation be used. My
16 question is I have concerns that we are going to
17 see not a small number of patients who will have
18 creatinine clearances less than 50, based either on
19 the fact that they are middle aged; they are
20 receiving concomitant nephrotoxic therapy. So, the
21 question I would have is that in patients with
22 febrile neutropenia you feel the oral formulation
23 would be effective for prophylaxis in this patient
24 population. Do we need to be checking blood levels
25 in these patients?

1 DR. BAILDON: That opens up a number of
2 interesting discussions actually. Let me first
3 come to the oral form. As you saw, we had over 90
4 patients in the empirical therapy study who were
5 able to switch to oral therapy. The cut-off of 2.5
6 mg/dL creatinine is one that was used throughout
7 the program and has not led to problems. We have a
8 few patients in whom, based on an individual
9 benefit/risk assessment, the investigators felt
10 that they needed the I.V. despite having at least
11 temporary higher creatinines. The recommendation
12 of 2.5 just comes out of the clinical program. We
13 did not determine creatinine clearance. We have
14 studied it relative to creatinine clearance and we
15 can say that there is no influence on the
16 voriconazole exposure across the spectrum of
17 creatinine clearance that we studied, but we
18 clearly see that relationship to the excretion of
19 the solubilizing agent. That is why we have that
20 limit.

21 Now, the other question around blood level
22 monitoring is a totally different question. I am
23 happy to address it but I think it takes a bit
24 longer to explain our approach to that.

25 DR. GULICK: Go ahead.

1 DR. BAILDON: Obviously, when you study
2 non-linear drug with that kind of variability and
3 with all the factors influencing this variability
4 and none of them actually being predominant, that
5 is a major issue.

6 [Slide]

7 I can highlight what we have done but I do
8 need a couple of slides to explain the story there
9 a little bit.

10 DR. GULICK: Sure.

11 DR. BAILDON: This is what we asked
12 physicians to do, investigators in our study -- to
13 collect random samples throughout the treatment
14 period. Actually, it is quite impressive. We have
15 samples from over 75 percent of our patients.

16 This is a patient from our empirical
17 therapy study who actually developed breakthrough
18 pulmonary aspergillosis and then was treated for a
19 total of 80 days -- successful outcome I am happy
20 to report. This investigator took the effort of
21 sampling quite seriously and continued to sample
22 throughout the 80-day period. For every dot I have
23 highlighted here, this is plotted as a result of
24 that plasma level concentration versus the time of
25 dosing throughout that 80-day period.

1 So, what you see is that they are all
2 normalized to the time of dosing, and it is
3 impressive and I talked about the low within
4 subject variability and it is examples like that
5 that confirm our modeling exercise and our complex
6 PK analyses. Actually, over the 80 days there is
7 quite low within subject variability.

8 Then to address the question around what
9 can I do for the benefit of monitoring these
10 patients, we have taken a mean concentrations --
11 not all patients had this many; it is 3.5 samples
12 per patient on average, but we have taken the mean
13 concentration as a point estimate for each patient.

14 [Slide]

15 We have related that point estimate of a
16 patient for exposure to the relevant outcomes, here
17 efficacy in our global comparative aspergillosis
18 study, and we have done that across the other
19 indications as well.

20 What you can see here is that each patient
21 is now placed in one of these pockets according to
22 the mean concentration observed, and then we looked
23 at the success rate in the global comparative
24 aspergillosis study across that. As you can see,
25 there is no obvious relationship here and that is

1 actually confirmed by the modeling exercises.

2 The only group that sticks out is these 14
3 patients who had actually higher exposure, more
4 than 6 mcg/mL, and when we reviewed these cases
5 this does not indicate a kind of inverted dose
6 response, these are 14 patients who were septic;
7 who were extremely ill, already close to
8 multi-organ failure and they actually fail early
9 on. They die or they fail within the first week or
10 10 days of therapy. So, we think that is more
11 related to impaired hepatic function already at
12 that state and some of these 14 patients received
13 early dose escalations, as I described, which was
14 allowed sometimes too to try to rescue the patient.
15 So, that is not indicative of dose response. We
16 don't see that across our exposures.

17 [Slide]

18 We have done the same relating ALT
19 abnormalities, and here we take weekly plasma level
20 with weekly occurrence of ALT abnormality, again
21 across the population. Here, this is our
22 therapeutic studies population. So, we received
23 samples from everybody. Again, each patient is
24 placed within one pocket but now that patient might
25 appear several times because that patient had

1 plasma concentration at week 1 and ALT at week 1
2 and then again at week four and that patient could
3 contribute two data points here.

4 Here you can see, and our modeling
5 confirms that, somewhat of a relationship there
6 which has a slight positive slope. So, that would
7 then be the starting point for saying would
8 therapeutic drug level monitoring add any benefit
9 to that?

10 [Slide]

11 I want to highlight the approach we used
12 for that. The methodology used is receiver
13 operating characteristics. I am sure some of you
14 are familiar with that. That is a graphical
15 depiction of the false-positive rate versus the
16 true-positive rate, and then you can use several
17 different thresholds to try to determine is my
18 threshold predictive of the outcome. This is an
19 example from a recent publication by Min et al.,
20 using that for predicting renal allograft rejection
21 with cyclosporine, and you can see a reasonably
22 good predictive value here of the sensitivity of
23 about 60 percent and a specificity that is
24 definitely beyond 80 percent. If a test is not
25 evaluable you will progress along the line of

1 identity as you take different cut-off levels.

2 [Slide]

3 This shows you the result for what I
4 showed you earlier, the determinations in
5 aspergillosis. So, we have taken the ROC approach
6 and taken very low cut-offs. Our detection limit
7 is 0.1 mcg/mL. As we move up in cut-offs we,
8 unfortunately do not see a certain line of
9 identity. So, the plasma level for efficacy
10 doesn't add any value, which is not surprising
11 given the correlation I showed you.

12 [Slide]

13 This also holds true actually for the ALT
14 prediction. We can identify in our database a
15 linear or some kind of correlation but the
16 predictive value for ALT abnormality again yields a
17 more appropriate starting at a higher exposure
18 level. Our conclusion, to answer your question
19 however, then to monitor for efficacy we recommend
20 clinical judgment which we expect to be up here.
21 To monitor for hepatic enzyme elevation, which we
22 consider dose limiting, we suggest to monitor the
23 hepatic enzyme elevation which is also more
24 predictive. Does that address that?

25 DR. GULICK: Thanks. I think that was

1 useful. Another question, Dr. Morrison?

2 DR. MORRISON: Just a very brief question.
3 With regard to your Aspergillus data, obviously for
4 the right reasons most of your cases are with
5 fumigatus. Do you want to make any comments with
6 regard to treating other non-fumigatus Aspergillus
7 infections with this agent?

8 DR. BOUCHER: I would be happy to.

9 [Slide]

10 As you said, Dr. Morrison, most of the
11 species identified were A. fumigatus. In this
12 slide we depict the success according to species
13 from patients with definite or probable invasive
14 aspergillosis according to the data review
15 committee. So, these are species obtained just
16 from those patients in the modified
17 intention-to-treat population.

18 At the top we see that, indeed, the
19 majority of patients had A. fumigatus. There was a
20 small number of patients with flavis, terreus,
21 niger and nidulans and we see some efficacy
22 although the numbers are extremely small, but those
23 are the data that we have in this study.

24 DR. GULICK: Dr. Wong?

25 DR. WONG: The principal question I want

1 to ask is about the assessment of efficacy in the
2 global aspergillosis treatment trial. The problem
3 I am having is that the patients who were assigned
4 to voriconazole received voriconazole for a median
5 of 70-some odd days, whereas those who were
6 assigned to receive amphotericin B received it for
7 a much shorter period of time. Can you break out
8 patients who were assigned to amphotericin B, for
9 example, who received amphotericin B initially and
10 then also received it for a significant period of
11 time after the 10-14 day range, or received
12 conventional amphotericin B and then liposomal
13 amphotericin B thereafter so we can compare those
14 results to those who received voriconazole? Or,
15 alternatively, can you show us some assessment of
16 clinical efficacy in the voriconazole group at a
17 time point comparable to the period of time that
18 patients received amphotericin B?

19 DR. BOUCHER: I think I can address your
20 first question most easily.

21 [Slide]

22 Here we can look at success in patients,
23 at the top, who just received their initial
24 randomized therapy and then in those who switched
25 to other licensed antifungal therapy. So, if we

1 look first in the voriconazole arm we can see that
2 5/13 voriconazole patients who received lipid
3 preparations, or 38.5 percent, had success compared
4 to 29.8 percent in the amphotericin B arm.

5 Looking at itraconazole, 64.7 percent of
6 voriconazole and 50 percent of amphotericin B
7 patients had success. So, that is looking at the
8 success according to other licensed antifungal
9 therapy used.

10 Returning to your question about a
11 different time period, to answer your question
12 about the time periods, we can't give you success
13 other than the two time points from the study, end
14 of randomized therapy or week 12, because you
15 couldn't be a success until you got there. So, we
16 know that the patients who were a success at the
17 end of randomized therapy is 70 percent. You know,
18 they were on their way to success at two weeks but
19 they did not have a formal assessment.

20 DR. WONG: I guess another way to look at
21 it is if we see a Kaplan-Meier curve for survival
22 over the course of 84 days, and it looks like maybe
23 there is a separation of those curves early on but
24 it is so small at that point that it is difficult
25 to see. Do you have a form of the Kaplan-Meier

1 curve that really highlights the early events, and
2 did you do a statistical analysis of survival at an
3 earlier point? What I am driving at is that at a
4 point where the patients were still receiving their
5 initial randomization treatments.

6 DR. BAILDON: If I can go back to my main
7 slides that highlight the survival --

8 [Slide]

9 We have not done the analysis you describe
10 at any interim time points. This is the safety
11 population so it is all patients receiving drug.
12 What you can see, if you look at day 14 here, is
13 that there is already somewhat of a difference here
14 which is maintained and progresses. We have never
15 cut this in another way. We could prepare a slide
16 for after lunch that blows up this part. But I
17 think one of the problems in treating fungal
18 disease is that it does take a while to actually
19 see some efficacy.

20 DR. GULICK: Dr. Rodvold and then Dr.
21 Stanley.

22 DR. RODVOLD: I would like to follow-up on
23 a couple of the questions that were previously
24 asked and ask you to extend maybe your comments.
25 In poor metabolizers where they do have higher

1 concentrations, did you further break that down by
2 taking a poor metabolizer and separate out gender
3 as well as separate out age, in other words,
4 looking for the worst scenario -- an older female
5 that is a poor metabolizer? Are they even further
6 at risk for higher exposure than, say, a male that
7 is a young poor metabolizer?

8 DR. BAILDON: We have not broken it out
9 that way. We only have relatively few poor
10 metabolizers --

11 DR. RODVOLD: Yes, I know.

12 DR. BAILDON: With two percent of the
13 population it is actually difficult to capture
14 that.

15 DR. RODVOLD: I would think that that
16 might be worthwhile to either explore or put in
17 further studies to look at just because of the
18 potential of specific Asian populations in certain
19 areas that may get drug in the future. So, that
20 might be something you want to come back to.

