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

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING
NDA 21-266, Vfend (voriconazole) Tablets
NDA 21-267, Vfend I.V. (voriconazole) for Injection
Pfizer Global Research and Development

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Thursday, October 4, 2001

8:30 a.m.

The Town Center Hotel
8727 Colesville Road
Maryland Ballroom
Silver Spring, Maryland

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Roy M. Gulick, M.D., M.P.H., Chair
Tara P. Turner, Pharm.D., Executive Secretary

Members:

John D. Hamilton, M.D.
Wm. Christopher Mathews, M.D.
Sharilyn Stanley, M.D.
Brian Wong, M.D.
Ram Yogev, M.D.

Consultants (voting) Pending New AVAC Members:

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Jonathan M. Schapiro, M.D.
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Keith A. Rodvold, Pharm.D.

Industry Representative (non-voting):
Eugene Sun, M.D.

Guest (non-voting):
Vicki A. Morrison, M.D.

FDA:

Renata Albrecht, M.D.
Marc Cavaille-Coll, M.D., Ph.D.
Mark Goldberger, M.D., M.P.H.
ohn Powers, M.D.
Rosemary Tiernan, M.D., M.P.H.

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P R O C E E D I N G S

Call to Order

1
2
3 DR. GULICK: Good morning. I am Trip
4 Gulick from Cornell. I am happy to call this
5 meeting of the Antiviral Drug Advisory Committee to
6 order.

7 For those of you who were here yesterday,
8 you will be happy to know that a plague of locusts
9 was sighted on Colesville Road; we don't think they
10 are going to be interfering with the meeting this
11 morning.

12 I would like to remind the committee and
13 all the speakers to be aware of the mikes, to make
14 sure that you are about--I was told six to eight
15 inches is optimal, so that everyone can hear
16 people's comments.

17 I would like to start the meeting by
18 having the members of the committee introduce
19 themselves. Dr. Sun, we will go to you to start.
20 Please state your name and where you are from.

Introductions

22 DR. SUN: Eugene Sun, Abbott Laboratories.

23 DR. MORRISON: Vicki Morrison, VA
24 Hospital, Minneapolis.

25 DR. RODVOLD: Keith Rodvold, University of

1 Illinois, Chicago.

2 DR. STANLEY: Sharilyn Stanley, Texas
3 Department of Health.

4 DR. WOOD: Lauren Wood, National Cancer
5 Institute, Bethesda, Maryland.

6 DR. MATHEWS: Chris Mathews, University of
7 California, San Diego.

8 DR. HAMILTON: John Hamilton, Duke
9 University and Durham VA Medical Center.

10 DR. ENGLUND: Janet Englund, Department of
11 Pediatrics, University of Chicago.

12 DR. TURNER: Tara Turner, executive
13 secretary for the committee.

14 DR. SCHAPIRO: Jonathan Schapiro, Stanford
15 University and Tel Aviv University.

16 DR. WONG: Brian Wong, the West Haven
17 Connecticut VA Hospital and Yale University.

18 DR. DEGRUTTOLA: Victor DeGruttola,
19 Harvard School of Public Health.

20 DR. POWERS: John Powers, medical officer,
21 FDA.

22 DR. TIERNAN: Rosemary Tiernan, medical
23 officer, FDA.

24 DR. ALBRECHT: Renata Albrecht, Acting
25 Director, Division of Special Pathogen Immunologic

1 Drug Products, FDA.

2 DR. CAVAILLE-COLL: Mark Cavaille-Coll,
3 the Office of Drug Evaluation I.V., FDA.

4 DR. GULICK: Thank you very much. Tara
5 Turner will now read the conflict of interest
6 statement.

7 **Conflict of Interest**

8 DR. TURNER: The following announcement
9 addresses the issue of conflict of interest with
10 regard to this meeting, and is made a part of the
11 record to preclude even the appearance of such at
12 this meeting.

13 Based on the submitted agenda for the
14 meeting and all financial interests reported by the
15 committee participants, it has been determined that
16 all interests in firms regulated by the Center for
17 Drug Evaluation and Research which have been
18 reported by the participants present no potential
19 for an appearance of a conflict of interest at this
20 meeting, with the following exceptions:

21 In accordance with 18 USC 208(b)(3), full
22 waivers have been granted to Dr. Courtney Fletcher,
23 Dr. Roy Gulick, Dr. Brian Wong, Dr. Ram Yogev and
24 Dr. Lauren Wood. A copy of these waiver statements
25 may be obtained by submitting a written request to

1 the agency's Freedom of Information Office, Room
2 12A-30 of the Parklawn Building.

3 Further, in accordance with 21 USC
4 355(n)(4), Dr. Courtney Fletcher, Dr. Brian Wong,
5 Dr. Ram Yogev and Dr. Victor DeGruttola have been
6 granted waivers that permit them to vote on matters
7 related to today's discussions.

8 We would like to disclose for the record
9 that Dr. Victor DeGruttola and Dr. Keith Rodvold
10 have interests which do not constitute financial
11 interests within the meaning of 18 USC (208)(a) but
12 which could create the appearance of a conflict.
13 The agency has determined, notwithstanding these
14 interests, that the interest of the government in
15 their participation outweighs the concern that the
16 integrity of the agency's programs may be
17 questioned. Therefore, Drs. DeGruttola and Rodvold
18 may participate fully in today's discussion and
19 vote concerning Vfend.

20 In addition, we would like to note that
21 Dr. Eugene Sun is Division Vice President,
22 Infectious Diseases and Virology Development
23 Department, Pharmaceutical Products Division at
24 Abbott Laboratories. He is participating in this
25 meeting as an industry representative acting on

1 behalf of regulated industry. As such, he has not
2 been screened for any conflicts of interest.

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

9 With respect to all other participants, we
10 ask in the interest of fairness that they address
11 any current or previous financial involvement with
12 any firm whose products they may wish to comment
13 upon. Thank you.

14 DR. GULICK: Just to clarify, Dr. Courtney
15 Fletcher was unable to make this meeting. And,
16 good morning, Dr. Yogev, and will you introduce
17 yourself, please, and state your affiliation?

18 DR. YOGEV: Ram Yogev, Children's Memorial
19 Hospital in Chicago.

20 DR. GULICK: Thanks. I would like to turn
21 to Dr. Goldberger who will present some
22 introductory remarks from the agency.

23 **FDA Introductory Remarks**

24 DR. GOLDBERGER: Thank you, Dr. Gulick. I
25 would like to welcome you, advisory committee

1 members, invited guests, Pfizer, FDA staff and
2 those in the audience to the second day of this
3 Antiviral Advisory Committee.

4 Today we will be discussing NDAs for
5 voriconazole tablets and voriconazole for
6 injection. The applicant has actually requested a
7 series of indications: invasive aspergillosis,
8 empiric antifungal therapy of febrile neutropenic
9 patients, treatment of Candida esophagitis, serious
10 Candida infections, serious fungal infections due
11 to Fusarium and Scedosporium, and serious fungal
12 infections in patients refractory or intolerant to
13 other therapy.

14 In general, we are in agreement with the
15 applicant with regards to the numerical results of
16 the studies supporting these different indications,
17 as well as to the data in the overall safety
18 profile in this drug. We have, after discussions
19 with the applicant, chosen to focus the
20 presentations at this meeting on two of the
21 indications, treatment of invasive aspergillosis and
22 empiric antifungal therapy of febrile neutropenic
23 patients as well as, of course, a complete
24 discussion of the safety profile of this product,
25 including drug interactions.

1 We have chosen to focus on these two
2 indications first, because as a practical matter,
3 it is very difficult to review detailed data on so
4 many indications in a single day. Secondly, as I
5 noted, we are in general agreement with the
6 numerical results on all these indications and
7 because we feel that in the case of invasive
8 aspergillosis the applicant will be presenting data
9 from a randomized trial for therapy in this
10 indication. It is a type of study that
11 realistically has not been presented before and we
12 think the results are very important, both for
13 presentation, discussion of indications for this
14 product, and possibly for future drug development.
15 So, we think this is an extremely important piece
16 of data and we wanted to have sufficient time to
17 discuss this.

18 In the case of empiric antifungal therapy
19 of febrile neutropenic patients, we are, as noted,
20 in general agreement with the sponsor with regards
21 to the numerical results of the study. However,
22 the numerical results are unclear as to the
23 appropriate regulatory action that ought to be
24 taken, and we feel that having a full discussion of
25 this indication, with a lot of input from the

1 committee, will be quite useful.

2 Finally, not surprisingly with a product
3 in theazole class and with treatment of a wide
4 variety of patients with serious underlying
5 disease, there are a number of issues from the
6 safety profile, both safety issues and issues
7 related to drug interactions. We feel it is very
8 important to have an adequate discussion of these
9 topics, as well as an adequate discussion of the
10 drug interaction topics, since they can certainly
11 affect decisions even on the first two indications
12 and certainly on some of the others as well.

13 With that, I will turn it over to Dr.
14 Gulick again.

15 DR. GULICK: Thanks, Dr. Goldberger. We
16 will begin with the presentation from the sponsor,
17 Pfizer Global Research and Development. Dr.
18 Baildon will be beginning.

19 **Sponsor Presentation**

20 **Introduction**

21 DR. BAILDON: Thank you very much, Dr.
22 Gulick. Good morning.

23 [Slide]

24 My name is Reinhard Baildon. I am from
25 Pfizer Global Research and Development. I

1 appreciate the opportunity today to present our
2 data on the efficacy and safety of our new
3 antifungal agent, voriconazole.

4 [Slide]

5 This is the order of our presentation
6 today. I will provide some of the background to
7 the discovery and development of voriconazole and
8 describe the in vitro and in vivo activity. We
9 will then focus our discussion on the questions Dr.
10 Goldberger asked.

11 Before I start on the voriconazole data,
12 however, I would like to ask Dr. Tom Patterson,
13 Professor of Medicine at the University of Texas at
14 San Antonio, to highlight key aspects on the
15 invasive fungal infections and why there is still a
16 high unmet medical need in this population. Those
17 are actually the first slides in the document that
18 you have in front of you. Dr. Patterson?

19 **Invasive Fungal Infections:**

20 **Management and Medical Need**

21 DR. PATTERSON: Thank you, Dr. Baildon and
22 thank all of you for the opportunity for me to
23 discuss with you today the management and medical
24 needs for invasive mycoses.

25 [Slide]

1 This slide outlines the mortality due to
2 invasive mycoses over the last two decades in the
3 United States, from data published this last month
4 by the CDC. You can see significant increases in
5 mortality due to invasive mycoses. Notably
6 mortality due to Candida, in the yellow line, has
7 recently declined perhaps due to better recognition
8 of these infections and earlier antifungal therapy.

9 However, I think you will also see
10 significant increases in mortality due to
11 Aspergillus, in the purple line, with those rates
12 in mortality rising four-fold over that period.
13 Although not as common, other mycoses, particularly
14 molds and Fusarium, for which limited therapeutic
15 options exist, are associated with even higher
16 rates of mortality.

17 [Slide]

18 One of the most challenging of these
19 opportunistic fungal pathogens is Aspergillus.
20 This slide shows mortality associated with invasive
21 aspergillosis. From a review by Lin and colleagues
22 of almost 2000 patients with invasive aspergillosis
23 from 50 published studies, you can see overall
24 mortality rates were 58 percent but were
25 dramatically higher in some groups. For example,

1 in those patients undergoing bone marrow
2 transplantation mortality was 87 percent, while
3 those with leukemia or lymphoma had a mortality of
4 49 percent.

5 Extent of infection also correlates with
6 outcome. Patients with pulmonary infection had
7 mortality of 59 percent, while those who developed
8 central nervous system or disseminated infection
9 had mortality approaching 90 percent, suggesting
10 that an early diagnosis and therapy could be a way
11 to reduce the mortality of this often lethal
12 disease.