21 The second issue to tag onto that, is that
22 a population that may need therapeutic drug
23 monitoring? In other words, not the whole
24 population but a real specific population? And, I
25 am not saying therapeutic drug monitoring is the

1 ultimate here but is there a real small population,
2 like poor metabolizers, that need it?

3 DR. BAILDON: Yes, as I showed you in our
4 surrogate race parameters looking at the exposure
5 we actually observed in patients is overlapping
6 exposure and I think one of our interpretations
7 around that is that the genotype status is very
8 important in a Phase I population that receives
9 only voriconazole. Once you go into a patient
10 population with all the other factors influencing
11 exposure, it becomes somewhat less important.

12 DR. GULICK: Dr. Stanley and then Dr.
13 Schapiro.

14 DR. STANLEY: Thank you. I am just trying
15 to still get a handle on the abnormal visual
16 toxicities. You say that the vast majority of them
17 occur within the first week and that then they
18 either resolve or the patients stop complaining
19 about it, one or the other. The only hard data you
20 have shown us this morning is on your challenge
21 trial with 28 days of treatment and then showing
22 documented resolution of the changes. When I try
23 to go back into the data that we had ahead of time,
24 I see charts that show me, like in the global
25 trial, 33 percent of patients complained of visual

1 abnormalities; only 1 percent discontinued drug
2 because of visual abnormalities. But I don't see
3 any documentation of any actual testing being done
4 of visual acuity or impairment. There is referral
5 in both the empiric trial and in the esophageal
6 candidiasis trial that they had similar low rates
7 of discontinuation and that visual function testing
8 showed no difference. But your longest drug
9 exposures in your global trial was 77 median days
10 of exposure. Is there any actual testing of visual
11 acuity or retinal changes that you did in patients
12 that have seen drug for that long?

13 DR. BAILDON: Yes.

14 [Slide]

15 This shows you the acuity results I showed
16 you for the esophageal candidiasis study where we
17 observed no change over usually the 14 days of
18 therapy. This is the same presentation for the
19 empirical therapy study, again testing acuity at
20 baseline and at follow-up. One of the problems we
21 have in that patient population is, because they
22 are more severely ill, we have a large number of
23 patients who don't have a baseline value. But if
24 you look at those where we have baseline values,
25 you see there is a very similar percentage of

1 improvement or no change, deterioration of one line
2 or two lines.

3 [Slide]

4 We have the same presentation for our
5 global comparative aspergillosis study. Again, it
6 is the same presentation. Again, we have an issue
7 that not all patients are able to either do it at
8 baseline or follow-up but we have tested for acuity
9 and you can again see -- well, here is actually
10 more improvement or no change but it does not
11 differentiate between the comparator agent. It
12 reflects more the underlying disease of the
13 patient. Does that address your question?

14 DR. GULICK: Dr. Schapiro and then Dr.
15 Englund.

16 DR. SCHAPIRO: Dr. Boucher, you mentioned
17 the success anecdotally with non-albicans Candida.
18 Do you have a summary of the clinical experience
19 with those?

20 DR. BOUCHER: I do.

21 [Slide]

22 It is in the esophageal candidiasis trial
23 as well as from our series of patients collected
24 across the program to date. Dr. Baildon showed the
25 organisms in the esophageal candidiasis trial.

1 Just to refresh your memory, most of the isolates
2 here were albicans; 56 were glabrata but there are
3 very small numbers of other non-albicans species.

4 The other thing to note is that these were
5 isolated, virtually all except for two, in the
6 presence of C. albicans and we saw the same
7 efficacy overall in this study, whether you had
8 pure albicans or you had a mix.

9 [Slide]

10 Turning then to our series of patients, we
11 can first look at our series of Candida krusei
12 patients. This shows a series of 12 patients with
13 Candida krusei from across the program, six of whom
14 were non-neutropenic and 6 of whom were neutropenic
15 at baseline. Most of these patients were severely
16 immunosuppressed with hematologic malignancy and
17 transplantation and in either case the total of
18 eight of ten patients had success. The numbers are
19 small.

20 DR. SCHAPIRO: Thank you. Can you also
21 show the data on the interaction study with
22 Coumadin?

23 DR. BAILDON: The warfarin interaction
24 study? Do we have that? I have to ask my PK
25 colleagues which slide number that one is. Maybe I

1 will take another question first?

2 DR. SCHAPIRO: My last question would be
3 on your summary slide you mention I think that it
4 is better tolerated than the ampho formulations.
5 Was that specifically relating also to the lipid
6 ampho, that it was better tolerated? I don't
7 remember actually seeing data that there was
8 superior toleration.

9 DR. BAILDON: Dr. Boucher highlighted that
10 in the infusion-related reactions in that study,
11 which we monitored prospectively, there was an
12 imbalance with more infusion-related reactions on
13 the amphotericin B and the liposomal amphotericin B
14 arm, except for the visual disturbances which were
15 more frequent on the voriconazole arm.

16 DR. SCHAPIRO: So, it is not a global
17 statement that relates to the infusion --

18 DR. BAILDON: If we would go to renal
19 function we would see some imbalance as well
20 because liposomal amphotericin B also has an effect
21 on the renal function. Do we have the warfarin
22 study?

23 DR. GULICK: We can have it after the
24 break. We can come back to that. Oh, there you
25 go.

1 [Slide]

2 We recommend monitoring the biologic
3 effect and dose adjusting as appropriate. This is
4 for voriconazole exposure 300 mg twice a day. That
5 is our high dose plus warfarin. This is only
6 warfarin so the prothrombin time is higher. That
7 is right. So you would need to dose adjust and
8 monitor biologic effect as I highlighted in one of
9 my interaction slides.

10 DR. GULICK: Dr. Englund and then Dr.
11 Mathews.

12 DR. ENGLUND: Yes, I am interested in the
13 Candida susceptibilities to your drug, particularly
14 in your empiric therapy trial and your esophageal
15 candidiasis trial. You have data nicely presented
16 from pre-therapy but do you have data during and
17 even post-therapy, and if you treated them for 14
18 days, many of them were HIV patients and I am sure
19 it comes back. Do you have longer-term follow-up?

20 DR. BOUCHER: We do in the esophageal
21 trial. I can come back after the break with a
22 slide -- very few patients with isolates, but I can
23 show you a slide on that. In the empirical therapy
24 study we don't. We have very few patients who had
25 subsequent isolates in that study.

1 DR. ENGLUND: You had two failures I
2 believe with Candida.

3 DR. BOUCHER: I will present details of
4 those two when we come back from the break.

5 DR. GULICK: Dr. Mathews?

6 DR. MATHEWS: Can you show us some of the
7 outcomes on the 25-28 percent of patients that were
8 excluded from the modified intention-to-treat
9 analysis in the global comparative study?

10 DR. BOUCHER: Certainly. Just to confirm,
11 the modified intention-to-treat included those
12 patients who met the data review committee's
13 criteria for definite or probable aspergillosis.
14 So, we can look at the intention-to-treat
15 population in the global comparative aspergillosis.

16 DR. MATHEWS: Well, my question is not
17 about that inclusive group but to break out
18 separately the 102 patients.

19 DR. BOUCHER: Okay, that is the non-MITT
20 population and we do have those data, if you will
21 bear with me one moment.

22 [Slide]

23 These are the 50 and 52 patients excluded
24 because we were unable to confirm the presence of
25 invasive aspergillosis. Again, this is 12-week

1 response assessed by the data review committee.
2 Here, again, we see 44 percent success in the
3 voriconazole arm, 23 in the amphotericin B arm, and
4 a difference of approximately 21 percent.

5 DR. MATHEWS: And mortality? Do you have
6 that?

7 DR. BOUCHER: It is similar.

8 DR. BAILDON: That was included in the
9 safety population. As you can see, the
10 Kaplan-Meiers for the MITT in the safety population
11 look actually very similar. So, the Kaplan-Meier
12 for the non-MITT would be identical to those. The
13 hazard ratio is the same across all three, 0.6.

14 DR. MATHEWS: A different question, you
15 stated that the drug interaction studies that you
16 had done would provide guidance to the practicing
17 physician, but there occurred to me a number of
18 other interactions of potential importance. For
19 example, I was curious why you picked indinavir to
20 do the protease inhibitor interaction when I would
21 have thought that ritonavir would have been the
22 most obvious one to look at because of its more
23 potent effect on cytochrome P450 system.

24 DR. BAILDON: That is correct, and we are
25 actually planning a ritonavir study. The point of

1 that was that our early in vitro work indicated
2 that indinavir would not have an interaction and we
3 wanted to confirm that in Phase I so we could offer
4 a treatment choice to physicians treating HIV
5 patients.

6 DR. MATHEWS: I wonder also about, you
7 know, you looked at two-way interactions but
8 obviously these patients are on multiple drugs that
9 may have more than one inducer or more than one
10 inhibitor, for example, somebody on phenytoin and
11 rifabutin. I would have no way of knowing what
12 would happen with the levels of voriconazole.

13 DR. BAILDON: Well, I highlighted that the
14 number of concurrent medications, for example in
15 the global comparative aspergillosis study, was 26
16 in the populations, and I am sure many of these
17 concurrent medications contribute to the
18 variability of exposure I showed you in my plasma
19 concentration slides. The statement about general
20 manageability is more that this is a patient
21 population of close to 200 patients who were able
22 to be maintained on voriconazole for a median of 77
23 days despite receiving a median of 26 concurrent
24 medications. We have not studied multiple
25 interactions specifically but this indicates to me

1 that in that population at least it was manageable,
2 otherwise these patients would not have been
3 maintained for 77 days on voriconazole. But these
4 interactions would certainly contribute to the
5 variability we observed.

6 DR. GULICK: Dr. Yogev?

7 DR. YOGEV: You mentioned that you picked
8 out the maximum tolerated dose, 4 mg/kg, because
9 6/21 had hepatic function problems, and we were
10 looking today basically at only one who got 5
11 mg/kg, the rest were 4 mg/kg. So, I was just
12 wondering, taking into account that you didn't show
13 any difference in hepatic toxicity between the
14 amphotericin group and the voriconazole, basically
15 showing that the 5 mg/kg did not increase it, do
16 you have any correlation between the peak level or
17 area under the curve and liver toxicity? Because
18 that would be, to me, much more meaningful if the
19 drug really has any effect on the liver.

20 DR. BAILDON: Let me just clarify a point.
21 There was one patient in the dose group that we
22 currently recommend as the highest dose group who
23 experienced an ALT abnormality.

24 [Slide]

25 That was this patient, in green, who had 4

1 mg and 300 mg orally. That is our current highest
2 dose recommendation. The other subjects on this
3 slide actually received the one that was the
4 highest in the study, which was 5 mg followed by
5 400, and we considered that exceeded actually the
6 maximum tolerated dose.

7 DR. YOGEV: What happened to the other 15
8 out of the 21? Because this is only 6/21. Were
9 the other 15 on 5 mg or higher?

10 [Slide]

11 DR. BAILDON: They did not show ALT
12 elevations. I only picked out those five that I
13 showed you over the time course who had an ALT
14 elevation. The other nine here did not show an ALT
15 elevation.

16 DR. YOGEV: No, my basic 101
17 pharmacokinetics is that the MTD is defined as 50
18 percent of the population are getting that
19 toxicity, or something like that, and I wonder if
20 this is not an accidental finding because of the
21 small number. Do you have any levels in the blood
22 or area under the curve that correlate toxicity or
23 liver elevation?

24 DR. BAILDON: Well, let me state that for
25 us this was close enough to 50 percent in healthy

1 volunteers.

2 DR. YOGEV: The reason why I am asking
3 that is because I am confused from your pediatric
4 data that --

5 DR. BAILDON: Can I just answer your C-max
6 question? I showed you our modelling approach to
7 the PK/PD relationship using the mean
8 concentrations. We used the mean because that gave
9 us use of the full information in the data. We
10 have also repeated that both for efficacy and
11 safety using either the maximum concentration per
12 patient or using the minimum concentration per
13 patient. As far as ALTs, for example, are
14 concerned, it doesn't show any more. There is a
15 relationship in our database but it does not
16 provide us with more predictive value than
17 otherwise.

18 DR. YOGEV: Because in the pediatric --
19 correct me if I am wrong, because it is non-linear
20 and everything else, your recommendation is going
21 to be 4 mg/kg as a maintenance dose, and I presume
22 that means you are going to give 8 mg/kg as a
23 loading dose?

24 DR. BAILDON: No, we use the same loading
25 dose.

1 DR. YOGEV: So, you will go with six, six
2 and then you will go to four?

3 DR. BAILDON: Correct.

4 DR. YOGEV: Yet, you are suggesting that
5 in the adult to go from 3 mg/kg to 4 mg/kg for the
6 Aspergillus --

7 DR. BAILDON: Yes.

8 DR. YOGEV: Would one make an assumption
9 then that in pediatrics you would go to 5 mg/kg?

10 DR. BAILDON: That would certainly be one
11 consideration there. We have not studied that.
12 What we have studied is 3 mg and 4 mg in children
13 and in adults, and what we have seen is that the 3
14 mg/kg in adults and the 4 mg/kg in children results
15 in very similar exposures. I can show you a slide
16 on that actually.

17 DR. YOGEV: You showed it. Don't waste
18 your time. My problem is the five on one side you
19 say is toxic, on the other side it seems like a
20 dose for pediatrics -- add to that that you are
21 going to recommend that for less than 40 kg to
22 halve the dose. We have lots of pediatric patients
23 less than 12 years of age or less than 40 kg.
24 Should they get 4 mg/kg or should they get half of
25 the dose of the adult?

1 DR. BAILDON: There are two questions in
2 there. One is about dose and one is the
3 formulation I use in children. Currently, we are
4 recommending I.V. for very young children because
5 our tablets actually -- currently 50 mg is the
6 smallest tablet size we have. We have actually put
7 a fair amount of effort into developing an oral
8 suspension and we hope that we will be able to use
9 that oral suspension in clinical trials from next
10 year on. And, one of the studies we intend to do
11 then is actually an I.V. to oral switch in
12 children, which would allow us to explore the dose
13 range further. Right now our recommendation is in
14 children under 12 years of age -- we have studied 4
15 mg/kg and we know that that results in similar
16 exposure as 3 mg/kg in adults. We have treated I
17 think 60-some children compassionately and we have
18 seen efficacy in that population with that
19 recommendation. I have no data going beyond that.

20 DR. YOGEV: The last question is just that
21 I was impressed by your esophageal candidiasis
22 study that you chose the fluconazole as the
23 comparative drug when it is almost 100 times less
24 potent in vitro than your drug. What was the
25 reason not to choose itraconazole which has the

1 same efficacy? I didn't see any data comparing to
2 itraconazole which, in the in vitro data, seems to
3 be comparable.

4 DR. BAILDON: We have no clinical
5 comparisons to itraconazole. We chose fluconazole
6 because it is the accepted standard of care in
7 esophageal candidiasis, and you have seen the
8 results of our study looking at efficacy and
9 safety. We would not expect that to change.

10 DR. GULICK: Are there other committee
11 members who haven't yet had an opportunity to ask
12 questions who would like to ask a question? I have
13 two myself.

14 In talking about the proposed doses for
15 candidal infections for intravenous you are
16 suggesting 3 mg/kg q 12. Then an increased dose
17 for Aspergillus and other fungal infections. Yet,
18 the oral dose remains the same for the two. Could
19 you comment on that?

20 DR. BAILDON: Yes, and actually what we
21 see in our database is a decrease of exposure in
22 the global comparative aspergillosis study when we
23 switch from I.V. after about 10 days usually, 10,
24 14 days. As you switch to oral you see a decrease
25 in exposure. That is intentional. As I

1 highlighted, we wanted to be at the very upper end
2 of the dose-response curve for acute invasive
3 aspergillosis which is acutely life-threatening. I
4 think the experience from the previous versions of
5 amphotericin B dose regimen escalations used show
6 that it is not a good idea in that disease to spend
7 time waiting for the dose to come up. However, as
8 we are at the very upper end of the dose-response
9 curve we felt that it is justifiable then after the
10 two weeks when patients are stabilized to go back
11 down in the oral dose. It is a dose reduction in
12 that sense, and we see that actually in our
13 exposure. But the efficacy results are as you have
14 seen using that regimen. We have about 10, 15
15 percent of our patients who undergo dose escalation
16 from 200 mg to 300 mg. The efficacy results are
17 similar but it is not a comparative trial of the
18 two dosages.

19 DR. GULICK: My other question is
20 concerning the trial in empiric treatment of
21 febrile neutropenia, a non-inferiority based trial.
22 I was wondering if you could give us some insight
23 as to why minus 10 percent was chosen as the lower
24 bound for the 95 percent confidence interval,
25 particularly because in the background material we

1 noted that the itraconazole trial in a similar
2 setting chose minus 15 percent.

3 DR. BAILDON: Yes, our study was modeled
4 on the published MSG study led by Dr. Tom Walsh
5 before, with liposomal amphotericin B versus
6 amphotericin B, and they used the same criterion
7 and we found that appropriate as well in that
8 population.

9 DR. GULICK: Dr. Wood had some follow-up
10 questions.

11 DR. WOOD: I have a note here that there
12 was just an increased discontinuation of
13 voriconazole secondary to transaminitis and
14 treatment for esophageal candidiasis. Again, given
15 that many patients who need voriconazole for EC
16 would be individuals with HIV infection, I am aware
17 that data regarding hepatitis B and C status is not
18 available for all patients but I am curious as to
19 whether or not there has been any substudy analysis
20 for those patients in whom you do have a diagnosis
21 of hepatitis B or C, and whether or not there has
22 been an increased incidence of a need to
23 discontinue drugs specifically.

24 DR. BAILDON: We do actually.

25 [Slide]

1 This should show us the maximum total
2 bilirubin observed in our total therapeutic trial
3 population for any patient who had some indication
4 in the case record form of hepatic viral infection.
5 I think that is the subgroup you are talking about.
6 I haven't split it out further than that because it
7 gets to very small numbers then.

8 What that shows you is the distribution
9 here, baseline bilirubin either as normal or close
10 to normal in this population, or somewhat abnormal
11 or highly abnormal, and then the maximum bilirubin
12 observed during treatment of those that stay in the
13 group, and that is for the vast majority of
14 patients, and that reflects very similarly data we
15 see in the overall population or it shifts out.
16 This is all amphotericin B formulations; it is not
17 separating out the two studies. But it shows you
18 that that looks, if anything, better which again
19 confirms what we have seen in each of the
20 individual studies when we look at bilirubin. If
21 anything, we see less abnormality on voriconazole
22 than we observe on amphotericin B-treated patients.
23 Does that address your question?

24 DR. WOOD: It does. Would you
25 specifically recommend any alteration in doses if

1 you had an individual who you knew had cirrhosis
2 due to whatever cause?

3 DR. BAILDON: Yes, we would recommend a
4 halving of the maintenance dose; same loading dose
5 because that is a tissue distribution issue;
6 halving of the maintenance dose. DR. GULICK: Dr.
7 Wong?

8 DR. WONG: I just have one more question
9 about the empiric antifungal therapy trial. In
10 your table 7-43 in the yellow book you make a
11 distinction between a raw success rate and a
12 stratified success rate, and you give a little bit
13 of information about how that was done but I wonder
14 if you could elaborate a bit. And, was this
15 differentiation between the two success rates
16 specified in the protocol in advance?

17 DR. BAILDON: Maybe I could ask our senior
18 statistical consultant from Pfizer, Prof. Andy
19 Grieve, to come to the microphone and address that.

20 DR. GRIEVE: Thank you. Throughout the
21 program a stratified analysis, where appropriate,
22 was the primary efficacy analysis. So, in study
23 603 the primary efficacy analysis was stratified
24 for the variables in which stratification was
25 based, as well as one prognostic variable as well.

1 DR. GULICK: Dr. DeGruttola?

2 DR. DEGRUTTOLA: I have one question about
3 the empirical therapy study as well. For the
4 analyses that breakdown the response by high risk
5 and moderate risk, was that protocol specified, and
6 are the confidence intervals adjusted for the
7 multiple comparisons?

8 DR. BAILDON: I can answer that, that is a
9 simple one. The population was prespecified at
10 randomization. The subgroup analysis was not.
11 And, the confidence intervals Dr. Boucher showed
12 were not adjusted for multiple comparisons.

13 DR. DEGRUTTOLA: Thank you.

14 DR. GULICK: Would any other committee
15 members like to ask questions of the sponsor? Dr.
16 Yogev?

17 DR. YOGEV: Very quick, you, for some
18 reason, said that you are going to recommend to do
19 creatinine while in the 2000 patients you didn't
20 see any toxicity. What is the logic to do
21 creatinine?

22 DR. BAILDON: There are two points. For
23 one, that is what we recommended in the clinical
24 program, but the more important one is if
25 creatinine goes beyond 2.5 mg/dL we recommend oral

1 dosing because our solubilizing agent would
2 accumulate in those patients.

3 DR. YOGEV: I have no problem with the
4 beginning but you don't accept that your drug will
5 cause kidney toxicity. From what you suggested, it
6 sounds like that during giving it you should do
7 creatinine.

8 DR. BAILDON: We have not seen anything.

9 DR. GULICK: Let's thank the sponsor for
10 answering questions and the presentations. At this
11 point, let's take a ten-minute break. We will
12 reconvene at 11:35 for the FDA presentation.

13 [Brief recess]

14 DR. GULICK: There was a question the
15 sponsor would like to respond to before we go to
16 the agency for their presentation.