13 [Slide]

14 Recently guidelines were published by the
15 IDSA for management of Aspergillus infections.
16 These published guidelines suggested the importance
17 of a prompt, aggressive diagnosis and therapy to be
18 initiated at early suspicion of infection. It was
19 also recognized that that strategy was often the
20 one employed with the use of early empirical
21 antifungal therapies. Antifungal therapy was
22 suggested to be given intravenously in seriously
23 ill patients, utilizing maximum doses of
24 amphotericin B deoxycholate. Alternative agents at
25 that time included lipid forms of amphotericin

1 which were recommended largely for patients
2 intolerant of standard therapies, and itraconazole
3 for sequential use following initial amphotericin B
4 therapy, although the importance of adjunctive
5 therapies was also recognized, as well as the need
6 for new therapies and diagnostic tools for this
7 disease.

8 It should also be noted, however, that
9 most of these recommendations are based on clinical
10 opinion as few successful randomized trials have
11 been conducted in this area.

12 [Slide]

13 Unfortunately, outcomes using these
14 approaches are currently still very poor. This
15 slide shows data we recently published on the
16 outcomes of invasive aspergillosis. We reviewed
17 case records of 595 patients with invasive
18 aspergillosis and showed response rates overall of
19 37 percent. However, I will draw your attention to
20 those patients with more severe immunosuppression,
21 those undergoing marrow transplantation or with
22 hematologic malignancies, and those patients'
23 outcomes were favorable in only 28 percent.
24 Importantly, in the subgroups of allogeneic
25 transplant alone, favorable response occurred in

1 only 13 percent of those patients, while in
2 patients with hematologic malignancies the outcomes
3 were 39 percent.

4 In patients with less severe
5 immunosuppression overall outcomes were favorable
6 in about half the patients. Again, site of
7 infection was very important. Patients with
8 pulmonary infection had favorable outcomes in 40
9 percent, while those who developed later, more
10 advanced disease and dissemination had responses
11 that totalled less than half that. With central
12 nervous system involvement favorable responses
13 occurred in only 9 percent of the patients, again
14 suggesting the potential role for early
15 intervention.

16 [Slide]

17 Unfortunately, clinical trials have been
18 difficult to perform in this area. These issues
19 were recently addressed by a consensus panel led by
20 Dr. John Rex, as outlined on this slide.
21 Limitations would include the relative infrequency
22 of these infections as well as the difficulty in
23 establishing a diagnosis of these diseases. The
24 panel suggested the use of surrogate markers like
25 antigen testing, which is not available here in the

1 U.S., or the use of high resolution imaging like CT
2 scans, the halo finding specifically for
3 Aspergillus, which we, in fact, did demonstrate at
4 last year's ICAAC could be successfully used in
5 clinical studies.

6 Host factors and trial issues, including
7 the selection and use of approved comparators and
8 accepted definitions and endpoints, further hinder
9 clinical trial development. The panel identified
10 only two studies they classified as large
11 prospective, randomized trials that were really
12 ever successfully conducted for Aspergillus and
13 each of them contained about 100 patients.

14 [Slide]

15 Because of these clinical trial
16 limitations and the clear unmet medical needs of
17 this disease, most recent studies evaluating new
18 agents have employed either historical controls or
19 utilized smaller numbers of patients. This slide
20 shows three recent trials and the comparative
21 agents, along with the number of patients in each
22 arm. Historical controls were used to evaluate
23 ABLC for a salvage indication of Aspergillus and
24 more recently used to evaluate the new capsosfungin.

25 You can see, I think, the efficacy of

1 these compounds as compared to control patients who
2 were refractory to or intolerant of standard
3 therapies, although overall response rates were
4 slightly more than 40 percent in these patients
5 with very advanced disease.

6 In a small open, randomized trial which
7 also allowed the inclusion of suspected infection
8 you will see higher response rates, both with
9 liposomal amphotericin and its comparator
10 amphotericin B deoxycholate, perhaps due to the
11 inclusion of those patients with suspected disease
12 but, again, perhaps due to the earlier initiation
13 of therapy.

14 [Slide]

15 Because of these poor responses in
16 established invasive mycoses, the use of empirical
17 antifungal therapy is recommended. This slide
18 shows data from the recent mycosis study group
19 trial, published by Dr. Tom Walsh and colleagues,
20 which shows the clear decrease in fungal infections
21 that occurred with liposomal amphotericin as
22 compared with amphotericin B deoxycholate.
23 However, you will note that Aspergillus infections
24 continue to occur in each arm of the trial, again a
25 very significant concern and a major challenge in

1 clinical mycology.

2 [Slide]

3 In summary, the epidemiology of invasive
4 mycoses demonstrates an increasing number of
5 infections due to Aspergillus and other molds which
6 are associated with major causes of morbidity and
7 mortality. Clearly, prognosis is improved with a
8 very prompt diagnosis, although it remains very
9 difficult to establish. Host factors are also
10 critical in determining outcome.

11 Finally, the use of early aggressive
12 antifungal therapy appears to improve responses
13 but, clearly, new approaches and new agents are
14 needed for this disease. Thank you for your
15 attention.

16 **In Vitro/In Vivo Data, Clinical Pharmacology**

17 DR. BAILDON: Thank you. I will now
18 return to the voriconazole development program.

19 [Slide]

20 Voriconazole was first administered to
21 humans in 1991 and has undergone extensive
22 development since then. Clinical studies in the
23 United States were begun in 1955 and last year, in
24 November, we filed the NDA. In June of this year
25 we provided a substantial update, including the

1 results of our global comparative aspergillosis
2 study.

3 Throughout the development we have
4 benefited greatly from close interactions with the
5 Division and external experts. Through the use of
6 external data review committees and rigorous,
7 standardized assessments of patients throughout the
8 program, we aim to ensure a consistent approach
9 across varying study populations and study designs.

10 [Slide]

11 Voriconazole is used in a complex patient
12 setting against a background of serious disease and
13 concurrent use of multiple other medications and
14 invasive interventions. To help us in assessing
15 the efficacy and safety in this complex setting, we
16 have over the years consulted with many leading
17 experts in the field and are fortunate to have
18 those listed on this slide with us in the sponsor
19 section. As needed by the committee, they can be
20 active participants in our discussion later today.

21 [Slide]

22 As a high level summary, let me describe
23 our assessment of what voriconazole might
24 contribute to the setting of invasive aspergillosis
25 and other invasive fungal infections. We have seen

1 significantly improved outcome and survival benefit
2 in patients with acute invasive aspergillosis. We
3 think the efficacy seen in infections due to
4 emerging pathogens, like *Scedosporium* and *Fusarium*,
5 is very encouraging. The in vitro and in vivo data
6 seen with *Candida* infections, including infections
7 due to *Candida krusei* as well as the results in the
8 patients that we have treated to date, make us
9 believe that voriconazole is an appropriate
10 treatment for these infections as well.

11 The efficacy seen in patients with
12 documented fungal infections, as well as the
13 results seen in our empirical therapy study, led us
14 to conclude that voriconazole is an appropriate
15 option for empirical therapy of neutropenic
16 patients with persistent fever. The large safety
17 data base that we have collected led us to conclude
18 that voriconazole has an acceptable safety profile,
19 given the population targeted for its use, and is
20 better tolerated than amphotericin B formulations.

21 The availability of an I.V. and oral
22 formulations allows switching between these two,
23 especially as the oral formulation has very high
24 bioavailability. We feel that we have collected
25 sufficient data, and I will discuss this, to

1 provide detailed guidance to the prescribing
2 physician on managing the interactions, and we feel
3 that these are manageable given the populations
4 that are treated. Overall, we think that
5 voriconazole addresses an important currently unmet
6 medical need in patients with invasive fungal
7 disease.

8 [Slide]

9 The clinical program included patients
10 with documented fungal infections, aspergillosis,
11 candidiasis and emerging pathogens, and a large
12 empirical therapy study in patients with
13 neutropenia and persistent fever. In addition to
14 the controlled clinical trials, our program
15 included patients treated with compassionate use.
16 These patients are included in our pooled safety
17 database, and some of them are included in some of
18 the efficacy results that Dr. Boucher will be
19 discussing later.

20 In total, over 2000 patients received
21 voriconazole in the clinical program. As I
22 mentioned earlier, our discussion will focus today
23 on the aspergillosis and empirical therapy.

24 [Slide]

25 This slide illustrates the close proximity

1 of voriconazole to fluconazole in its structure.
2 Fluconazole is a well established drug with a very
3 large safety database, however, it is not active
4 against Aspergillus. Our design effort was focused
5 on introducing the broader spectrum against
6 Aspergillus. This was achieved with the
7 introduction of the fluoropyrimidine group here and
8 the methyl group at this location.

9 [Slide]

10 I would now like to turn to the in vitro
11 and in vivo characteristics of voriconazole. The
12 high in vitro potency of voriconazole has been
13 established in numerous published experiments. Dr.
14 Lingroff, from the Medical College of Virginia,
15 recently published an overview of this extensive
16 literature.

17 As a further illustration, I present here
18 the MICs observed in our esophageal candidiasis
19 study for the 546 Candida albicans isolates and the
20 87 non-albicans isolates. The MIC-90 for
21 voriconazole was about 60-100-fold lower than those
22 observed with fluconazole, and was well within the
23 reach of plasma exposure seen in our patient
24 populations.

25 [Slide]

1 Here, the data from this recent collection
2 of clinical isolates are presented graphically with
3 the MICs of fluconazole on a log scale along the X
4 axis and voriconazole susceptibility along the Y
5 axis. As you can see, the relationship between
6 fluconazole and voriconazole susceptibility is
7 linear, however, it is shifted by about two logs if
8 you look here or here, for example.

9 [Slide]

10 Extensive data on the in vitro activity of
11 voriconazole against molds have also been
12 published. Here I present the data on 212
13 *Aspergillus* isolates from the global comparative
14 aspergillosis study. This somewhat difficult to
15 read table is also included in your briefing
16 document.

17 I would just like to point out that across
18 the different *Aspergillus* species are shown MICs of
19 1 or lower for voriconazole. For example, maximal
20 MICs observed for *Aspergillus flavis* is 0.5 and for
21 *Aspergillus nidulans* 1.25, here. Fungicidal
22 concentrations are usually about twice the MIC and
23 so are well within the range of exposure achieved
24 in the majority of our patients for the majority of
25 these isolates.

1 [Slide]

2 To study the in vivo behavior of
3 voriconazole we used the immune compromised guinea
4 pig model as our standard antifungal model. These
5 animals are rendered severely neutropenic by
6 injection of cyclophosphamide, and then are
7 maintained immune compromised by steroid treatment.
8 They are challenged with a fungal load that is
9 sufficient to result in immediate invasive
10 disseminated disease. Outcome is assessed by
11 survival and tissue burden remaining in specific
12 organs. The guinea pig is a well established model
13 for azole activity and the kinetics of voriconazole
14 in this model are similar to those observed in
15 humans.

16 [Slide]

17 As an example of the extensive and
18 published data generated in this model, I have
19 shown here disseminated invasive aspergillosis from
20 experiments conducted in San Antonio and published
21 recently. The fungal burden injected in these
22 experiments was sufficient to kill all animals
23 within five days if untreated. Antifungal therapy
24 was begun 24 hours after inoculation and was
25 continued for five days. All were

1 voriconazole-treated; high dose
2 itraconazole-treated animals survived. The results
3 shown on this slide are fungal burden up to day
4 seven after challenge when the remaining animals
5 were sacrificed. Fungal burden is measured as
6 colony count as mean log 10 CFU expressed per gram
7 of tissue on the Y axis and relevant organs are
8 displayed on the X axis.

9 As you can see, voriconazole, itraconazole
10 and amphotericin B, the fungal agents tested,
11 reduced the fungal burden in all these organs. For
12 voriconazole, in the blue color, and itraconazole,
13 in green, the dose response is also visible. The
14 remaining fungal load at the highest dosages of
15 voriconazole, for example in the liver and in the
16 brain, are very low after treatment, and these
17 organs are important targets for *Aspergillus*
18 infections.

19 [Slide]

20 In summary, we believe that the in vivo
21 data indicate that the high potency and cidality
22 observed in vitro against yeasts and molds
23 respectively translates into an efficacy benefit
24 observed in the severely immune compromised animal
25 model.