17 DR. BAILDON: Right. There was a question
18 around the 38 patients who had continued therapy
19 for more than one year. In those 38 patients, five
20 subjects experienced a visual adverse event. So,
21 it is actually somewhat lower than we experienced
22 in the general population, but that is likely
23 related, as I said to the fact that they just don't
24 report it anymore. So, 5/38.

25 DR. BOUCHER: I have the answer for the

1 Candida empirical therapy study question. The
2 question was regarding high MICs in isolates
3 obtained during that study. And, we had two
4 Candida infections.

5 [Slide]

6 For one we had no isolate. For the
7 second, this is a 68-year old man with leukemia who
8 was in the empirical therapy study for 34 days and
9 developed grade 2 C. albicans with an MIC to
10 voriconazole of 0.01, and another isolate of less
11 than 0.007. He was dose escalated and had
12 mycological eradication and success at the end of
13 therapy.

14 [Slide]

15 We had one other patient. This was the
16 one patient from the study who had isolates and
17 high MIC. This patient had a baseline Candida
18 infection. This was a 36-year old lady with
19 leukemia who had prior allogeneic transplantation
20 and she had received prophylaxis for 20 days prior
21 to the study. She developed a baseline fungemia
22 with an MIC of 4. She was discontinued due to
23 persistent fever and fungemia and was switched to
24 amphotericin B later.

25 DR. GULICK: Thank you. I would like to

1 now call on Drs. Tiernan and Powers to present on
2 behalf of the agency.

3 **FDA Presentation**

4 DR. TIERNAN: Good morning.

5 [Slide]

6 My name is Rosemary Tiernan and I work in
7 the Division of Special Pathogen and Immunologic
8 Drug Products, and today I would like to begin the
9 FDA presentation of our review of NDA 21-266 and
10 21-267 for voriconazole tablets and voriconazole
11 for injection.

12 [Slide]

13 Before we begin the presentation, I would
14 just like to acknowledge the efforts of all of the
15 members of the voriconazole review team who are
16 listed on this slide, and I would like to
17 especially thank Dr. Regina Alivisatos, Dr.
18 Rosemary Johann-Liang and Dr. Edward Cox for their
19 help in this review.

20 [Slide]

21 The purpose of this advisory committee is
22 to specifically discuss the indications of
23 treatment of invasive aspergillosis and the empiric
24 antifungal therapy of febrile neutropenic patients.
25 However, it is important to note the other

1 indications submitted in this voriconazole NDA and
2 listed on this slide. We are in general agreement
3 with Pfizer that voriconazole is efficacious in the
4 treatment of Candida albicans esophagitis and in
5 the treatment of serious fungal infections due to
6 Fusarium and Scedosporium spp. Efficacy in these
7 areas should be taken into account when considering
8 the indication of empiric antifungal therapy of
9 febrile neutropenic patients.

10 [Slide]

11 Our presentation will cover the following
12 areas, I will summarize our review with study
13 307/602 and study 304 with the historical control
14 which was submitted to support the indication of
15 treatment of invasive aspergillosis. Dr. John
16 Powers will then discuss study 603 which was
17 submitted for the indication of empiric antifungal
18 therapy of febrile neutropenic patients. Then I
19 will return to summarize specific areas of clinical
20 safety. Finally, Dr. Goldberger will present the
21 questions to the advisory committee.

22 [Slide]

23 The basis of evidence to support the
24 treatment of invasive aspergillosis was supported
25 by two trials, study 307/602 and study 304. Study

1 307/602 was a randomized, controlled, open-label
2 initial therapy study of voriconazole versus
3 amphotericin B, both of which could be followed by
4 other licensed antifungal therapy. Because of the
5 open label nature of the trial, a blinded data
6 review committee was utilized to assess certainty
7 of diagnosis, global response to treatment and
8 cause of death, among other factors.

9 Study 304 was an uncontrolled study of
10 voriconazole use in primary and salvage patients,
11 conducted in Europe. A retrospectively designed
12 historical control study, study 1003, was used as
13 the comparator for study 304. Cases were obtained
14 both from the United States and Europe. The
15 Division is in general agreement with the
16 applicant's presentation of the aspergillosis data.
17 The goal of this presentation is to highlight the
18 main aspects of the aspergillosis trials.

19 [Slide]

20 The modified intent-to-treat, or MITT,
21 population, the primary analysis population,
22 consisted of 144 voriconazole subjects and 133
23 amphotericin B subjects. These subjects were
24 primarily white males with hematologic malignancies
25 as their underlying disease and pulmonary sites for

1 their Aspergillus infection.

2 The studies were designed to allow a
3 switch from randomized therapy to OLAT. More
4 amphotericin B patients switched to OLAT when
5 compared to patients randomized to voriconazole.
6 Details of the OLAT regimen for the amphotericin B
7 arm were reviewed and felt to represent adequate
8 antifungal therapy.

9 [Slide]

10 Recall that the primary efficacy endpoint
11 was outcome at week 12 as assessed by the DRC, and
12 satisfactory response rates of 52.8 percent for
13 voriconazole and 31.6 percent for the amphotericin
14 B regimen were seen. The 95 percent confidence
15 interval for the difference in satisfactory
16 response rates, stratified by protocol, was 9.6 to
17 33.6. Since the lower limit of the confidence
18 interval was greater than minus 20 percent,
19 voriconazole is considered to be non-inferior to
20 the amphotericin B regimen, and in this case the 95
21 percent confidence interval does not include zero
22 and, thus, voriconazole is statistically superior.

23 [Slide]

24 The Division performed three additional
25 analyses to assess the robustness of the previous

1 results. In the process plan and operating
2 procedures for the data review committee it was
3 possible to upgrade investigator assessment of
4 response. Consequently, the Division performed a
5 conservative analysis which did not allow the DRC
6 to upgrade the investigator assessment. In the
7 second analysis, modified week 12, the Division
8 treated voriconazole patients who switched to OLAT
9 as failures, with the exception of a few patients.
10 These few patients had completed at least 84 days
11 of voriconazole treatment with a satisfactory
12 response and then were placed on prophylaxis. In
13 addition, response at week 16 was assessed. All of
14 these analyses demonstrate that the response of
15 voriconazole was consistently greater than the
16 response of the amphotericin B regimen.

17 [Slide]

18 Survival through day 84 was a secondary
19 endpoint and voriconazole was shown to have a
20 survival advantage compared to the amphotericin B
21 regimen.

22 [Slide]

23 In study 304 the expert evaluable
24 population, the primary analysis population,
25 consisted of 112 voriconazole subjects. The

1 experts classified 58 patients into the primary
2 therapy group and 54 patients as salvage therapy.
3 As assessed by the experts, a patient was
4 considered to be on primary voriconazole therapy if
5 they received less than 10 days of adequate
6 antifungal treatment. All other patients were
7 considered to be on salvage therapy.

8 As seen in study 307/602, these subjects
9 were primarily white males with hematologic
10 malignancies as their underlying disease, and
11 pulmonary sites for their Aspergillus infection.
12 This study, 304, was conducted solely in Europe.

13 [Slide]

14 The primary endpoint was the expert's
15 global response at the end of treatment, and the
16 overall satisfactory response rate was 49.1
17 percent. A satisfactory response of 60.3 percent
18 was seen in the primary patients, and a
19 satisfactory response of 37 percent was seen in the
20 salvage patients.

21 [Slide]

22 Since study 304 was a non-comparative
23 study, the Division requested that a retrospective
24 historical control study be performed to act as the
25 comparison group to the primary treated patients in

1 study 304. It should be noted that for this
2 comparison the definition of primary therapy was
3 less than five days of prior antifungal therapy.
4 In order to provide the most comparable population,
5 patients were matched on a 2:1 basis by the
6 prognostic factors of certainty of diagnosis,
7 underlying disease and site of infection.

8 [Slide]

9 The best matched, less than five-day prior
10 therapy population consisted of 50 study 304
11 voriconazole subjects and 92 historical control
12 patients. Satisfactory global response rates were
13 52 percent for study 304 voriconazole patients and
14 25 percent for the historical control patients.
15 The probability of survival was 0.554 for
16 voriconazole and 0.417 for the historical control.

17 [Slide]

18 Even though the applicant took substantial
19 efforts in the design of the historical control,
20 all of the inherent potential biases were not
21 adequately controlled. Differences in patient
22 populations can impact the success rate of
23 treatment if patient care and support differ across
24 countries. Study 304 was conducted exclusively in
25 Europe, whereas the historical control included

1 both European and U.S. patients. Satisfactory
2 global response and probability of survival were
3 lower in the U.S. historical control population.
4 This may be due to the fact that the majority of
5 the U.S. historical control patients had bone
6 marrow transplants or other underlying diseases
7 whereas the majority of the European historical
8 control patients and the study 304 voriconazole
9 patients had hematologic malignancies as their
10 underlying disease. When these U.S. historical
11 control patients are removed, the difference in
12 global response remains but the difference in
13 survival between the European and historical
14 controls and the study 304 voriconazole group
15 become smaller.

16 [Slide]

17 Additional issues regarding the historical
18 control included differences in the total days of
19 treatment, with the voriconazole-treated group
20 having a longer duration of therapy and differences
21 in the inclusion and exclusion criteria which could
22 possibly allow for sicker patients to be included
23 in the historical control. All in all, these
24 differences in study populations could predispose
25 the historical control to lower success rates and

1 the voriconazole-treated group to have higher
2 success rates independent of treatment with
3 voriconazole.

4 [Slide]

5 In summary, the historical control trial,
6 study 1003, was a good effort but concerns still
7 persist regarding the comparability of study
8 populations. Study 304 results are being used to
9 support the randomized controlled study 307/602.
10 Study 307/602 demonstrated a non-inferior global
11 response and actually met the definition of
12 statistical superiority as well. In addition,
13 voriconazole demonstrated a survival benefit.

14 We applaud Pfizer's efforts and success at
15 being able to complete the randomized, controlled
16 aspergillosis trial.

17 Now Dr. John Powers will discuss empiric
18 therapy of febrile neutropenia.

19 DR. POWERS: Thank you, Dr. Tiernan.

20 [Slide]

21 I would like to discuss with you today the
22 FDA perspectives on study 603, which is the study
23 in empiric antifungal therapy in febrile
24 neutropenic patients that compares voriconazole to
25 liposomal amphotericin B.

1 [Slide]

2 I would like to start out first by
3 discussing some scientific and regulatory
4 background in this indication of empiric antifungal
5 therapy in febrile neutropenic patients. Then we
6 will go on and discuss some of the issues around
7 the primary composite endpoint and the statistical
8 definition of non-inferiority used in this trial.
9 Then we will go on to discuss some of the selected
10 issues with the secondary endpoints and the
11 analyses of these that are used in the trial.

12 As Dr. Boucher presented this morning, the
13 five secondary endpoints here are breakthrough
14 infections within seven days of end of therapy;
15 survival at seven days after end of therapy;
16 discontinuations due to lack of efficacy or
17 toxicity; defervescence prior to recovery from
18 neutropenia; and global response in baseline fungal
19 infections. Then we will make a quick summary of
20 these points.

21 [Slide]

22 Neutropenia is one of the major risk
23 factors for development of invasive fungal
24 infections, and the risk of such infections varies
25 with the depth and the duration of neutropenia.

1 The most common infecting organisms in neutropenic
2 patients are Candida species and Aspergillus
3 species.

4 Autopsy studies show an incidence of
5 somewhere between 12 and 43 percent incidence of
6 invasive fungal infections in neutropenic cancer
7 patients. The actual incidence in patients that do
8 not come to autopsy really remains unknown, and
9 part of the reason for that is the difficulty in
10 premortem diagnosis. It is felt that up to 50
11 percent of neutropenic cancer patients may have
12 occult fungal infections that are not able to be
13 diagnosed by our current culture methods or antigen
14 or antibody detection methods. Once a neutropenic
15 cancer patient develops a fungal infection, they
16 tend to have quite a high mortality, ranging
17 between 48-80 percent depending upon which study
18 you look at.

19 [Slide]

20 Therefore, the idea of empiric therapy was
21 introduced for two reasons. One was to treat these
22 occult fungal infections which would not be
23 diagnosed by conventional means, and also to
24 prevent infections in patients who then remain at
25 high risk during their period of neutropenia.

1 There are two randomized trials which
2 address this question of empiric antifungal
3 treatment in neutropenic patients. The first was
4 performed by Pizzo and colleagues, at the National
5 Institutes of Health, on patients in the late 1970s
6 and this was published in The American Journal of
7 Medicine in 1982. The second trial was really a
8 compilation of four different trials, performed by
9 the European Organization for the Research and
10 Treatment of Cancer, and this was published several
11 years after the Pizzo trial, in the same journal in
12 1989. In the succeeding 20 years empiric
13 antifungal therapy in neutropenic patients, after a
14 period of antibacterial therapy if they still
15 remained febrile, has become the standard of
16 practice.

17 [Slide]

18 There were two public meetings conducted
19 by the FDA in 1994 and 1995 to discuss issues of
20 study design in antifungal drugs. Some of the
21 important issues that came out of these two
22 meetings referable to empiric therapy in
23 neutropenic patients were that a non-inferiority
24 study design was recommended for future trials in
25 this indication. Amphotericin B deoxycholate was

1 suggested as the comparator as, in 1994, it really
2 was the only effective drug that was available.
3 Amphotericin B deoxycholate is not officially
4 approved by the FDA for this indication but this
5 drug was licensed in 1956, prior to our current
6 regulations on efficacy, and it is also a generic
7 drug and there really hasn't been any interest in
8 submitting an NDA for this particular indication.

9 It was also suggested at these meetings
10 that for approval in the indication of empiric
11 therapy in neutropenic patients that an applicant
12 would need to submit at least one study showing
13 efficacy in another fungal indication of proven
14 disease, plus one study in the empiric therapy of
15 febrile neutropenic patients. Since many of these
16 patients who are treated may not actually have
17 fungal infections, it is important that the drug
18 have proven efficacy in documented infections with
19 Candida and Aspergillus.

20 Some of the other points from those two
21 workshops were, again, that idea that it was
22 important to prove the efficacy of the drug since
23 resolution of fever, rather than proven infection,
24 would be used to determine sample size in trials of
25 empiric therapy in febrile neutropenic patients.

1 The lower bound of the 95 percent confidence
2 interval suggested to determine non-inferiority was
3 minus 10 percent, as indicated at these particular
4 workshops.

5 Just as a brief aside, Dr. Gulick asked
6 earlier why was minus 15 percent chosen in the
7 itraconazole trial, in fact, when one looks through
8 the medical officer's review of that, it never came
9 up for discussion. So, it is important to realize
10 that that was not a conscious decision to make it a
11 minus 15 percent in that particular trial.

12 The composite endpoint was also
13 recommended in trials of empiric therapy of febrile
14 neutropenia because the primary endpoint of
15 breakthrough infections may result in a sample size
16 that would be so prohibitively large that trials
17 would not be able to be conducted for this
18 particular indication.

19 Finally, the workshop included that some
20 other things that were important to detect in these
21 trials would be differences in proven fungal
22 infections; differences in mortality between the
23 two arms of the trial; differences in fever within
24 a 10 percent confidence interval; and, finally,
25 differences in safety especially since, again, some

1 patients here will receive treatment that do not
2 have infections.

3 [Slide]

4 In a 1997 advisory committee surrounding
5 issues on the approval of liposomal amphotericin B,
6 Dr. Alan Sugar summed up some of the issues in
7 empiric therapy. He stated that empiric therapy is
8 given to patients because some will actually need
9 it. However, others will not. That is, they are
10 treated unnecessarily. At issue was the diagnosis
11 of invasive fungal infections and the difficulties
12 associated with that. Also at issue is the degree
13 of neutropenia. What places the patient at higher
14 risk? Overall consensus is that patients with an
15 absolute neutrophil count of less than 100 cells
16 per cubic millimeter are at highest risk. The
17 duration of neutropenia also contributes to risk.
18 So, this quotation sums up the fact that some
19 patients will have fungal infections; some will
20 have fever for other reasons; and, given our
21 current problems with diagnosis, it really is
22 impossible to tell which group the patient falls
23 into.

24 [Slide]

25 Dr. Boucher already went over with you

1 this morning the important points about this trial
2 design and I am just going to highlight some of
3 these things again to refresh your memory.

4 Study 603 was designed as a
5 non-inferiority trial, with a non-inferiority
6 margin of minus 10 percent. The primary analysis
7 population in this trial was the modified
8 intent-to-treat population, defined as any patient
9 who received at least one dose of the study drug
10 who also had information available on their outcome
11 at least 7 days after the end of therapy. Patients
12 in this trial were stratified by risk of fungal
13 infections, whether they received antifungal
14 prophylaxis, and by duration of neutropenia.

15 This was an open-label study design for
16 two reasons. One is there is no orally
17 systemically active form of liposomal amphotericin
18 B. The other reason is that the applicant
19 questioned the ethics of giving two I.V. infusions
20 in seriously ill patients that may have problems
21 with their volume status.

22 Finally, a data review committee blindly
23 assessed the incidence of fungal infections and the
24 outcomes of these patients as well.

25 [Slide]

1 There are two agents currently approved in
2 the indication of empiric therapy of febrile
3 neutropenic patients, and the approval for these
4 drugs used a composite endpoint that was similar to
5 that used in study 603. The first one to be
6 approved was liposomal amphotericin B, or Ambisome.
7 The label states that this drug is indicated for
8 empirical therapy for presumed fungal infections in
9 febrile neutropenic patients.

10 The other drug approved in this indication
11 is itraconazole injection and oral solution. The
12 label for this drug states that empiric therapy of
13 febrile neutropenic patients with suspected fungal
14 infections is the indication. There is also a note
15 in the Sporanox label that states that the overall
16 response rate was greater for itraconazole than
17 amphotericin B deoxycholate in the study used to
18 license this drug, but there were more
19 discontinuations due to lack of efficacy in the
20 itraconazole arm of the trial, and there were more
21 discontinuations due to toxicity in the
22 amphotericin B deoxycholate arm of the trial.

23 [Slide]

24 Again just to refresh your memory, the
25 primary endpoint was the stratified overall

1 response rate to the composite 5-component
2 endpoint, again, stratified by risk of fungal
3 infection, duration of neutropenia and receipt of
4 antifungal prophylaxis.

5 The lower bound of the confidence interval
6 to select the sample size and define statistical
7 non-inferiority was defined as minus 10 percent for
8 this trial based on the 50 percent overall response
9 rate in mycosis study group 32 which compared
10 Ambisome to amphotericin B deoxycholate and, again,
11 that was, in turn, based on the 1994 or '95
12 workshop recommendations.

13 The stratified response rates that we see
14 in study 603 show a 23.7 percent response rate in
15 the voriconazole arm and a 30.1 percent overall
16 response rate in the Ambisome arm. This gives us a
17 difference of 6.1 percent in favor of Ambisome with
18 a 95 percent confidence interval that ranges from
19 minus 12 percent to minus 0.1 percent.

20 We performed our analysis at the FDA,
21 again weighted for those three risk factors, and
22 came out with a 95 confidence interval that ranges
23 from minus 11.6 percent to a positive 0.1 percent.
24 As we noted earlier, in either one of these
25 analyses the lower bound of the 95 percent

1 confidence interval falls below the prespecified
2 minus 10 percent.

3 [Slide]

4 Just to make some overall statistical
5 points about the finding of non-inferiority in
6 non-inferiority trials, the lower bound of the 95
7 percent confidence interval, when it falls below or
8 that is more negative than the prespecified limit,
9 implies that that test drug may not be non-inferior
10 to the control drug. However, defining
11 non-inferiority implies that we have some knowledge
12 already about the efficacy of the control drug over
13 placebo, or in this case it would be no treatment,
14 in a superiority trial. The lower bound of the 95
15 percent confidence interval that is used to define
16 the non-inferiority margin in any non-inferiority
17 trial cannot be greater than the difference in
18 control drug over placebo or no treatment.

19 [Slide]

20 Let me give you a hypothetical example to
21 try to illustrate this. If in a superiority trial
22 the lower bound of the 95 percent confidence
23 interval in a trial which tests a placebo or no
24 treatment versus a control drug -- suppose this
25 comes out to be 7 percent, if then we do another

1 trial, a non-inferiority trial of control versus
2 test drug, if the lower bound of the 95 percent
3 confidence interval then, say, hypothetically comes
4 out to be minus 11 percent, then we have a test
5 drug that may be 11 percent worse than the control
6 but the control may be no more than 7 percent
7 better than no treatment. Therefore, the
8 possibility exists that the test drug may actually
9 be no better than placebo or no treatment.

10 [Slide]

11 So, what we do know is that it is clear
12 that neutropenic patients do develop invasive
13 fungal infections. What is the issue when we come
14 to decide about clinical trials in selecting a
15 non-inferiority margin are three issues. Do
16 antifungal drugs prevent breakthrough infections in
17 neutropenic patients? If so, what is the magnitude
18 of this benefit relative to no treatment? Then,
19 thirdly, how does this impact the selection of a
20 non-inferiority margin in clinical trials where we
21 are not using breakthrough infections as the
22 primary endpoint but in which we are using a
23 composite endpoint?

24 [Slide]

25 The two trials done by Pizzo and the EORTC

1 comparing amphotericin B deoxycholate to no
2 treatment had some issues that were associated with
3 them. Neither of these trials were adequately
4 powered to determine a difference in breakthrough
5 infections. The Pizzo trial had 16 and 18 patients
6 per arm in that trial, and there were 60 of so
7 patients in each arm of the EORTC trial.