1 [Slide]

2 I would now like to turn to the
3 pharmacokinetics of voriconazole. I will discuss
4 the results of our extensive clinical pharmacology
5 program, addressing the topics outlined here. Our
6 goal was to be able to provide specific guidance to
7 prescribers based on this extensive investigation
8 into the pharmacokinetic behavior of voriconazole
9 in healthy volunteers and in patients.

10 Voriconazole is well absorbed and has a
11 high bioavailability of 96 percent. This allows
12 switching between the I.V. and oral formulations,
13 which was allowed in all clinical trials using both
14 formulations. Voriconazole has a high volume of
15 distribution and moderate protein binding,
16 suggesting significant tissue distribution.

17 [Slide]

18 This is illustrated in the top part of
19 this slide, here, where we show the tissue
20 distribution in a male rat five minutes after
21 infusion. You can see, for example, that brain
22 concentrations are about those seen in blood. This
23 is further illustrated by the detection of
24 voriconazole in the cerebrospinal fluids of guinea
25 pigs after multiple dosing, where we observed

1 similar levels in the cerebrospinal fluid to those
2 seen in plasma. We also received samples of
3 cerebrospinal fluids from patients, collected in
4 their routine medical care, where we also detected
5 voriconazole. In autopsy samples of brain, kidney,
6 lung and liver tissue, the levels seen in those
7 tissue samples were consistent with the data in the
8 animals that I showed here.

9 [Slide]

10 Voriconazole is metabolized primarily by
11 cytochrome P450 isoenzymes 2C19 and 2C9 and, to a
12 lesser degree, by 3A4. The isoenzyme 2C19 exhibits
13 genetic polymorphism, with about two percent of the
14 Caucasian population being poor metabolizers.

15 The major circulating metabolite in humans
16 is also the major circulating metabolite in our
17 toxicology species discovered by our preclinical
18 program. In vitro data indicate that this
19 metabolite does not contribute to efficacy.

20 [Slide]

21 The pharmacokinetics of voriconazole are
22 non-linear due to saturation of metabolism.
23 Increasing dose will result in a disproportionate
24 increase in exposure. For example, our
25 pharmacokinetic model predicts an average 2.5-fold

1 increase in exposure for a 1.5-fold increase in
2 dose from, for example, 200 mg to 300 mg.

3 [Slide]

4 Without a loading dose it takes
5 approximately six days to reach steady state. The
6 clinical program used a loading dose regimen of two
7 doses of either 400 mg or 6 mg/kg I.V. twice on the
8 first day and then followed with a maintenance
9 dose.

10 On this slide, here, you can see the
11 concentration time curve for the first day using
12 the 400 mg twice daily oral dosing, loading dose
13 regimen on day one and then the concentration time
14 curve seen on day ten when this treatment is
15 followed with 200 mg twice daily. As you can see,
16 concentrations that are close to those seen in
17 steady state are reached on day one, and we think
18 this is important in acutely life-threatening
19 disease such as invasive aspergillosis.

20 [Slide]

21 We have also investigated factors
22 influencing voriconazole exposure in more than 1000
23 healthy volunteers. We have also analyzed over
24 3000 plasma samples from more than 1000 patients.
25 Within subject variability is low, however, between

1 subject variability is high, with a coefficient of
2 variation close to 100 percent. I will discuss
3 specific factors influencing this between subject
4 variability as listed on this slide.

5 Genotype distribution varies according to
6 race and contributes significantly to the observed
7 variability of voriconazole exposure in healthy
8 volunteers, where we studied this specifically.
9 After accounting for genotype, race did not further
10 contribute to variability in the Phase I
11 population.

12 In patients we did not determine genotype,
13 but subdividing the clinical trial population by
14 race showed a continuous and overlapping
15 distribution of plasma concentrations.
16 Furthermore, there was no difference seen in the
17 safety profile across the various subgroups of our
18 patients. However, I want to point out that the
19 majority of our patients treated were actually
20 Caucasian. Based on the data we have, we do not
21 recommend dose adjustment based on race or
22 genotype.

23 [Slide]

24 We observed higher exposure in female and
25 elderly volunteers in our Phase I program.

1 Analysis of the patient population again showed
2 widely overlapping exposure and no difference in
3 the safety profile. We concluded that no dosage
4 adjustment is needed according to age or gender.

5 [Slide]

6 We also studied the kinetics of
7 voriconazole in children. In a single dose and a
8 multiple dose study including pediatric patients at
9 risk for fungal infections, we observed somewhat
10 higher metabolic capacity in children from two
11 years to under 12 years of age. We, therefore,
12 recommend using the higher maintenance dose of 4
13 mg/kg as the usual dose in this population.

14 [Slide]

15 Body weight has some influence on exposure
16 and when using oral dosing we recommend halving the
17 maintenance dose for patients under 40 kg of
18 weight. This recommendation was also used
19 throughout our Phase III program and resulted in
20 similar exposure in the two groups.

21 [Slide]

22 Because of the hepatic metabolism, hepatic
23 impairment has a major effect on voriconazole
24 exposure. Guided by the results of a multiple dose
25 study in patients with Child's A or B cirrhosis, we

1 recommend halving the maintenance dose in such
2 patients.

3 [Slide]

4 Renal impairment has no effect on
5 voriconazole exposure as such, however, in the I.V.
6 formulation we use a substituted SBECD, as our
7 excipient for the solubilization of voriconazole.
8 The SBECD is excreted exclusively renally and
9 accumulates with renal dysfunction. We, therefore,
10 recommend oral therapy for patients with a serum
11 creatinine over 2.5 mg/dL and, again, this was a
12 recommendation that was used in our clinical
13 program.

14 [Slide]

15 I would now like to turn to drug-drug
16 interactions. These were evaluated in 19 studies
17 with 365 volunteers, assessing the effects of nine
18 drugs on voriconazole and the effects of
19 voriconazole on 11 medications. The resulting data
20 were analyzed with a view to whether voriconazole
21 exposure with that of the concurrent medication
22 would change significantly.

23 From these analyses we concluded that some
24 drugs should be contraindicated; some would require
25 dose adjustment of either voriconazole or the

1 concurrent medication; and for some we could rule
2 out an interaction. I will describe each group of
3 these interactions in turn.

4 Rifampin is contraindicated when using
5 voriconazole as even a dose decrease of
6 voriconazole could not overcome the enzyme
7 induction due to rifampin. This is also predicted
8 to occur with the use of long-acting barbiturates
9 and carbamazepine.

10 The interaction with sirolimus results in
11 an 11-fold increase of exposure to sirolimus and
12 co-administration is, therefore, contraindicated.
13 Concomitant administration of voriconazole with
14 terfenadine and the other medications shown here is
15 contraindicated because increased plasma exposure
16 to these medications could result in Q-T
17 prolongation. Ergot alkaloids are contraindicated
18 as voriconazole is predicted to increase exposure
19 to this concurrent medication significantly.

20 [Slide]

21 Because of enzyme induction, when
22 voriconazole is used concurrently with phenytoin or
23 rifabutin the dose of voriconazole needs to be
24 increased to 5 mg/kg I.V. or 400 mg orally to
25 achieve adequate exposure. For rifabutin toxicity

1 complete blood counts should be monitored, as is
2 routine, and for phenytoin, phenytoin serum
3 concentrations should be monitored, as is also
4 routine.

5 [Slide]

6 Voriconazole acts as a P450 inhibitor and
7 as exposure to the drugs listed on this slide
8 increases, we recommend monitoring of either the
9 plasma level of the concurrent medication or the
10 biologic effect to avoid overexposure to these
11 medications. For some drugs, listed here, the data
12 from our interaction studies provided guidance for
13 dose adjustments of the concurrent medication, as
14 listed. We have included detailed guidance on
15 monitoring and on these dose adjustments in our
16 proposed package insert.

17 [Slide]

18 Voriconazole exposure is not affected by
19 co-administration of 3A4 inhibitors such as
20 erythromycin and indinavir. Similarly,
21 non-specific P450 inhibition with cimetidine has no
22 significant effect on voriconazole exposure. This
23 absence of effect of P450 inhibitors on
24 voriconazole exposure is likely related to the
25 multiple pathways open to the metabolism of

1 voriconazole. Likewise, there was no interaction
2 with drugs not metabolized by the P450 system such
3 as ranitidine, digoxin or mycophenolate. The
4 ranitidine data also indicate that gastric pH has
5 no influence of bioavailability of voriconazole.
6 For the drugs on this slide then, dose adjustment
7 is not necessary for voriconazole or the concurrent
8 medication and no special monitoring is
9 recommended.

10 [Slide]

11 In summary then, the pharmacokinetic
12 behavior of voriconazole is described by rapid and
13 consistent absorption with high bioavailability.
14 The high volume of distribution and high tissue
15 concentrations observed indicate extensive tissue
16 distribution. There is non-linear elimination,
17 primarily by metabolism via the P450 enzyme system.
18 In hepatic cirrhosis this leads to increased
19 exposure, requiring dose adjustment. The metabolic
20 drug interactions are well characterized. Our in
21 vitro data indicate that voriconazole is actually
22 less potent as an inhibitor of the most important
23 cytochrome, 3A4, than itraconazole or ketoconazole
24 for example. The data we have allow us to provide
25 specific guidance on managing the interactions and

1 we, thus, feel that they are manageable in the
2 population targeted for the use of voriconazole.

3 [Slide]

4 Before Dr. Boucher discusses the outcome
5 of our efficacy studies, I want to briefly
6 highlight our rationale for selecting the doses
7 used in the clinical program. In considering dose
8 selection for antifungal agents there are a variety
9 of factors that play a role. I have already
10 highlighted the variability around voriconazole
11 exposure.

12 Other factors of importance include the
13 variability in pathogen susceptibility. Minimum
14 inhibitory concentrations for clinical isolates
15 were mostly well below 0.1 mcg/mL for Candida and
16 other yeasts and below 1 mcg/mL for Aspergillus.
17 However, they vary greatly between different
18 isolates. Lastly, host factors will be of critical
19 importance in this disease. Patients who do not
20 recover their own immune competence generally
21 experience much poorer outcome following fungal
22 infections.

23 [Slide]

24 When deciding on the dose for the clinical
25 studies we considered these factors. Because of

1 the severity of the disease and the extremely poor
2 outcome in patients suffering from invasive fungal
3 infections, as outlined by Dr. Patterson earlier,
4 we intentionally targeted the upper end of the
5 dose-response curve to achieve maximum benefit for
6 patients.

7 We further aimed to reach plasma
8 concentrations that are above MIC for the common
9 pathogens. We would expect this to result in
10 tissue concentrations above MIC as well, and we
11 realize that these are likely to be a more relevant
12 parameter, however, it is much more difficult to
13 measure.

14 [Slide]

15 These considerations led to the regimen as
16 shown on this slide. A loading regimen as an I.V.
17 is 2 doses of 6 mg/kg or orally 400 mg 12 hours
18 apart on the first day. For serious Candida
19 infections and empirical therapy we then recommend
20 a maintenance dose of 3 mg/kg I.V. every 12 hours
21 or 200 mg orally.

22 For the invasive Aspergillus infections
23 and molds, highlighted with MICs as somewhat higher
24 than for yeasts, we recommend an initial
25 maintenance dose of 4 mg/kg I.V. but then also a

1 switch to 200 mg twice daily. Based on the
2 clinical response, investigators were allowed to
3 escalate dose to 4 mg/kg I.V. or 300 mg orally
4 across our program.

5 I will now hand it over to Dr. Helen
6 Boucher, one of the lead clinicians closely
7 involved in the program, to discuss the efficacy
8 results.

9 **Efficacy**

10 DR. BOUCHER: Good morning.

11 [Slide]

12 My name is Helen Boucher, and I am an
13 infectious disease physician for Pfizer Global
14 Research and Development. Thank you for inviting
15 me to present the efficacy data for the
16 voriconazole clinical program.

17 [Slide]

18 As Dr. Baildon mentioned, we conducted an
19 extensive clinical program investigating the
20 efficacy and safety of voriconazole in the
21 treatment of invasive fungal infections.