8 The EORTC trial also used resolution of
9 fever as the primary endpoint and breakthrough
10 infections were secondary analysis in that trial.
11 Also, these two trials included mucosal as well as
12 invasive disease in their descriptions of what they
13 would call breakthrough infections, which is not
14 what we do in the current trials. Neither of these
15 trials included deaths and discontinuations as
16 failures in an analysis of breakthrough infections.
17 The reason that is important to do is that if a
18 patient dies before they had a chance to develop a
19 breakthrough infection one could consider them a
20 failure. The other issue is that since we can't
21 tell who actually has fungal infections that may be
22 occult, given our current diagnostic techniques, a
23 patient who dies and doesn't undergo an autopsy may
24 have had an actual occult fungal infection.

25 [Slide]

1 The true difference of amphotericin B
2 deoxycholate versus no treatment in those two
3 trials in the prevention of breakthrough infections
4 may range anywhere from 60 percent better to 8
5 percent worse than no treatment. Again, this
6 raises the question how does this impact on studies
7 that use our current composite endpoint, not a
8 single endpoint of breakthrough infections? Which
9 then, for the purposes of this trial, again raises
10 the very germane question of what is the clinical
11 relevance of a non-inferiority margin of minus 10
12 percent in studies in empirical therapy in febrile
13 neutropenic patients?

14 Finally, how can we extrapolate from these
15 studies, which were done almost 20 years ago, to
16 our current rate of emergent fungal infections
17 given the difference in care that exists now versus
18 those studies?

19 [Slide]

20 Well, when the primary endpoint in the
21 trial is not met one can attempt to explain the
22 failure to meet that primary endpoint by looking by
23 secondary and subset analyses. However, one must
24 also keep in mind that these secondary and subset
25 analyses are considered hypothesis generating in

1 the setting of a trial which does not meet its
2 primary endpoint.

3 The subset analyses of patients was
4 stratified according to the risk of fungal
5 infections and receipt of antifungal prophylaxis in
6 this trial. And, the secondary endpoints were the
7 five individual components of the composite
8 endpoint.

9 [Slide]

10 In an attempt to adjust for multiple
11 comparisons for these five secondary endpoints, as
12 Dr. DeGruttola brought up this morning, we opted to
13 use 99 percent, rather than 95 percent, confidence
14 intervals to describe the differences between the
15 study arms and the secondary endpoints. Since
16 these were not the primary endpoint of the trial,
17 obviously the trial was not adequately powered to
18 determine true differences in the secondary
19 endpoints and subsets.

20 Also, these secondary and subset analyses
21 may actually contain small numbers of patients in
22 each group, and you will see the numbers as I
23 present them. Also, one of the things that is
24 important is to look for consistency in outcomes of
25 these secondary endpoints. In other words, do all

1 the secondary endpoints trend in the direction
2 favoring one drug or the other, or do some of the
3 endpoints go in one direction and others go in the
4 opposite direction?

5 [Slide]

6 Well, if we look at the overall response
7 rate as a subset analysis by patients according to
8 risk of fungal infection, you have already seen
9 this morning, as Pfizer presented, that in high
10 risk patients it appears that the difference is 1.7
11 percent in favor of voriconazole. If we then look
12 at the 95 percent confidence intervals only in high
13 risk patients, they range from minus nine percent
14 to a positive 12.4 percent. Again, this would meet
15 the statistical definition of non-inferiority,
16 however, this is a subset analysis. In moderate
17 risk patients the difference is minus 7.8 percent,
18 that is, 7.8 percent in favor of Ambisome with a 95
19 percent confidence interval that ranges from minus
20 15.2 percent to minus 0.4 percent.

21 The other thing I would like to point out
22 on this is that it appears that the response rate
23 is consistent in the Ambisome arm between the high
24 risk and the moderate risk patients, with 30
25 percent of patients being judged an overall success

1 in the higher risk Ambisome patients and 31 percent
2 being judged an overall success in the moderate
3 risk Ambisome group.

4 On the other hand, in the voriconazole arm
5 of the trial there is a 32 percent success rate,
6 similar to that seen in the two stratifications
7 here for Ambisome, but the moderate risk group in
8 voriconazole has a 23 percent response rate.

9 [Slide]

10 If then we go on to look at the various
11 secondary endpoints -- the reason that I put all
12 five of them on here is to address the issue of do
13 they all go in the same direction favoring one drug
14 or another? Here again is the overall stratified
15 response which shows the 6.1 percent in favor of
16 Ambisome, with the lower bound of the confidence
17 interval or minus 12.1 percent and the minus 0.1
18 percent upper bound of the confidence interval as
19 presented by the applicant.

20 No breakthrough infections showed a
21 difference in favor of voriconazole of positive 3.1
22 percent. Survival showed a difference in favor of
23 Ambisome of 2.1 percent. No discontinuations. So,
24 the difference in favor of Ambisome of minus 3.3
25 percent. The defervescence prior to recovery from

1 neutropenia showed a difference of three percent in
2 favor of Ambisome, and the response in baseline
3 infections showed a difference of 21 percent in
4 favor of Ambisome.

5 I have presented all of these as
6 positives. I will flip some of these around so I
7 can actually show you the number of deaths, but I
8 just wanted to make the point that all the
9 subsequent 99 percent confidence intervals are
10 based on these differences but I put it this way so
11 you can always focus on the lower bound of the 95
12 percent confidence interval in the succeeding
13 presentations.

14 [Slide]

15 There were fewer breakthrough infections
16 in the voriconazole arm compared to the Ambisome
17 arm of the trial. In voriconazole there were 1.9
18 percent breakthrough infections versus 5 percent in
19 the Ambisome arm. This is a difference of 3.1
20 percent in favor of voriconazole. The 99 percent
21 confidence intervals for this ranged from minus
22 0.37 percent to a positive 6.5 percent. As
23 presented earlier this morning, the difference was
24 greatest in Aspergillus breakthrough infections,
25 with four breakthrough infections caused by this

1 pathogen in the voriconazole arm versus 13 in the
2 Ambisome arm.

3 These breakthrough infections included
4 proven and probable disease, and most of the
5 patients had proven disease, with 6/8 patients in
6 the voriconazole arm and 20/21 patients having
7 proven disease in the Ambisome arm of the trial.

8 [Slide]

9 If one wants to perform a sensitivity
10 analysis considering breakthrough infections as the
11 primary endpoint, one would also want to consider
12 patients who die as failures, for reasons that I
13 talked about earlier. If one includes the 30
14 people who died prior to their end of therapy and
15 the 18 patients who died prior to the end of
16 therapy in the Ambisome arm, this results in a
17 breakthrough infection rate of 9.2 percent in both
18 the voriconazole and the Ambisome arm with a
19 symmetrical 95 percent confidence interval here.
20 This is 95 instead of 99 since this is the primary
21 endpoint here because we are doing a sensitivity
22 analysis using breakthroughs as the primary
23 analysis.

24 [Slide]

25 Again, we do a subset analysis by risk of

1 infection and prophylaxis, we can also see some
2 differences occur here. If we look in the
3 right-hand column we see that the difference is
4 greatest in the high risk group, with 1.4 percent
5 of patients having a breakthrough on voriconazole
6 and 9.2 percent having a breakthrough infection in
7 the Ambisome arm.

8 If we look at the moderate risk group the
9 differences are not as large, with 2.2 percent
10 patients experiencing a breakthrough infection in
11 the voriconazole arm and 2.8 percent experiencing a
12 breakthrough infection in the Ambisome arm.

13 The other way to look at this is by prior
14 antifungal prophylaxis, as well along the bottom
15 column, here, and here the difference is greater in
16 patients who received prior antifungal prophylaxis,
17 with 0.9 percent of patients developing a
18 breakthrough infection in the voriconazole arm
19 versus 5.2 percent in the Ambisome arm. There is
20 still a difference here of 3.1 percent in the no
21 prophylaxis group in the voriconazole arm versus
22 4.7 percent in the Ambisome group that did not
23 receive prophylaxis.

24 Important to note here is that some of the
25 numbers in these individual cells are actually

1 quite small, with only one or two patients included
2 in each group.

3 [Slide]

4 If we then move on to look at survival at
5 seven days after end of therapy, there were more
6 deaths in the voriconazole arm compared to the
7 Ambisome arm of the trial, with eight percent of
8 patients dying in the voriconazole arm within seven
9 days of end of therapy and 5.9 percent in the
10 Ambisome arm. This is a difference of 2.1 percent
11 in favor of Ambisome with a 99 percent confidence
12 interval, ranging from minus 6.9 percent to
13 positive 2.7 percent.

14 The problem in any trial of patients this
15 ill is the difficulty in attribution of death. As
16 Dr. Boucher presented this morning, many of these
17 patients had more than one reason checked off for
18 the reason for which they died. Also, half of the
19 patients who had sepsis also had progression of the
20 malignancy, and half of the patients with
21 progression of malignancy had sepsis, showing that
22 the investigators have a difficult time picking out
23 the actual cause of death.

24 The other difference between this trial
25 and the global aspergillosis trial is that death

1 here was not blindly reviewed by the data review
2 committee as it was in that trial, and death was
3 attributed by the investigators only in this trial.

4 [Slide]

5 If we then discuss discontinuations, there
6 were more discontinuations due to lack of efficacy
7 or toxicity in the voriconazole arm, with 9.9
8 percent of patients discontinuing therapy on
9 voriconazole versus 6.6 percent in the Ambisome arm
10 of the trial. This is a 3.3 percent difference in
11 favor of Ambisome with a 99 percent confidence
12 interval, ranging from minus 8.4 percent to 1.8
13 percent.

14 One of the issues with the composite
15 endpoint is that it combines discontinuations due
16 to lack of efficacy with those due to toxicity.
17 This is really combining an efficacy and a safety
18 endpoint in one and can obscure important
19 differences in outcome. Therefore, it is important
20 to look at the various reasons for discontinuations
21 in these patients.

22 [Slide]

23 There were more discontinuations due to
24 lack of efficacy in the voriconazole arm compared
25 to the Ambisome arm or the trial, and 5.3 percent

1 of patients discontinued in the voriconazole arm
2 versus 1.2 percent in the Ambisome arm, which is a
3 difference of 4.1 percent in favor of Ambisome.

4 However, on the other side, there are
5 fewer discontinuations due to toxicity in the
6 voriconazole arm compared to Ambisome, with 4.6
7 percent of patients discontinuing in the
8 voriconazole arm and 5.5 percent. This was a
9 difference of 0.9 percent in favor of voriconazole.
10 Since these numbers were so small we didn't present
11 99 percent confidence intervals because we would
12 have to further adjust them even for more multiple
13 adjustments.

14 As Dr. Boucher pointed out this morning,
15 more patients temporarily discontinued Ambisome
16 than temporarily discontinued voriconazole,
17 however, the discontinuation was actually specified
18 as people who permanently discontinued in the
19 protocol.

20 This actually brings up the issue of what
21 happens in an open-label trial. The toxicities of
22 amphotericin B are well known and, also, physicians
23 may have been more likely to stop a patient on a
24 new test drug versus a drug such as Ambisome which
25 people have a more favorable opinion of as far as

1 its efficacy, or at least they are more used to
2 using.

3 [Slide]

4 There were more discontinuations with
5 persistent fever as the reason checked off for lack
6 of efficacy in the voriconazole arm of the trial,
7 14/22 patients discontinued because of persistent
8 fever although two of those patients didn't have
9 documented persistent fever. So, that would be
10 12/22. In the Ambisome group 2/5 patients were
11 discontinued due to persistent fever.

12 The issue here is that the failure to
13 become afebrile in a neutropenic patient may
14 indicate the presence of an occult fungal infection
15 and, as we have discussed already, current
16 diagnostic techniques aren't good enough to pick
17 out that a patient who only has fever may still
18 have the presence of an occult fungal infection.

19 [Slide]

20 If we then move on to discuss
21 defervescence prior to recovery from neutropenia,
22 there were fewer patients in the voriconazole arm
23 that met the protocol specified definition of prior
24 to recovery from neutropenia. In the voriconazole
25 arm there were 32.5 percent of patients who met

1 this criterion versus 36.5 percent in the Ambisome
2 arm, which was a difference of 4 percent in favor
3 of Ambisome with a 99 percent confidence interval
4 here, ranging from minus 12.7 percent to positive
5 4.7 percent.

6 However, these results are highly
7 dependent on the definition of defervescence.
8 Previous trials with itraconazole actually used
9 different criteria for defervescence and allowed
10 the patient to be considered a success if they
11 defervesce at any time prior to recovery from
12 neutropenia. However, in study 603 it required
13 that the patient be afebrile for 48 continuous
14 hours prior to recovery from neutropenia to be
15 considered a success in this particular part of the
16 composite endpoint.

17 [Slide]

18 If we look at the results of defervescence
19 prior to recovery from neutropenia in the current
20 study, 603, we can compare that to the two other
21 drugs that are currently approved in empiric
22 therapy of febrile neutropenia. In the Ambisome
23 trial it was 58 percent and 58 percent were
24 considered successes by this particular criterion.
25 Again, there are important differences between

1 these trials. For instance, this particular trial,
2 which is mycosis study group, study number 32,
3 actually included patients all the way down to two
4 years of age. The current study actually includes
5 patients only from 12 years of age on up.

6 The itraconazole trial allowed patients to
7 defervesce at any time 28 days after randomization.
8 So, it was clearly a different definition, and that
9 is reflected in the different cure rates here -- 73
10 percent for itraconazole and 70 percent defervesce
11 prior to recovery from neutropenia based on that
12 definition in that trial. You can see the numbers
13 I have already presented here, 33 percent for
14 voriconazole and 36 percent for Ambisome, and you
15 can just compare that to the other Ambisome trial
16 and show that the 58 percent here for Ambisome and
17 36 percent here in the current trial for Ambisome.

18 [Slide]

19 So we performed a sensitivity analysis for
20 the overall response rate and changed the
21 definition of defervescence in study 603 to look
22 more like the definition in the other trials.
23 First we did a sensitivity analysis which changed
24 the definition to the patient being afebrile for 24
25 hours prior to recovery from neutropenia. Here we

1 see that this raises the success rate to 35.9
2 percent for this overall success in the
3 voriconazole arm and 40.8 percent in the Ambisome
4 arm, which gives us a difference of 4.9 percent in
5 favor of Ambisome. Again, since we are looking at
6 the overall response here we are using 95 percent
7 confidence intervals that range from minus 11.7
8 percent to positive 1.9 percent.

9 If we then change the definition to
10 defervescence at any time prior to recovery from
11 neutropenia, these results look much more like the
12 previous mycosis study group, study number 32, with
13 a 50.1 percent success rate in the voriconazole arm
14 and 56.2 percent success rate in the Ambisome arm.

15 Although this raises it to the level that
16 is consistent with the prior trial, there is still
17 a 6.1 percent difference in favor of Ambisome here
18 with a 95 percent confidence interval, ranging from
19 minus 13.1 percent to 0.9 percent, which again
20 still would not meet the statistical definition of
21 non-inferiority of minus 10 percent used in this
22 trial.

23 [Slide]

24 Finally, to look at baseline infections,
25 part of the exclusion criteria in this trial were

1 that any patient with a known baseline infection
2 was to be excluded from the trial. So, it is not
3 surprising that there were very few of these
4 patients in the trial. The reason that this is
5 included as part of the composite endpoint is to
6 try to get an idea of how good are these drugs at
7 actually determining efficacy in documented
8 infections. Unfortunately, you really can't
9 determine that given the small numbers that are
10 present in this trial. Five of ten patients and
11 two of three in the voriconazole and Ambisome arms
12 respectively had cures of their candidal
13 infections, and there were only two patients in
14 each arm with baseline Aspergillus infections. One
15 patient in each arm recovered from those.

16 [Slide]

17 If we also look at some of the differences
18 here between them, these small numbers make it very
19 hard to draw an interpretation. Again, most of
20 these patients are excluded from the trial at
21 baseline and the only difference between these
22 patients and the patients that are excluded is that
23 their culture happened to come back a couple of
24 days later.

25 Also, two of six patients in the

1 voriconazole arm were considered successes at the
2 end of therapy. However, they developed
3 disseminated candidiasis, one patient at one month
4 and one patient at two months after end of therapy.
5 There was one patient out of those four successes
6 in the Ambisome arm who developed disseminated
7 candidiasis 20 days after end of therapy. So,
8 although we would consider these people cures based
9 on the definition in the protocol, they may
10 clinically be considered failures. Again, that is
11 not a fair comparison because by definition the
12 people that are in this trial remain neutropenic
13 and some of the cure rates of these patients are
14 highly dependent upon whether they recover their
15 neutrophil count or not.

16 [Slide]

17 So finally, to sum up, drugs in the
18 empiric therapy of febrile neutropenia should have
19 proven efficacy versus documented Candida and
20 Aspergillus infections given the nature of these
21 trials. The aspergillosis global study, presented
22 here today, shows efficacy in Aspergillus and
23 Pfizer has presented data on Candida esophagitis
24 and study 608 on candidemia is still ongoing.
25 Since therapy in this indication is empiric,

1 patients in the empiric therapy of febrile
2 neutropenia may actually receive treatment and not
3 have fungal infections, which makes it important to
4 look at the safety profile of the drug.

5 To sum up the points that we have made
6 today, in this particular trial voriconazole fails
7 to meet its statistical definition of
8 non-inferiority as it falls below the minus 10
9 percent lower bound of the confidence interval that
10 was prespecified in the protocol.

11 The subset analyses of the overall
12 composite endpoint showed a numerical advantage of
13 voriconazole in high risk patients but an advantage
14 of Ambisome in the moderate risk patients.

15 The secondary analyses of breakthrough
16 infections showed a numerical advantage of
17 voriconazole, especially in the prevention of
18 Aspergillus infections. However, a sensitivity
19 analysis that included deaths as failures showed no
20 difference between the drugs in the incidence of
21 breakthrough infections.

22 Finally, secondary analyses of the other
23 four components, other than breakthrough in
24 infections, were in favor of Ambisome.

25 [Slide]

1 So, the considerations that we would like
2 the committee to discuss today include what is the
3 clinical relevance of a non-inferiority margin of
4 minus 10 percent in trials in empiric therapy of
5 febrile neutropenia that use this composite
6 endpoint, given what we know about this indication?

7 Finally, how do we look at secondary
8 analyses in a study which did not meet its primary
9 endpoint? Finally, we need to consider the safety
10 profile of a drug in empiric therapy where some
11 patients may receive the drug who do not actually
12 have infections and, therefore, would derive no
13 benefit from the drug.

14 Given that last consideration, I will pass
15 the baton back to Dr. Tiernan who will give the FDA
16 perspective on the safety issues associated with
17 voriconazole.

18 [Slide]

19 DR. TIERNAN: For the safety section of
20 this I will pretty much focus on the following five
21 areas: ocular, cardiac, hepatic safety, rash and
22 drug interactions.

23 [Slide]

24 In the preclinical evaluation of this drug
25 pharmacology-toxicology studies have demonstrated

1 that voriconazole produced dose-related effects in
2 the ERG of dogs exposed to voriconazole. The
3 voriconazole plasma levels which produced these
4 results in dogs were similar to those plasma levels
5 achieved in human studies.

6 Histopathology results for female rats
7 which received 50 mg/kg of voriconazole, which is
8 equivalent to 8 mg/kg I.V., demonstrated mild
9 thinning of the outer layer of the retina at 24
10 months. During the clinical trials the incidence
11 of visual symptoms was one out of every three
12 subjects, and the symptoms included decreased
13 vision, photophobia, altered color perception and
14 ocular discomfort. The exact mechanism underlying
15 these visual symptoms is unknown. There is no
16 human histopathology data and ocular biomicroscopy
17 has not detected ocular lesions.

18 [Slide]

19 Results from study 150-1004, a study in
20 which voriconazole was given to healthy volunteers
21 at a dose of 400 mg q. 12 hours for one day and 300
22 mg q. 12 hours for 27 days, are listed as follows.

23 Effects were noted in the ERG,
24 Mamsworth-Munsell 100 hue test for color vision,
25 and Humphrey Perimetry studies for visual field.

1 Voriconazole has effects on both rod and cone
2 function. Decreased visual function is present on
3 the first day and continued through 28 days of
4 therapy. At 14 days after the end of therapy the
5 visual function returns to normal.

6 [Slide]

7 Additional issues regarding the use of
8 this drug include that there is insufficient
9 information to predict what the ophthalmologic
10 effects will be in patients who are either
11 rechallenged or retreated with voriconazole.
12 Ultimately, if this drug is considered for use in
13 children less than nine years of age, we do not
14 have sufficient data to predict the effect of
15 voriconazole on the eye which is not yet fully
16 developed. A careful risk-benefit assessment will
17 have to be made when considering the use of
18 voriconazole in patients with underlying eye
19 disease, such as CMV retinitis. We cannot predict
20 that visual changes will resolve if this drug is
21 used beyond 28 days of therapy.

22 [Slide]

23 In vitro studies of this drug demonstrated
24 no major effects for voriconazole in HERG channel
25 studies or in dofetilide studies when compared to

1 ketoconazole. In vivo data demonstrated that in
2 dogs high doses of voriconazole produced
3 arrhythmia, PVCs and prolonged QT intervals.

4 As already discussed by the applicant,
5 there was one sudden death in the Phase III
6 clinical trials for which a role for voriconazole
7 could not be excluded. In response to this event,
8 investigators were asked to monitor patients with
9 telemetry if the patient had underlying heart
10 disease and was to receive intravenous
11 voriconazole. The applicant planned to further
12 investigate the effect of three intravenous doses
13 of voriconazole at 4 mg/kg, 8 mg/kg and 12 mg/kg on
14 QTc interval in healthy subjects aged 18-65 years.
15 However, this study was terminated because of
16 anaphylactoid reactions, and the applicant has
17 conducted a thorough investigation and no causative
18 factor has been found for those anaphylactoid
19 reactions and the applicant has committed to
20 complete a similar study but utilizing the oral
21 preparation of voriconazole.