22 Most of this morning's presentation will
23 be devoted to the results of the comparative
24 controlled trials in acute invasive aspergillosis
25 and empirical therapy. We will also present

1 supportive efficacy data from the non-comparative
2 aspergillosis study, the contemporaneous historical
3 control study, as well as data on the efficacy of
4 voriconazole in the treatment of infections due to
5 emerging pathogens, including *Scedosporium* and
6 *Fusarium* as well as *Candida* infections. This will
7 provide a framework for an in-depth review of the
8 data from our empirical therapy study.

9 [Slide]

10 The global comparative aspergillosis
11 study, a large comparative study in the primary
12 treatment of acute invasive aspergillosis, was
13 completed in April of this year. The goal of this
14 study was to evaluate the efficacy, safety and
15 tolerability of voriconazole compared to
16 conventional amphotericin B in the primary
17 treatment of acute invasive aspergillosis in
18 immunocompromised patients.

19 [Slide]

20 Before discussing the design I will
21 provide some history of this challenging large
22 global trial. The global comparative aspergillosis
23 study began with two identical protocols in 1997,
24 study 602 led by the United States and study 307
25 led by the EORTC in Europe.

1 From early in the development of these
2 protocols there was a prospectively defined
3 umbrella analysis of the combined interim data. In
4 October of 2000, a consensus recommendation was
5 made by the U.S. investigative group, the EORTC and
6 the sponsor to close enrollment in each of the two
7 studies due to changes in medical practice and
8 choice of comparative agents. This recommendation
9 was shared with FDA and the European regulators.

10 [Slide]

11 As I mentioned, the goal of the study was
12 to examine primary therapy for acute invasive
13 aspergillosis in a severely ill patient population.
14 This is shown here in the major inclusion criteria.
15 This was a study of primary therapy. So, prior
16 antifungal therapy was allowed for less than 96
17 hours. Patients were immunocompromised as a result
18 of malignancy, chemotherapy or transplantation.
19 Patients were required to have definite or probable
20 acute invasive aspergillosis based on modified MSG
21 or EORTC criteria. Again, the goal was to examine
22 the efficacy in the treatment of definite or
23 probable acute invasive aspergillosis in
24 immunocompromised patients.

25 [Slide]

1 The statistical plan was developed in
2 order to fully power the study to properly compare
3 the two treatment strategies. A 50 percent
4 response rate was assumed based on prior studies.
5 We intended at least a 90 percent power to exclude
6 a difference of minus 20 percent in success
7 according to the data review assessment at week 12.

8 The sample size estimate assumed a 25
9 percent exclusion in the modified intention to
10 treat population. So, a total sample size of 368
11 patients was required to enroll the necessary 276
12 patients. Patients were stratified using a central
13 randomization system according to three factors,
14 site of infection, underlying disease and
15 neutrophil count.

16 [Slide]

17 A great deal of time was spent on the
18 design of these studies and some of the issues are
19 listed here. High dose amphotericin B has
20 historically been the standard and only treatment
21 indicated for the primary treatment of acute
22 invasive aspergillosis. It is only available in an
23 intravenous formulation and is not well tolerated.

24 Newer therapies, including itraconazole
25 and lipid formulations of amphotericin which have

1 less associated toxicity, while licensed only for
2 salvage therapy, were being used more and more in
3 the treatment of acute invasive aspergillosis. Our
4 investigative groups, thus, developed the concept
5 of following conventional amphotericin B with other
6 licensed antifungal therapy, or OLAT, ultimately
7 allowing the comparison of treatment strategies for
8 voriconazole as a start-up regimen compared to
9 conventional amphotericin B as a start-up regimen.
10 This also provided the ability to assess response
11 at a fixed time point, here, 12 weeks.

12 [Slide]

13 This diagram shows how patients progressed
14 through the study. I would like to take a few
15 moments to discuss details of the study design.
16 All patients initially received their randomized
17 therapy. For voriconazole patients received
18 standard loading doses followed by 4 mg/kg I.V.
19 every 12 hours for at least seven days. They then
20 had the option of oral dosing at 200 mg twice a
21 day.

22 In the conventional amphotericin B arm
23 patients received a minimum dose of 1 mg/kg/day
24 which was to continue for 14 days. Patients could
25 stay on the randomized therapy through the study.

1 Patients also had the option, at the discretion of
2 the investigator, to switch to other licensed
3 antifungal therapies if they developed problems
4 with toxicity or lack of efficacy. For a few
5 patients it was necessary to withdraw from
6 randomized therapy, for example due to withdrawal
7 of consent.

8 [Slide]

9 This diagram shows progress to week 12.
10 Again, the major goal was to ensure that patients
11 could remain on the study for the entire 12 weeks
12 and be followed for as long as possible. So,
13 again, patients could start on randomized therapy
14 and continue through to week 12 on their randomized
15 therapy. For these patients the assessment of
16 response at week 12 is the same as the assessment
17 at the end of randomized therapy.

18 For our patients who switched to other
19 licensed antifungal therapy, they had an assessment
20 of success at the time of the switch on a
21 randomized therapy and continued in the study on
22 their other licensed antifungal therapy through
23 week 12, when they had a second assessment of
24 success at week 12.

25 For the few patients who withdrew from the

1 study, for instance due to withdrawal of consent,
2 they had their assessment of success at the time of
3 withdrawal. Even though these few patients
4 withdrew, we were able to collect survival data
5 through day 84 for all patients.

6 [Slide]

7 This led to the three endpoints in our
8 trial, which are shown here. First, success in a
9 test for non-inferiority at week 12, the primary
10 efficacy endpoint. This allows comparison of the
11 two treatment strategies.

12 Second, success in a test for superiority
13 at the end of randomized therapy. This was
14 intended to allow direct comparison of drug to
15 drug, voriconazole with amphotericin B, and was a
16 secondary efficacy endpoint. Third, survival
17 through day 84 was a secondary efficacy endpoint.

18 [Slide]

19 Because of the nature of the treatment
20 comparison, only an open design was possible.
21 Therefore, we convened a data review committee and
22 used a central randomization system in order to
23 minimize bias. The data review committee was a
24 global effort of leading experts in the field of
25 antifungal therapy and included infectious disease

1 physicians, hematologists, oncologists, as well as
2 radiologists. We understood that much of the
3 assessment of certainty of diagnosis, as well as
4 assessment of outcome, was based on radiology so we
5 had radiologists participate in the data review
6 committee process. The DRC had two subgroups, a
7 U.S. subgroup selected by the sponsor and a
8 European subgroup selected by the EORTC.

9 [Slide]

10 In their review, the data review committee
11 utilized mycology reports, clinical evaluations,
12 investigator responses, as well as digitized
13 radiology studies in a blinded review in order to
14 assess the certainty of infection at baseline, the
15 outcome at the end of randomized therapy, the
16 outcome at week 12 and the cause of death relative
17 to fungal infection in the patients who died.

18 There was a standard operating procedure
19 that involved the exchange of cases between the DRC
20 subgroups in order to ensure consistency. In all,
21 approximately 20 percent of the cases were
22 exchanged. Review was done after the first 37
23 cases were exchanged and resulted in 92 percent
24 major agreement, that is, in success or failure.
25 This process and these results were shared at last

1 year's ICAAC by Dr. Patterson and colleagues.

2 [Slide]

3 Here we see an example of the classic halo
4 sign. As I mentioned, diagnosis, particularly
5 radiographic diagnosis, was an important element of
6 our study design. I would like to review some key
7 criteria before going on to discuss the results.

8 This high resolution chest CT is of a
9 45-year old man with relapse of acute myelogenous
10 leukemia, from our study 602. He was status post
11 allogeneic bone marrow transplantation two months
12 prior to the study and had complications with
13 graft-versus-host disease in the skin and liver.

14 Here we see his CT scan, a nodular
15 infiltrate with the surrounding opacities in the
16 characteristic halo sign. This patient also had a
17 bronchoalveolar lavage positive for *Aspergillus*
18 *fumigatus*. So, he met the criteria for definite
19 acute invasive aspergillosis.

20 This same patient had had a negative BAO
21 or had not had a bronchoalveolar lavage because of
22 his specific host factors, the allogeneic
23 transplantation. He would meet the criteria for
24 probably invasive aspergillosis based on the halo
25 sign.

1 [Slide]

2 I will now present the results of the
3 study.

4 [Slide]

5 This table illustrates some of the
6 challenges in conducting a comparative trial in
7 aspergillosis. As illustrated here, of the 199
8 centers approved to enroll patients, only 95
9 contributed to the 392 patients enrolled over the 4
10 years of the study.

11 [Slide]

12 This chart displays disposition of
13 patients in the global comparative aspergillosis
14 study. And, 392 patients were enrolled and 11
15 received no therapy. For two patients
16 investigators had difficulty in assessing the
17 electronic randomization system and inappropriately
18 allocated patients to voriconazole, leaving 194
19 voriconazole and 85 amphotericin B patients in the
20 intention-to-treat population. For 50 voriconazole
21 and 50 amphotericin B patients the data review
22 committee was unable to confirm the presence of
23 invasive aspergillosis, definite or probable
24 invasive aspergillosis. This leaves 144
25 voriconazole and 133 amphotericin B patients in the

1 modified intention-to-treat population, a primary
2 efficacy population. In all, 277 patients were
3 assessed by the data review committee as having
4 definite or probable invasive aspergillosis. So,
5 the target of the umbrella analysis was achieved.

6 [Slide]

7 Looking at demographic characteristics,
8 this chart shows that patients were well matched
9 according to age, sex and race.

10 [Slide]

11 This table presents the baseline
12 characteristics according to the three
13 stratification factors. As we see at the top, most
14 patients had pulmonary aspergillosis, and 25
15 voriconazole and 21 amphotericin B patients had
16 extrapulmonary aspergillosis.

17 In terms of underlying disease,
18 approximately 25 percent of the patients in each
19 arm had prior allogeneic bone marrow
20 transplantation. This includes 27 voriconazole and
21 20 amphotericin B patients with documented
22 graft-versus-host disease. The majority of our
23 patients fell into this middle category, the
24 patients with autologous transplantation or other
25 underlying neoplasms, in this case mostly leukemia.

1 For the third stratification variable,
2 neutrophil status, patients were well balanced,
3 with 63 and 60 neutropenic patients in each
4 treatment arm. Therefore, patients were well
5 balanced according to each of the three
6 stratification variables.

7 [Slide]

8 Looking at certainty of infection which
9 could not be stratified at randomization as it was
10 established by the data review committee, we see in
11 this table that there were more definite infections
12 on the voriconazole treatment arm and more probable
13 on the amphotericin B arm.

14 Also, there was an imbalance in the
15 individual sub-studies, with more definite
16 infections in the U.S. led study 602, than in the
17 EORTC led study 307.

18 [Slide]

19 Before presenting the results, I would
20 just like to remind you of the three endpoints --
21 success at week 12, success at the end of
22 randomized therapy, and survival through day 84.

23 [Slide]

24 Now I will review the actual progress of
25 our patients over time during the study. This

1 stack-bar chart shows the progress of all the 144
2 patients in the voriconazole arm, the modified
3 intention-to-treat population, primary efficacy
4 population through each of the 84 days of the
5 study.

6 The height of the blue bars represents the
7 number of patients receiving voriconazole as
8 randomized therapy. The median duration of therapy
9 was 77 days. At week 12, 62 patients remained on
10 voriconazole.

11 The bars above the blue bars, these red
12 dotted bars which are a little bit difficult to
13 see, represent the patients receiving other
14 licensed antifungal therapy, those patients who
15 switched during the study. There were 22 patients
16 receiving other licensed antifungal therapy at week
17 12.

18 The green bars represent the patients in
19 the post treatment follow-up period. These are
20 patients who had completed therapy and had a
21 response assessed but were still being followed in
22 the study. There were 13 patients in the follow-up
23 period at week 12.

24 The yellow bars represent those few
25 patients who withdrew from the study, for instance

1 due to withdrawal of consent. There were five
2 patients who had withdrawn at week 12.

3 At the top of the chart, in the grey bars,
4 are the patients who had died, 42 patients died by
5 day 84.

6 [Slide]

7 This stack bar chart shows the progress of
8 all the 133 patients in the modified
9 intention-to-treat population on the amphotericin B
10 arm through each of the 84 days of the study.

11 Looking at initial randomized therapy,
12 here in red -- again, these bars represent our
13 patients receiving amphotericin B and we note a
14 contrast to that seen for voriconazole. On the
15 amphotericin B arm only two patients remained
16 receiving conventional amphotericin B as randomized
17 therapy at week 12. It is important to note that
18 the median daily dose of the amphotericin B was 1
19 mg/kg/day during the first two weeks and the
20 average duration of therapy was 11 days.

21 Again, the red dotted bars represent the
22 patients receiving other licensed antifungal
23 therapy, and there were 57 patients receiving other
24 licensed antifungal therapy at week 12.

25 The green bars represent the patients in

1 the post treatment follow-up period. There were 11
2 by week 12.

3 In the yellow are represented the patients
4 who withdrew from the study and there were seven
5 patients who had withdrawn at week 12.

6 The grey bars at the top represent the
7 patients who had died, and 56 patients had died by
8 day 84.

9 [Slide]

10 I will now present the results in each of
11 the three endpoints, first, addressing success as
12 assessed by the data review committee at week 12, a
13 primary efficacy endpoint.

14 [Slide]

15 This bar chart shows success in each
16 treatment arm, and 52.8 percent of patients
17 initially treated with voriconazole had success as
18 assessed by the data review committee at week 12
19 compared to 31.6 of those initially treated with
20 amphotericin B. This difference is 21.2 percent
21 and 2.8 percent when adjusted for protocol. In
22 both cases 95 percent confidence intervals of the
23 difference do not include zero.

24 [Slide]

25 The chart on the left again displays

1 success in the umbrella analysis. Recall that the
2 treatment difference seen was 21.2 percent.

3 The bars on the right show data review
4 committee assessment of success at week 12 for each
5 individual study. The treatment difference
6 observed in the umbrella analysis is consistent in
7 both the U.S. led study 602 and the EORTC led study
8 307. In both studies the 95 percent confidence
9 interval does not include zero and, therefore, it
10 meets the statistical criteria for superiority.

11 [Slide]

12 I would like to take a minute to look
13 further at data review committee assessed success
14 at week 12, the primary efficacy endpoint according
15 to the stratification factors and certainty of
16 infection.

17 This chart displays the treatment
18 difference along with the associated 95 percent
19 confidence interval in the overall umbrella
20 analysis at the top, and then in our stratification
21 variables. On the right is the success presented
22 in percent.

23 If we look first at site of infection, you
24 see that whether patients had pulmonary or
25 extrapulmonary disease this treatment difference of

1 just over 20 percent is maintained. Among the
2 patients with extrapulmonary aspergillosis were ten
3 patients who had documented CNS infection, five in
4 each treatment arm. Two of the five voriconazole
5 patients had success at week 12, while none of
6 those treated with amphotericin B had success.

7 In terms of underlying disease, whether
8 patients had prior allogeneic transplantation,
9 autologous transplantation of leukemia or other
10 cause of immunocompromise, again we see that the
11 absolute treatment difference of over 20 percent is
12 maintained in each arm.

13 Looking at neutrophil status, we see that
14 whether patients were neutropenic or not
15 neutropenic at baseline the treatment difference
16 was maintained.

17 Turning back to certainty of infection, we
18 note that whether patients had definite
19 aspergillosis or probably invasive aspergillosis
20 that treatment difference was maintained.

21 So to summarize for our primary efficacy
22 endpoint, the data review committee assessed
23 success at week 12 the treatment difference between
24 voriconazole and amphotericin B to be maintained in
25 both individual protocols, three stratification

1 groups, and in patients with definite and probable
2 infection.

3 [Slide]

4 I will now turn to the second efficacy
5 endpoint, success at the end of randomized therapy.
6 Here success was seen in 53.5 percent of
7 voriconazole and 21.8 of amphotericin B patients.
8 Note that the median duration of randomized therapy
9 was 77 days for voriconazole and just 11 days for
10 amphotericin B. This reflects the well-known
11 problems of maintaining patients on conventional
12 amphotericin B due to its associated toxicity.
13 This difference is 31.7 percent and 31.9 percent
14 when adjusted for protocol. In both cases 95
15 percent the confidence interval does not include or
16 cross zero. The results were consistent in each
17 individual substudy.

18 [Slide]

19 The third endpoint was survival through
20 day 84. Recall that survival data was collected
21 for every patient through day 84.

22 [Slide]

23 Looking at deaths as an efficacy endpoint
24 in the modified intention-to-treat population, 71
25 percent of the patients on the voriconazole arm and

1 58 percent of those on the amphotericin B arm
2 survived through day 84. This is an absolute 13
3 percent difference in survival.

4 This Kaplan-Meier plot demonstrates an
5 early separation which is maintained through day 84
6 and the associated hazard ratio of 0.6 and 95
7 percent confidence interval of 0.4 to 0.89.

8 [Slide]

9 As I mentioned earlier, the data review
10 committee was asked to address the cause of death,
11 specifically addressing the impact of Aspergillus
12 for all patients who died while in this study up to
13 day 84. This table shows that more than twice the
14 number of patients treated initially with
15 amphotericin B died due to aspergillosis than did
16 voriconazole patients.

17 [Slide]

18 In summary, this large comparative study
19 demonstrates, both at 12 weeks and end of
20 randomized therapy, that the data review committee
21 assessed success as higher in voriconazole-treated
22 patients than for amphotericin B patients.

23 The treatment difference is maintained
24 whether we look at stratification groups or
25 certainty of infection, and includes success for

1 voriconazole therapy in patients with central
2 nervous system infection, allogeneic bone marrow
3 transplantation and documented graft-versus-host
4 disease. Treatment difference is also maintained
5 for each individual study and the criteria for
6 non-inferiority at week 12 and superiority at the
7 end of randomized therapy are met. We further
8 observed a 13 percent absolute survival benefit at
9 day 84.

10 [Slide]

11 I would now like to return briefly to our
12 other data supporting the use of voriconazole
13 treatment in acute invasive aspergillosis.

14 This table displays outcome in a
15 non-comparative aspergillosis study or earlier
16 European study. In this study success was seen in
17 approximately 50 percent of patients in the
18 intention-to-treat and expert evaluable
19 populations. Here, again, success included
20 patients with central nervous system infections as
21 well as allogeneic transplantation.

22 I would like to draw your attention to
23 this column on the right. These 50 patients from
24 the per protocol population received voriconazole
25 as primary therapy following five days or less of

1 prior antifungal therapy, and this is the group
2 that was used in our contemporaneous historical
3 control study. In this study, these 50 patients
4 from the non-comparative aspergillosis study were
5 matched with patients from U.S. and European
6 centers who were treated during the same time
7 period.

8 [Slide]

9 This chart shows success in the
10 non-comparative aspergillosis study and its
11 historical control. At the top we see that success
12 was seen in 26/50, or 52 percent, of the
13 voriconazole-treated patients in the matched
14 primary population, those 50 that we just saw from
15 the non-comparative study. This is compared to
16 success in 23/92 patients, 25 percent of the
17 patients, from the historical control population.
18 These global response data are actually consistent
19 with what we later saw in the global comparative
20 aspergillosis study.

21 [Slide]

22 In summary then, voriconazole has been
23 used to treat 476 patients with documented invasive
24 aspergillosis from our clinical program, most of
25 whom were severely immunocompromised and critically

1 ill. We saw superior efficacy and a survival
2 benefit in our large comparative study. This was
3 consistent with what was seen in our earlier
4 non-comparative aspergillosis study which compared
5 favorably with the historical control study.

6 [Slide]

7 Before presenting the efficacy data in
8 empirical therapy I would like to briefly highlight
9 other areas of therapy with voriconazole, first in
10 the treatment of emerging pathogens.

11 [Slide]

12 Infections due to the more rare fungal
13 pathogens, such as *Scedosporium* and *Fusarium*, are
14 increasingly recognized, especially in the era of
15 the increased use of non-myeloablative
16 transplantation and solid organ transplantation.
17 These organisms are poorly susceptible to available
18 antifungal agents, as shown on the MIC table drawn
19 from the medical literature.

20 Clinically, these infections are
21 associated with high morbidity and mortality. For
22 *Scedosporium*, mortality reaches 87 percent in the
23 published literature. For *Fusarium*, attributable
24 mortality approaches 80 percent and is largely
25 dependent on the recovery of neutrophil function.

1 [Slide]

2 Across our clinical program we have
3 treated a total of 35 patients with infections due
4 to Scedosporium. Success was seen in 16/27
5 patients with Scedosporium apiospermum. This
6 includes patients with S. abortia. As expected,
7 success was less, seen in two of eight patients
8 with Scedosporium prolificans. For Scedosporium,
9 successes include patients with central nervous
10 system infection as well as disseminated and
11 pulmonary infections. In the patients with central
12 nervous system infection, these 13 patients at the
13 top, it is important to note that 10 of these 13
14 patients received voriconazole for greater than 90
15 days and several of our successes here included
16 children.

17 [Slide]

18 In Fusarium, a total of 15 patients from
19 across our clinical program have been treated with
20 voriconazole and six of these 15 had success while
21 on voriconazole therapy. In Fusarium success was
22 seen in patients with eye, sinus, skin and
23 disseminated infections.

24 [Slide]

25 Turning now to Candida infections,

1 voriconazole has been studied in esophageal
2 candidiasis as well as in patients with invasive
3 Candida infections.

4 [Slide]

5 This chart shows success in our
6 comparative, double-blind, double-dummy study of
7 oral voriconazole versus oral fluconazole in the
8 treatment of endoscopically and mycologically
9 proven esophageal candidiasis. The study was
10 conducted in Europe predominantly.

11 As shown here, endoscopic success was seen
12 in 98.3 percent of voriconazole and 95 percent of
13 fluconazole-treated patients. The difference is
14 3.2 percent and the lower limit of the 95 percent
15 confidence interval is minus 1.08, which falls well
16 within the prespecified minus 15 percent limit.
17 Endoscopic successes in this study included
18 patients with advanced AIDS as defined by CD4
19 counts of less than 50.

20 I would also like to note here that the
21 side effects seen with voriconazole therapy in this
22 study are consistent with those of other azoles but
23 were seen more frequently in the voriconazole
24 treatment arm. Dr. Baildon will discuss this in
25 greater detail during his safety presentation.

1 [Slide]

2 This table shows success in patients with
3 non-esophageal Candida infections who received
4 voriconazole as salvage therapy following greater
5 than five days of prior systemic antifungal
6 therapy. This group includes patients enrolled in
7 clinical trials as well as those from our
8 compassionate use program.

9 In this salvage population success was
10 seen in 22.43 or 51 percent of the patients.
11 Importantly, most of these patients, 36 as shown
12 here in the top row, received voriconazole
13 following documented efficacy failure to prior
14 antifungal therapy. This includes 26 patients who
15 had received prior fluconazole. Successes here
16 also include patients with infections due to
17 non-albicans species.

18 [Slide]

19 In summary, voriconazole has demonstrated
20 efficacy in treating Candida infections.
21 Voriconazole was equivalent to fluconazole in
22 endoscopically and mycologically proven esophageal
23 candidiasis. We have seen reassuring efficacy in
24 cases of patients with invasive Candida infections,
25 particularly in those who failed other therapies

1 including fluconazole, as well as infections due to
2 non-albicans species. This confirms our earlier in
3 vitro and in vivo work where we see potency in
4 clinical isolates and efficacy in standard animal
5 models of disseminated candidiasis, including
6 published studies of disseminated *Candida krusei*.

7 Our comparative study of voriconazole in
8 the primary treatment of candidemia in
9 non-neutropenic patients, study 608, is ongoing.
10 As of this week, 256 of our targeted 426 patients
11 have enrolled in that study.

12 [Slide]

13 Having presented the data on
14 voriconazole's efficacy in treating documented
15 infections due to yeast and mold, I would now like
16 to turn to a discussion of empirical therapy.