22 [Slide]

23 In the controlled clinical trials, studies
24 307-602, 603 and 305, no major differences between
25 voriconazole and controls have been detected in the

1 cardiac adverse event reporting or rate of
2 discontinuations specifically for events such as
3 arrhythmias and congestive heart failure. However,
4 the voriconazole arm in study 307-602 did have more
5 grade 3 cardiac adverse events and a role for the
6 drug could not be excluded.

7 It is important to note that these
8 clinical studies were not specifically designed to
9 assess the risk of developing arrhythmia in a
10 population who may be on multiple medications, have
11 underlying heart disease and may also be on
12 antiarrhythmic drugs.

13 [Slide]

14 Pfizer has already presented information
15 on the hepatic safety of voriconazole and, in
16 general, we are in agreement with the information
17 as presented by Pfizer. Our conclusions are
18 similar in that the data from Phase I/Phase II
19 studies support that there is a positive dose or an
20 exposure response relationship between voriconazole
21 and transaminase increases, and a possible
22 association with alkaline phosphatase increases.

23 In the Phase III comparative studies
24 hepatic adverse events and abnormalities of
25 transaminases and alkaline phosphatase were more

1 frequent among patients taking voriconazole than
2 fluconazole. The hepatic adverse events were
3 similar between voriconazole and its amphotericin B
4 comparators, with the exception of bilirubin
5 elevations which were more frequent among those
6 treated with amphotericin B formulations. While
7 the numbers are small, serious adverse events were
8 reported more frequently among patients receiving
9 voriconazole in the Phase III comparative studies.

10 Regarding hepatic failure deaths, Pfizer
11 has already described the findings of the expert
12 panel of hepatologists who reviewed those specific
13 deaths.

14 [Slide]

15 We agree with the applicant that rash is a
16 potential hazard associated with the use of this
17 drug. Patients in the clinical studies were often
18 on concomitant medications that could either cause
19 rash themselves, or concomitant medications such as
20 antihistamines and steroids that might affect the
21 type and severity of skin symptoms observed.
22 Conditions such as graft-versus-host disease can
23 also make it difficult to completely assess a
24 causative role for study drug and the development
25 of rash.

1 [Slide]

2 In the controlled clinical trials rash was
3 observed in voriconazole study patients at a rate
4 similar to that of its comparators. Overall, rash
5 develops in about 18.6 percent of patients
6 receiving voriconazole. The applicant has already
7 presented several descriptions of the various types
8 of skin examples observed. No specific rash is
9 characteristic of voriconazole exposure, and there
10 is insufficient information at this time to
11 conclude that the rash is due to photosensitivity.

12 Most rashes were of mild to moderate
13 severity. There were no major differences in the
14 discontinuations for rash between voriconazole and
15 its comparators. However, the applicant, in their
16 briefing package, has already described four
17 non-fatal cases of Stevens-Johnson syndrome which
18 were noted in patients on voriconazole. Two of
19 these cases developed rash; discontinued drug and
20 then re-exacerbated upon rechallenge. It should
21 also be noted that there was a case of toxic
22 epidermal necrolysis reported for amphotericin B in
23 the trial as well in the database.

24 [Slide]

25 We will finish with drug interactions. To

1 address the safety implications of drug
2 interactions with voriconazole, the in vitro
3 metabolism studies performed with human hepatic
4 microsomes and genetically engineered cell lines
5 indicate that voriconazole is both a substrate and
6 an inhibitor of three cytochrome P450 enzymes,
7 2C19, 2C9 and 3A4.

8 The substrate affinity and inhibition
9 potency of voriconazole is greater for 2C19 and 2C9
10 compared to 3A4. For comparison, the potency of
11 voriconazole as an in vitro inhibitor of 3A4
12 appears to be weaker than ketoconazole and
13 itraconazole. The in vitro potency of voriconazole
14 to inhibit the metabolism of 3A4 substrates, and
15 for 3A4 substrates to inhibit voriconazole varies
16 among classes of drugs, including HIV protease
17 inhibitors, non-nucleoside reverse transcriptase
18 inhibitors and immunosuppressant drugs.

19 [Slide]

20 The applicant has evaluated representative
21 substrates, inhibitors and inducers of the three
22 CYP enzymes both in vitro and in vivo, however, it
23 is not possible to evaluate every potential drug
24 interaction. To illustrate, representative
25 protease inhibitors and non-nucleoside reverse

1 transcriptase inhibitors were studied in vitro but
2 not in vivo. The exception is indinavir which was
3 studied under both conditions and found not to
4 interact with voriconazole. However, other
5 protease inhibitors and non-nucleoside reverse
6 transcriptase inhibitors are known inhibitors
7 and/or inducers of CYP3A4, and the clinical
8 significance of an in vivo interaction with
9 voriconazole is currently unknown. Therefore, the
10 potential for drug interactions with voriconazole
11 presents a therapeutic challenge for the prescriber
12 when attempting to manage patients on multiple
13 concomitant medications.

14 The applicant states that these drug
15 interactions are manageable but, please, keep in
16 mind that this is predicated on experience within
17 the setting of a carefully monitored clinical trial
18 and we look to the advisory committee for advice
19 regarding additional drug interactions that may
20 need to be explored.

21 This concludes the safety presentation. I
22 can take some questions.

23 DR. GULICK: Thanks, Drs. Tiernan and
24 Powers. We will open it up to the committee for
25 questions of detail or information. Dr. Stanley?

1 **Questions from the Committee**

2 DR. STANLEY: Again obsessing with the
3 ocular abnormalities, did I miss it -- they did
4 have in the briefing document a little bit about
5 some pediatric dosing trials but there was nothing
6 that I saw about evaluation of ocular effects in
7 the pediatric population, or did I miss it?

8 DR. TIERNAN: I am not familiar with any
9 of the pediatric data, to be honest.

10 DR. GULICK: Dr. Schapiro?

11 DR. SCHAPIRO: I think you mentioned that
12 there was retinal thinning in an animal model. I
13 wonder if you could elaborate on that?

14 DR. TIERNAN: Yes, and I will call on our
15 pharmacology/toxicology staff to answer that, and
16 that was at 24 months I believe.

17 DR. MCMASTER: Could you repeat the
18 question, please?

19 DR. SCHAPIRO: Yes, there was mention that
20 in an animal there was a finding of retinal
21 thinning. We hadn't heard before about any
22 histopathology regarding the retinal damage. Could
23 you elaborate on the findings in the animals?

24 DR. MCMASTER: There were a number of
25 studies that were done -- shorter studies, one

1 year, six-month studies and up to 24 months in
2 rats. The earlier studies did not show findings.
3 The later studies, in particular one 24-month rat
4 study in which the sponsor examined the thickness
5 of the retinal layers, as mentioned earlier, the
6 center of the retina was fine but as they looked to
7 the outer layers, the outer layers were thinner in
8 the female rats on the high doses. This was not
9 found in the male rats and this was not found in
10 the animals that were dosed for shorter durations.
11 So, this a longer-term finding, which is very
12 consistent with the findings that we had in the
13 patients and findings in the dogs.

14 DR. GULICK: Dr. Wong?

15 DR. WONG: What we heard from the sponsor
16 was that this seemed to be a functional abnormality
17 that was completely reversible upon withdrawal of
18 the drug. If with prolonged exposure at high doses
19 we have a morphologic abnormality or structural
20 abnormality, that is really different from what we
21 heard about earlier this morning, isn't it?

22 DR. BAILDON: I could comment on that.

23 DR. GULICK: Okay, let's go ahead and do
24 that just to clarify this one issue.

25 [Slide]

1 DR. BAILDON: This is the 24-month
2 carcinogenicity study. That is actually where this
3 was observed in rats. This is a 24-month study
4 which actually covers the full lifetime of the
5 rats, and these are albino rats that are sensitive
6 to light and actually show retinal thinning as an
7 age phenomenon. That retinal thinning as an age
8 phenomenon is somewhat dependent on light exposure
9 and varies between animal and animal.

10 What you see here in carcinogenicity
11 studies -- at that time two controlled groups were
12 usually used for these studies -- and if you look
13 at the thickness of the peripheral retina, this is
14 a cell count of cell layers in that retina and you
15 can see there is considerable variability between
16 the control groups, and the same here for female
17 animals where you see some variability, less so in
18 the peripheral retina. The finding that the
19 colleagues at FDA described is in the female who,
20 in the peripheral retina, had a thinning at the 50
21 mg/kg dose at 24 months compared to the control
22 group. It was not observed in the same animals in
23 the central retina, and it was not observed in the
24 male rats.

25 [Slide]

1 Then, this slide shows our findings. The
2 same analysis in dogs treated for 12 months, and my
3 assessment was related to the dogs which display
4 the same electrophysiological phenomenon that we
5 have observed in humans. These dogs were treated
6 for 12 months at 12 mg/kg, which is a toxic dose.
7 It shows abnormalities at that dose. There, we see
8 no difference in central or peripheral retina
9 between dogs treated with voriconazole or control
10 animals.

11 DR. GULICK: Thanks for that
12 clarification. I don't know if the agency has
13 further comment.

14 DR. MCMASTER: We agree that there is, in
15 fact, only mild thinning but, if there is an age
16 effect, it would be expected to affect all the
17 animals because they are all at the same age. We
18 maintain that there is a slight change, however, in
19 the context of the very remarkable findings in the
20 patients, and in the context of the findings in the
21 dogs this represents an actual histopathological
22 change which might, in fact, reflect something that
23 could be found when patients are treated for a long
24 time.

25 DR. GULICK: One other comment?

1 DR. TIERNAN: Yes, this is Dr. Chambers,
2 our ophthalmologist at FDA, who did the ocular
3 safety.

4 DR. CHAMBERS: Yes, I am Wiley Chambers.
5 What we observed is that the findings in the animal
6 have shown up before in histopathology findings.
7 We don't have any long-term human findings that
8 would correlate to the same degree as what was seen
9 within the animals. Yes, there is a natural
10 decrease in layers, but what you saw, what was just
11 displayed, is that all the groups go down but there
12 is a statistical difference from the control group
13 in that one set and we don't know what that means,
14 and we have no corresponding long-term human data
15 to match up and tell you whether that occurs in the
16 species or does not. With the other animals, the
17 dog animals, you don't have a comparable long-term
18 history. As was pointed out, this was a
19 carcinogenicity study so it was carried out for the
20 lifetime of the animal. We have nothing comparable
21 in any other groups.

22 DR. GULICK: Thank you. Other questions
23 of clarification or detail? Dr. Yogev?

24 DR. YOGEV: Maybe I missed it, but was
25 there any data about the teratogenicity at all?