17 [Slide]

18 The practice of empirical antifungal
19 therapy is based on historical data from Dr. Pizzo,
20 in the EORTC, who demonstrated that treatment
21 intervention with conventional amphotericin B
22 reduced the number of documented breakthrough
23 invasive fungal infections. More recently,
24 comparative study MSG32 showed that liposomal
25 amphotericin B was as effective as conventional

1 amphotericin B in a composite endpoint and formed
2 the basis for our study.

3 [Slide]

4 We conducted a large randomized study in
5 73 international centers in collaboration with the
6 mycosis study group. The primary goal was to
7 evaluate the efficacy of voriconazole compared to
8 liposomal amphotericin B in a composite endpoint.

9 In this endpoint success required meeting
10 each of the five criteria listed here: no
11 documented breakthrough of invasive fungal
12 infections during therapy or for seven days
13 following end of therapy; survival for seven days
14 following the end of therapy; no premature
15 discontinuation of therapy due to toxicity or lack
16 of efficacy; sustained defervescence for 48 hours
17 prior to the recovery from neutropenia; and a
18 successful response to treatment of any diagnosed
19 baseline invasive fungal infections.

20 [Slide]

21 Patients were required to have persistent
22 fever and neutropenia in the setting of 96 hours or
23 parenteral empirical antibiotics. In this study an
24 additional criterion was that patients had to have
25 an absolute neutrophil count of less than 250 in

1 the 24 hours prior to randomization.

2 [Slide]

3 The statistical plan was developed to
4 compare the two treatments in a previously
5 published composite endpoint. The statistical
6 calculations assumed a 50 percent response rate
7 based on the prior study, MSG32. Our intention was
8 to have at least 80 percent power to exclude a
9 difference in success in the composite endpoint of
10 minus 10 percent. The sample size estimate assumed
11 a 10 percent exclusion. So a total sample size of
12 866 patients was necessary to enroll 786 patients
13 in the modified intention-to-treat population.

14 [Slide]

15 Patients were stratified at randomization
16 by a central randomization system, first according
17 to risk of developing invasive fungal infection.
18 High risk patients include those with allogeneic
19 transplantation or relapsed leukemia. Moderate
20 risk patients are those with newly diagnosed
21 leukemia, autologous transplantation or other
22 underlying neoplasm. Patients were also stratified
23 according to the presence or absence of prior
24 systemic antifungal prophylaxis.

25 [Slide]

1 A blinded data review committee reviewed
2 all potential invasive fungal infections. Our
3 experts included infectious disease specialists as
4 well as hematologists and oncologists. They used
5 mycology and radiology reports, clinical
6 assessments and investigator responses in order to
7 assess the presence of infection; the type of
8 infection, baseline versus breakthrough; the
9 certainty of infection; as well as the global
10 response at the end of therapy, and a standard
11 operating procedure was followed when assessing all
12 cases.

13 [Slide]

14 Now I will present the results from our
15 empirical therapy study.

16 [Slide]

17 As shown here, a total of 871 patients
18 were randomized; 22 patients did not receive
19 therapy, leaving 421 voriconazole and 428 liposomal
20 amphotericin B patients in this safety population.
21 An additional 12 patients, six in each arm, did not
22 have sufficient information available to confirm
23 the investigator's assessment. We, therefore, have
24 415 voriconazole and 422 liposomal amphotericin B
25 patients in the modified intention-to-treat

1 population, a primary efficacy population. In all,
2 837 patients made up the modified
3 intention-to-treat population so the target of 786
4 was achieved.

5 [Slide]

6 Looking at demographics, patients were
7 well matched according to age, sex and race.

8 [Slide]

9 Patients were also well matched according
10 to stratification factors. Of note, seen in the
11 middle row of the table, over 50 percent of
12 patients in each arm received prior systemic
13 antifungal prophylaxis, mostly with fluconazole.
14 This is more than seen in prior studies. Also,
15 approximately 50 percent of patients in each arm
16 underwent bone marrow transplantation, including 18
17 percent in each arm who had allogeneic
18 transplantation.

19 [Slide]

20 Median duration of therapy was seven days
21 in each arm. Importantly, 91 voriconazole patients
22 were able to receive oral therapy in addition to
23 their intravenous therapy.

24 [Slide]

25 This table displays the results in our

1 primary efficacy analysis, success in the composite
2 endpoint. Twenty-six percent of the voriconazole
3 and 31 percent of liposomal amphotericin B patients
4 had success. The difference is minus 4.5 percent,
5 and the lower limit of the 95 percent confidence
6 interval is minus 10.6 percent. This is outside
7 the prespecified minus 10 percent limit.

8 When these results are adjusted for the
9 risk of developing fungal infections, the presence
10 or absence of systemic antifungal prophylaxis and
11 the duration of neutropenia at baseline, success is
12 seen, here at the bottom, in 23.7 percent of
13 voriconazole and 30.1 percent of liposomal
14 amphotericin B patients. In this stratified
15 analysis, the primary efficacy analysis, the
16 difference is minus 6.1 percent and, again, the
17 lower limit of the 95 percent confidence interval
18 is minus 12 percent which is outside the
19 prespecified minus 10 percent.

20 [Slide]

21 I would now like to present the results in
22 each of the five components of the primary efficacy
23 endpoint, first examining breakthrough fungal
24 infections.

25 [Slide]

1 Eight voriconazole and 21 liposomal
2 amphotericin B patients developed breakthrough
3 invasive fungal infections. These were definite or
4 probable invasive fungal infections as assessed by
5 the blinded data review committee and diagnosed
6 greater than 24 hours following the first dose of
7 study drug.

8 [Slide]

9 Here we see a breakdown of these fungal
10 infections and I would like to spend a moment on
11 these. First and most notably at the top, while
12 four voriconazole patients developed breakthrough
13 pulmonary aspergillosis, 13 liposomal amphotericin
14 B patients developed breakthrough aspergillosis,
15 nine involving the lungs; two involving the
16 sinuses; one involving the CNS and skin and another
17 which was disseminated.

18 Two voriconazole patients developed
19 breakthrough Candida infections while six liposomal
20 amphotericin B patients developed breakthrough
21 candidemia. While two voriconazole patients
22 developed infections due to Zygomycetes, two
23 liposomal amphotericin B patients developed
24 infections due to dematiaceous molds.

25 [Slide]

1 Turning to survival, this criterion
2 required survival for at least seven days following
3 the end of therapy. Thirty-three voriconazole and
4 25 liposomal amphotericin B patients died within
5 seven days of the end of therapy.

6 [Slide]

7 This table lists the investigator reported
8 cause of death for all patients who died. I would
9 just like to note that the number of causes is
10 greater than the number of patients as
11 investigators frequently listed more than one cause
12 of death per patient.

13 In the voriconazole arm more patients died
14 due to progression of malignancy, sepsis and
15 pneumonia. In the liposomal amphotericin B arm
16 patients died due to progression of malignancy,
17 sepsis and hemorrhage.

18 [Slide]

19 Looking at discontinuation from study
20 medication due to toxicity or lack of efficacy
21 prior to recovery from neutropenia, we see on this
22 table 41 voriconazole and 28 liposomal amphotericin
23 B patients discontinued prematurely.

24 [Slide]

25 There was no difference between treatment

1 arms in discontinuation due to toxicity, as you see
2 in the top row, with 19 voriconazole and 23
3 liposomal amphotericin B patients discontinuing due
4 to toxicity. It is important to note that this
5 endpoint included patients who permanently
6 discontinued only. It does not include the seven
7 voriconazole and 52 liposomal amphotericin B
8 patients who discontinued temporarily or had dose
9 reductions during therapy.

10 [Slide]

11 On the other hand, there was a difference
12 in discontinuation due to lack of efficacy in this
13 open-label study, with 22 voriconazole versus five
14 liposomal amphotericin B patients discontinuing due
15 to lack of efficacy. This difference is primarily
16 due to more patients, 14, discontinuing due to
17 fever alone. These included three patients with
18 bacterial infections; one with TTP; and two with no
19 documented fever.

20 [Slide]

21 The fourth component of the primary
22 endpoint was defervescence during neutropenia.
23 Success here required having a temperature of less
24 than 38 for 48 hours prior to recovery from
25 neutropenia.

1 [Slide]

2 Here we see the number of patients who met
3 the defervescence criterion. Thirty-three percent
4 of voriconazole and 36 percent of liposomal
5 amphotericin B patients met this criterion. This
6 is less than expected and may be related to the
7 shorter than expected duration of neutropenia seen
8 during our study. The median time to recovery from
9 neutropenia after randomization was 4.8 days in the
10 voriconazole arm and 5.4 days in the liposomal
11 amphotericin B arm. This is less than that seen
12 for liposomal amphotericin B, 8 days, in the prior
13 MSG32 study. So, in our study there was less time
14 during the study in which to defervesce.

15 [Slide]

16 The last component of the endpoint is
17 success in treatment of any diagnosed baseline
18 invasive fungal infections, those diagnosed within
19 24 hours of randomization.

20 [Slide]

21 This table shows that six of 13
22 voriconazole and four of six liposomal amphotericin
23 B patients had success following treatment of
24 baseline fungal infections.

25 [Slide]

1 Returning then to our composite endpoint,
2 this graph shows overall success at the top,
3 expressed in treatment difference with the
4 associated 95 percent confidence intervals. In
5 both the raw and stratified analysis the lower
6 limit extends beyond the prespecified minus 10
7 percent limit. This overall lower than expected
8 success, approximately 30 percent rather than the
9 expected 50 percent, is driven mostly by the
10 failure to defervesce.

11 However, if we look at one clinically
12 important secondary endpoint, the breakthrough of
13 invasive fungal infections, we see that
14 voriconazole was associated with greater success
15 here. On the other hand, the survival and
16 premature discontinuation data trend in the other
17 direction. We learn that the deaths were more
18 often due to progression of underlying disease, not
19 fungal infections. Further, they occurred among
20 the patients at moderate risk for developing
21 invasive fungal infections.

22 [Slide]

23 This led us back to reexamine our
24 stratification factors. When we look at
25 breakthrough fungal infections according to risk we

1 see that the prevention of breakthrough fungal
2 infections was enhanced in the high risk strata,
3 those at high risk of developing invasive fungal
4 infections, allogeneic transplants and relapsed
5 leukemia patients.

6 Here we see, just to recall, that eight
7 voriconazole and 21 liposomal amphotericin B
8 patients developed breakthrough invasive fungal
9 infections. In the high risk group, shown here at
10 the top, 1.4 percent of voriconazole and 9.2
11 percent of liposomal amphotericin B patients
12 developed breakthrough invasive fungal infections.
13 Among these, one voriconazole and nine liposomal
14 amphotericin B patients had received prior
15 prophylaxis, mostly with fluconazole. So, again,
16 in this clinically important parameter prevention
17 of breakthrough of invasive fungal infections
18 voriconazole provided protection in the patients at
19 high risk.

20 [Slide]

21 Looking at overall efficacy in our
22 composite according to risk, in this unadjusted
23 subgroup analysis the results for overall success
24 in the high risk group are within the prespecified
25 minus 10 percent bounds.

1 [Slide]

2 This graph again displays outcome for
3 overall success at the top and for each of our five
4 components in the high risk group, in yellow, and
5 the moderate risk group, in blue. These results
6 are unadjusted for the other stratification
7 variables.

8 This table shows that the results are
9 consistent in the high risk group stratum and
10 suggest that voriconazole's empirical therapy may
11 be associated with benefits in this population.

12 [Slide]

13 Turning briefly to toxicity, infusions
14 were prospectively monitored with daily bedside
15 infusion work sheets. This table shows several
16 infusion-related reactions of interest in each
17 treatment arm shown in the order of voriconazole
18 frequency. In the voriconazole arm abnormal
19 vision, an adverse event frequently associated with
20 voriconazole, was seen in 22 percent of patients
21 during infusion. This will be discussed in greater
22 detail by Dr. Baildon during his safety
23 presentation.

24 In the liposomal amphotericin B arm we saw
25 the expected infusion-related reactions of chills

1 and fever. We also saw some unexpected reactions
2 including wheezing, tachypnea, chest pain and
3 anaphylactoid reactions in a syndrome of acute
4 infusion-related reactions that will be presented
5 at ICAAC in December.

6 [Slide]

7 In conclusion, voriconazole has
8 demonstrated superior efficacy and a survival
9 benefit in the treatment of documented acute
10 invasive aspergillosis, including high risk
11 patients with prior allogeneic transplantation,
12 central nervous system disease, as well as
13 documented graft-versus-host disease.

14 We have also seen efficacy against
15 infections due to emerging pathogens, including
16 *Scedosporium* and *Fusarium*, as well as efficacy in
17 *Candida* infections. These data suggest that
18 voriconazole is an appropriate option for empirical
19 antifungal therapy in patients with persistent
20 fever and neutropenia, particularly those at high
21 risk.

22 Thank you very much, and Dr. Baildon will
23 now continue with the safety presentation.

24 **Safety and Conclusions**

25 DR. BAILDON: I would now like to turn to

1 the safety and provide an overview of the
2 investigations into the safety profile of
3 voriconazole as experienced in over 3000 healthy
4 volunteers and patients.

5 [Slide]

6 Therapeutic studies of voriconazole
7 included 1493 patients, mainly drawn from the large
8 comparative trials that you have seen in Dr.
9 Boucher's presentation. Including compassionate
10 patients, this provides an overall pooled
11 population of 2090 patients. The numbers shown
12 here for the comparative studies are the safety
13 patient population in these trials, including all
14 patients who received study drug.

15 [Slide]

16 We also have experience in 443 healthy
17 volunteers who received only voriconazole,
18 comparing that to placebo. This excludes the Phase
19 I volunteers treated in drug interactions and
20 various special populations.

21 [Slide]

22 The 172-year exposure seen in the
23 therapeutic trial population allows us to
24 characterize the voriconazole safety profile. Many
25 of the compassionate patients included in the

1 pooled population were treated for a long time, and
2 we have experience now of more than 500 patients
3 treated for longer than 12 weeks. Thirty-eight
4 patients in total have received voriconazole for
5 more than one year.

6 [Slide]

7 In considering the safety profile in the
8 population, I would like to highlight that this is
9 a very ill patient population, frequently severely
10 immunocompromised and undergoing many invasive
11 procedures such as, for example, bone marrow
12 transplant as well as receiving many concurrent
13 medications. The serious illness of these
14 patients, the absence of a placebo control and the
15 many concurrent medications make it more difficult
16 to decipher what adverse events could be
17 attributable to voriconazole as compared to those
18 being related to some other medications received.

19 [Slide]

20 I will discuss the frequency of death and
21 discontinuations, and then turn to adverse events
22 as observed in the safety population. We have
23 carefully evaluated the emerging safety profile
24 throughout the development and have also
25 investigated any other special issues arising, and

1 I will address some of these as well.

2 [Slide]

3 The severe nature of the underlying
4 illness in the patients studied is also illustrated
5 by the mortality observed. On this slide deaths
6 reported to 30 days post last dose are shown.
7 There was no difference between the treatment
8 groups in the esophageal candidiasis study, at the
9 bottom of the slide, and Dr. Boucher already
10 discussed the results of the empirical therapy
11 study where more deaths occurred in the
12 voriconazole arm. However, these were mostly
13 related to progression of the underlying leukemia
14 in these patients.

15 In the global comparative aspergillosis
16 study treatment duration of initial randomized
17 therapy varied greatly. So, the numbers on this
18 slide reflect the variable length of follow-up and
19 a Kaplan-Meier presentation is actually more
20 informative.

21 [Slide]

22 When discussing the results of the global
23 comparative aspergillosis study, Dr. Boucher
24 outlined the observed mortality difference in the
25 modified intent-to-treat population. This slide

1 illustrates the same presentation for the safety
2 population of all patients treated with either
3 voriconazole or amphotericin B and then followed
4 for 84 days.

5 As you can see, the difference in the
6 safety population is of similar magnitude as in the
7 modified intention-to-treat population, with an
8 early separation of the curves that is maintained
9 out to day 84.

10 [Slide]

11 The overall rate of discontinuations for
12 safety reasons of 18 percent in the therapeutic
13 studies is low in the context of this patient
14 setting. There were more discontinuations in the
15 voriconazole group compared to fluconazole in our
16 esophageal candidiasis study, and the most common
17 reason for discontinuation here was hepatic enzyme
18 elevation.

19 In the global comparative aspergillosis
20 study, however, more patients had to discontinue
21 amphotericin B therapy than voriconazole therapy,
22 and there the discontinuations were mostly related
23 to renal function in the amphotericin B-treated
24 patients. Please note that in this comparison I am
25 comparing the two drugs as initial randomized

1 therapy only.

2 [Slide]

3 Because of the difficulty in deciphering
4 the safety profile of voriconazole in the
5 background of this severely ill patient population,
6 we have also carefully analyzed the adverse events
7 seen in healthy volunteers who received
8 voriconazole versus those receiving placebo.

9 Of the adverse events shown on this table,
10 visual adverse events are the most prominent
11 adverse event and were reported by 35 percent of
12 volunteers on a background of 12 percent in the
13 placebo group.

14 [Slide]

15 This slide shows adverse events sorted by
16 frequency on the voriconazole arm as observed in
17 the global comparative aspergillosis study. In
18 this presentation I am comparing all events on the
19 voriconazole initial randomized therapy arm with
20 those seen on amphotericin B, followed by other
21 licensed antifungal therapy. This results in a
22 more comparable treatment exposure of around 1200
23 days in both populations.

24 Again, visual adverse events are the most
25 common and occur more frequently on voriconazole

1 than on the comparator arm. Nausea, vomiting and
2 diarrhea occurred more frequently in the patients
3 treated with amphotericin B or other licensed
4 antifungal agents.

5 [Slide]

6 Turning to the ten most frequent adverse
7 events in the empirical therapy study, it provides
8 a similar picture. The frequency of abnormal
9 vision seen in voriconazole-treated patients was 26
10 percent and chills were more frequent among the
11 patients treated with liposomal amphotericin B.

12 [Slide]

13 In the double-blind esophageal candidiasis
14 study abnormal vision was also reported as the most
15 frequent adverse event in the voriconazole arm.
16 Increases in alkaline phosphatase and other hepatic
17 enzymes were also more common and, as I highlighted
18 previously, resulted in more discontinuations in
19 the study on voriconazole.

20 [Slide]

21 I would like now to turn to the special
22 safety topics of visual disturbances, hepatic
23 adverse events and skin reactions. As I mentioned
24 before, we also investigated the other topics
25 listed here.

1 [Slide]

2 The frequency of abnormal vision is
3 constant across the clinical trial population and
4 in health volunteers, around 25-35 percent. This
5 is also seen in the large comparator studies.
6 Visual disturbances occasionally lead to
7 discontinuations, however, this is a rare
8 consequence.

9 [Slide]

10 The descriptions patients provide when
11 asked what they are experiencing are enhanced
12 perception of light, blurred vision, photophobia or
13 changes in color perception. The top category
14 shown here is the most frequently encountered one.

15 [Slide]

16 The visual adverse events occur early on
17 in treatment, and this slide depicts time to
18 occurrence of the first event reported in patients.
19 As you can see, after the first week rarely are new
20 events reported by the patients. Each individual
21 event also occurs early on during therapy, usually
22 within the first half hour after initiation of
23 infusion, and typically lasts about 30 minutes.

24 [Slide]

25 We have conducted extensive investigations

1 into the mechanisms of these events, and identified
2 reproducible changes in the electroretinogram of
3 healthy volunteers. This indicates that the site
4 of action is in the retina. To analyze
5 reversibility of this underlying
6 electrophysiological phenomenon for the visual
7 disturbances, we conducted a multiple dose visual
8 function study in healthy volunteers, as shown
9 here.

10 This study used the high maintenance dose
11 of 300 mg twice daily and volunteers received this
12 dose for 28 days. Electroretinograms and other
13 visual function tests were performed as outlined.

14 The electrophysiological results are
15 summarized here and in my next slide. The Y axis
16 depicts a negative amplitude of the a-wave after
17 white stimulus, scotopic conditions. The a-wave
18 measures photoreceptor activity. The presentation
19 is of the range of values encountered, with a 25th
20 and 76th percentile and the median as the line.
21 The continuous line joins the means of each group.

22 As you can see, for the placebo patients
23 there is basically no change throughout the
24 treatment period up to day 29 and follow-up at day
25 43. For the voriconazole-treated patients there is

1 an immediate decrease in amplitude at initiation of
2 treatment, which is maintained throughout treatment
3 and then reverts to normal 2 weeks later.

4 [Slide]

5 This slide illustrates the effect on the
6 b-wave amplitude, again measured with white
7 stimulus and scotopic conditions. The b-wave
8 measures the activity of the inner nuclear layer of
9 the retina. As you can see again, there is no
10 change in the placebo-treated patients and on
11 voriconazole there is an immediate decrease of
12 amplitude on day one that is maintained throughout
13 treatment and then reverts back to normal two weeks
14 after discontinuation.

15 [Slide]

16 Visual acuity in this study also showed no
17 difference between voriconazole-treated volunteers
18 and those receiving placebo. Color vision and
19 visual field tests suggest an impact of
20 voriconazole on these, however, these also returned
21 to normal after discontinuation.

22 [Slide]

23 In the esophageal candidiasis study, where
24 patients were more ambulatory, we also evaluated
25 visual function at baseline and at follow-up.

1 Again as you can see, there is no difference
2 between the treatment groups on visual acuity.
3 Fundoscopy results in the patients also indicate no
4 difference in changes between voriconazole and
5 comparator treatment treated patients.

6 [Slide]

7 In our 24-month carcinogenicity rat study
8 the decrease in the cell number of the peripheral
9 retina was observed in female rats when compared to
10 the control group. This difference was not
11 observed in the central retina, nor was it observed
12 in male rats.

13 In dogs, where we have been able to
14 replicate the electrophysiological phenomenon, as I
15 showed you in human volunteers, we saw no changes
16 in the histopathology of the dog retinas or the
17 visual pathways after 12-month of high dose
18 treatment.

19 Our assessment of the visual disturbances
20 is that these are functional changes during therapy
21 without long-term sequelae. The underlying
22 electrophysiological phenomenon is reversible upon
23 discontinuation of treatment after one month of
24 therapy. We suggest including appropriate warnings
25 in the package insert, describing these events and

1 highlighting that patients should avoid activities
2 that could cause problems.

3 [Slide]

4 I would now like to turn to the hepatic
5 adverse events. We consider hepatic enzyme
6 elevations to be dose-limiting to the use of
7 voriconazole.

8 [Slide]

9 In the multiple dose escalation study the
10 usual loading dose of 6 mg/kg twice on the first
11 day was followed by either 3 mg/kg I.V. and then
12 200 mg orally, 4 mg/kg I.V. and then 300 mg orally,
13 or 5 mg/kg I.V. and then 400 mg orally. I.V.
14 treatment was for 5 days and then was switched to
15 oral. One of 7 volunteers at the middle dose group
16 experienced an ALT elevation, whereas 5/14
17 volunteers experienced that in the highest dose
18 group.

19 [Slide]

20 This slide shows the ALT time curve for
21 the 6 volunteers who experienced a rise in ALT.
22 The patient in green, S39, is a patient from the 3
23 mg/kg followed by 300 mg oral dose group. That is
24 the highest dose group we currently recommend. The
25 other colors are for the patients of the highest

1 dose group used in this study. Reassuringly, all
2 these elevations returned to normal within two
3 weeks after the end of dosing, which was on day 14.

4 The results from this study led us to
5 conclude that 4 mg/kg I.V. twice daily and 300 mg
6 orally twice daily are the maximum tolerated
7 dosages for voriconazole.

8 [Slide]

9 In the patient population we used a
10 criterion of ALT elevation of three times the upper
11 limit of normal to indicate clinically relevant
12 abnormality, without regard to baseline. This was
13 observed in about 12 percent of the therapeutic
14 study population. However, when we look at the
15 comparator study, the frequency that occurred was
16 similar when compared to amphotericin B
17 formulations but was somewhat higher when comparing
18 to fluconazole.

19 A conservative algorithm to capture
20 patients who discontinued is used here in counting
21 any patient in this column who discontinued and had
22 this ALT abnormality whether that was a primary
23 reason for discontinuation or not. The percentage
24 of patients discontinuing due to ALT elevations is
25 low.

1 [Slide]

2 This slide uses a similar presentation for
3 abnormal notal bilirubin, using a cut-off of 1.5
4 times the upper limit of normal to indicate
5 clinically relevant abnormality. In this
6 comparison the data comparing voriconazole to
7 amphotericin B formulations or to fluconazole
8 indicate no difference between comparative groups.
9 Again, the percentage of discontinuations due to
10 this is low.

11 [Slide]

12 We also investigated hepatic failures
13 leading to deaths across the program. To date, we
14 have received 26 such reports. Of these, 19
15 patients were treated with voriconazole and seven
16 received amphotericin B formulations. In the
17 comparative trials these patients were equally
18 distributed between the two treatment groups. The
19 global comparative aspergillosis was one comparator
20 and empirical therapy study, five in each arm.

21 We have also asked an independent panel of
22 hepatic experts, under the leadership of Dr.
23 Maddrey who is in the sponsor section today, to
24 review these cases in a blinded fashion. The
25 deliberations of this panel were recently added to

1 our submission. Of the cases, there were four
2 patients treated with voriconazole where either the
3 investigator or the sponsor could not rule out a
4 potential association with study drug and I will
5 discuss these cases in more detail.

6 [Slide]

7 This slides provides the relevant patient
8 details, as well as the most conservative expert
9 assessment of any one of the experts in our panel
10 that we convened.

11 The first patient was treated for five
12 days for overt aspergillosis. He then suffered
an acute hypoglycemic event and voriconazole therapy
was discontinued. On day 44 a liver biopsy was performed
Unfortunately, this resulted in intraperitoneal
hemorrhage and the patient died. The biopsy showed
cirrhosis, and the family later disclosed a history of
alcohol abuse in this patient. The impaired liver
function explains the high exposure observed in this
patient.

The next patient was a 64-year old male with
anemia and sepsis who had failed amphotericin B therapy
for pulmonary aspergillosis. The patient was treated for
19 days and then discontinued because of hepatic enzyme
elevation. The hepatic

1 enzymes returned to normal but the patient
2 continued to deteriorate and died on day 40.

3 The third patient suffered hepatic failure
4 due to graft-versus-host disease after an
5 allogeneic bone marrow transplant and received
6 voriconazole for 34 days. The patient then
7 deteriorated, suffered from CMV pneumonitis and
8 died eight days post last dose.

9 The last patient is the only case for
10 which one of the panel members in the blinded
11 evaluation thought that it could probably be
12 related to study drug, and the study drug was
13 voriconazole in this case. The patient had
14 responded well to voriconazole for central nervous
15 system aspergillosis and was treated for 257 days.
16 She then suffered an acute exacerbation of the
17 underlying systemic lupus erythematosus and this
18 flare involved an elevation of hepatic enzymes.
19 Voriconazole was discontinued because of that
20 hepatic enzyme elevation. The patient, however,
21 continued to deteriorate further and died of
22 hepatic failure and multi-organ failure on day 323,
23 about 60 days after discontinuation of
24 voriconazole.

25 [Slide]

1 From all the data reviewed, the expert
2 panel concluded that while a contribution of
3 voriconazole in some of these events could not be
4 excluded, there are no features that would clearly
5 point to a causal association. Our conclusion
6 around the hepatic effects of voriconazole are that
7 these are manageable for the patient population
8 targeted for treatment. As a consequence of the
9 potential for voriconazole to induce hepatic enzyme
10 elevations, we recommend monitoring liver function,
11 as is routinely done in this patient population.
12 Patients who develop liver function abnormality
13 should be monitored for signs of more severe
14 hepatic injury and voriconazole should be
15 discontinued if these are observed.

16 [Slide]

17 I would now like to turn to skin reactions
18 observed in the clinical program.

19 [Slide]

20 Skin reactions in general and rashes in
21 particular are described by investigators in a
22 number of ways. For example, here is a list taken
23 from our case record forms that would then code to
24 rash in our evaluation, or similarly, at the bottom
25 of the slide, to photosensitivity.

1 [Slide]

2 In each of the comparator studies the
3 frequency of rash amongst the voriconazole-treated
4 patients or amphotericin B formulations or
5 fluconazole was similar across the comparator
6 agents. The high rate seen in the population may
7 reflect the extensive use of drugs such as
8 penicillins and sulfa antibiotics. The patients
9 also frequently received blood products and have
10 underlying conditions such as graft-versus-host
11 disease. Only a low percentage of patients
12 discontinued while experiencing rash. Again, I
13 used a conservative presentation here, any patient
14 discontinuing while experiencing rash.

15 [Slide]

16 Photosensitivity was reported in 41
17 patients in the pooled population. Most of these
18 events occurred in patients treated for long
19 durations in the compassionate program or the
20 extension protocols. None of the patients in the
21 therapeutic trials discontinued with a
22 photosensitivity reaction, and the voriconazole
23 molecule as well as the anoxide metabolite do not
24 absorb UV light at the spectrum where one would
25 expect a photosensitivity reaction. Nevertheless,

1 from the clinical reports received to date we
2 cannot exclude a contribution of voriconazole to
3 these events.

4 We have also received two reports of
5 Stevens-Johnson syndrome. These were not assessed
6 as related to voriconazole treatment by the
7 investigator and both abated during voriconazole
8 treatment.

9 [Slide]

10 Our conclusions then around skin reactions
11 are listed on this slide. While the frequency of
12 rash is similar between voriconazole-treated
13 patients and those receiving fluconazole or
14 amphotericin B formulations, we cannot exclude the
15 photosensitivity potential at the current time. We
16 have included a warning in our proposed package
17 insert describing the data and providing guidance
18 for patient management.

19 [Slide]

20 I would now like to return to the other
21 topics investigated.

22 [Slide]

23 We examined cardiac adverse events because
24 of the sudden death of a patient recruited into the
25 empirical therapy study, which occurred about 30

1 minutes following the first infusion. This death
2 occurred in a 50-year old female patient, with left
3 ventricular dilatation who had recently received
4 idarubicin therapy acute myeloid leukemia. At the
5 time of the first voriconazole infusion the patient
6 was profoundly hypokalemic and had received a
7 potassium infusion as well as a bolus infusion of
8 potassium. During the voriconazole infusion the
9 patient experienced an episode of vomiting. Then,
10 about 20 minutes after the end of the first
11 infusion the patient experienced again nausea,
12 vomiting and diarrhea. The patient was found
13 convulsing shortly after. The cardiologist at the
14 scene observed cardiac arrest with ventricular
15 fibrillation. Resuscitation efforts were,
16 unfortunately, not successful. The autopsy
17 revealed pronounced left ventricular dilatation,
18 and the investigator assessed the conditions as
19 listed as cause of death. The sponsor could not
20 exclude a contribution of voriconazole to these
21 events.

22 [Slide]

23 We then examined the preclinical and
24 clinical program for other signals, including an
25 analysis of QTc intervals. This slide presents the

1 results of three separate experiments investigating
2 the potential for voriconazole and compares with
3 ketoconazole to influence cardiac depolarization.
4 The first is competitive dofetilide binding, which
5 is a sensitive assay we use to look at potential
6 influences on the HERG protein. The second is a
7 patch clamp study on HERG inhibition, shown in the
8 blue triangle curves here. Thirdly, we looked at
9 the effects on action potential as measured in
10 canine Purkinje's fibers.

11 The results of the in vitro tests are
12 reassuring, and ketoconazole differentiates from
13 voriconazole in terms of its effects on HERG
14 inhibition and dofetilide binding at concentrations
15 that would be relevant to those seen in patients.

16 [Slide]

17 We also analyzed ECG data collected from
18 197 participants in several Phase I studies. Using
19 the standard criteria for QT, here corrected using
20 Fridericia's formula, showed no difference from
21 placebo with regard to mean changes and outliers of
22 QTc, presented on this slide. The one occurrence
23 of a QTc greater than 470 msec was in an elderly
24 female volunteer 4 hours post dosing with 6 mg/kg.
25 Her baseline value had actually been 480 msec so

1 there was not much change. There were no
2 volunteers with an absolute QT greater than 500
3 msec. Using Bazett's formula for correction
4 results in very similar results.

5 [Slide]

6 On this slide I have presented all of the
7 QTc data from these volunteers against plasma
8 concentration observed at the time of C-max about 1
9 hour post single dose. Linear regression analysis
10 indicates a shallow slope, ending about here. The
11 results using Bazett's correction formula look very
12 similar to the plot.

13 Also, the results of this extensive
14 examination have thus far revealed no clear signal
15 for voriconazole to cause arrhythmias. We continue
16 our investigation into the potential cardiac
17 effects of voriconazole. In the patient population
18 we have observed at least one plasma concentration
19 being outside of this range in about nine percent
20 of patients. We currently have no QT data for that
21 kind of exposure. For this reason, we are
22 undertaking a Phase I study specifically targeted
23 at measuring QT effects across the full range of
24 exposures seen in the patient population. The
25 first attempt at such a study rises the next

1 special issue I would like to address,
2 anaphylactoid reactions.

3 [Slide]

4 The design of the QT study involved
5 escalating doses of voriconazole administered
6 intravenously to healthy volunteers. We have twice
7 attempted such a study and have stopped because of
8 the four events shown here. The first two in the
9 first trial and the second two in the second.

10 In the first study two female subjects
11 experienced events considered to be anaphylactoid
12 reactions and manifested principally by
13 vasodilatation during their second dosing period.
14 Both infusions were stopped within minutes of
15 starting, and abated with only oxygen with no
16 further therapy administered. In that study, one
17 subject, the first one, had been administered our
18 solubilizing agent, SBECD, whereas the other
19 subject received I.V. voriconazole which also
20 includes SBECD.

21 During the second study, two additional
22 anaphylactoid reactions were observed, again
23 principally vasodilatation, again in two young
24 females. In the first event there was no
25 treatment. Actually, the I.V. infusion continued

1 and the event abated spontaneously. The infusion
2 in that subject was stopped when the second
3 reaction occurred in the second subject. So, both
4 infusions at that time were discontinued. Again,
5 symptoms resolved without any further intervention
6 after about 17 minutes.

7 A full investigation into these events was
8 conducted. The subjects in the second group both
9 received I.V. voriconazole as SBECD. None of our
10 due diligence activities have identified a probable
11 cause for the infusion-related events seen in the
12 Phase I studies.

13 [Slide]

14 The clinical database does contain reports
15 of vasodilatation or flushing at low frequencies.
16 However, as Dr. Boucher had shown you, no
17 anaphylactoid reactions have been reported in our
18 comparative empirical therapy study where infusions
19 were prospectively monitored at the bedside of
20 these patients. The mechanism of the anaphylactoid
21 reactions in healthy female volunteers remains
22 unknown, and we currently intend to include
23 suitable warning statements in the package insert.
24 I just want to highlight that we also still remain
25 committed to the exploration of the potential for

1 acute QTc prolongation with voriconazole across the
2 full range of exposures seen, and we intend to
3 start that study again soon.

4 [Slide]

5 Renal function -- this was investigated
6 because of an observation of renal tubular
7 vacuolization in the preclinical toxicology program
8 using our excipient SBECD. Overall, a link to
9 renal adverse events in the clinical trials with
10 either voriconazole or SBECD is considered
11 unlikely; also monitoring of creatinine levels will
12 be recommended.

13 We investigated sepsis as a result of
14 literature reports of a link between sepsis and the
15 use of azole antifungal agents. In the large
16 comparative studies there was no difference between
17 voriconazole and comparator, neither was there a
18 delay in recovery from neutropenia observed in our
19 empirical therapy study. Overall, we conclude that
20 the voriconazole database does not provide any
21 additional evidence to support the hypothetical
22 link.

23 Hallucinations, also occurring at low
24 frequencies, show an imbalance in reporting
25 frequency, particularly in the empirical therapy