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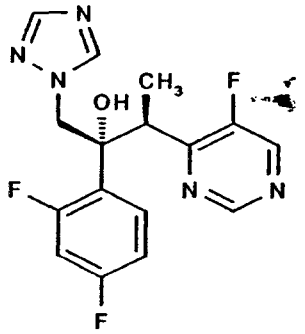
MEDICAL OFFICER

Medical Officer's Review of NDAs 21-266 and 21-267

VFEND (voriconazole)

INDICATION : Empiric Antifungal Therapy in Febrile Neutropenia

IDENTIFYING INFORMATION

NDA Submission number:	21-266 (oral) 21-267 (intravenous)
Applicant:	Pfizer Pharmaceuticals
Address:	
Contact person:	Maureen Garvey
Date of Submission:	November 22, 2000
CDER stamp date:	
Date submission received by reviewer:	February 1, 2001
Date Review Begun:	
Date Review Completed:	
Established name:	voriconazole
Proposed proprietary name	VFEND™
Chemical name:	(2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H* -1,2,4-triazol-1-yl)-2-butanol
Chemical structure:	

Molecular formula:	$C_{16}H_{14}F_3N_5O$
Molecular weight:	349.3
Pharmacologic category:	azole
Dosage form:	film-coated tablets (21-266) injection (white lyophilized powder) (21-267)
Route of administration:	oral (21-266) intravenous (21-267)
Strength	50mg or 200mg tablets (21-266) 200 mg in a 30 ml clear glass vial (21-267)
Related Drugs:	
Regulatory History:	EOP2 meeting February 25, 1998 Pre-NDA meeting July 26, 2000 Pediatric telecon February 5, 2001

Proposed Indications and Usage:

Draft labeling excerpt from INDICATIONS AND USAGE section:

Empirical treatment of presumed fungal infections in febrile immunocompromised patients.

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations on Approvability

The medical officer's recommends the applicant receive a **non-approval** for voriconazole (VFEND) injection and tablets for the indication of empiric antifungal therapy in neutropenic patients. This recommendation is based on two points; 1) the one study submitted by the applicant in support of this indication failed to meet the statistical definition of non-inferiority as specified in the analysis plan, and 2) the applicant has not demonstrated efficacy in invasive candidal infections.

In support of this indication, Pfizer Pharmaceuticals has submitted data from one non-inferiority study (Study 603) of voriconazole compared to liposomal amphotericin B (Ambisome, L-AMB) in patients with neutropenia secondary to cancer chemotherapy. The results of the study showed an overall response rate of 26% (108/415) in the voriconazole group and 30.6% (129/422) in the L-AMB group using a 5 component composite endpoint in a non-stratified analysis. Using this raw data, the difference in the point estimates of the efficacy of the two therapies was -4.5% with a 95% confidence interval of -10.6% to +1.6%. The study was designed to stratify patients by risk of fungal infection and previous use of antifungal prophylaxis. The stratified results, which were the primary endpoints in the analysis plan, yielded an overall response rate using the same composite endpoint of 23.7% in the voriconazole group and 30.1% in the L-AMB group. The difference in the point estimates of the two therapies in the stratified analysis was –6.08% with a 95% confidence interval of –12.0% to –0.1%. The pre-specified lower bound of the 95% confidence interval used to define non-inferiority in this trial was –10%. Thus, in both the raw and stratified analyses, voriconazole did not meet the statistical definition of non-inferiority.

Two other drugs, liposomal amphotericin B for injection (Ambisome) and itraconazole injection and oral solution (Sporanox), have been FDA-approved for the indication of empiric therapy of fungal infections in febrile neutropenic patients. The licensing studies for these drugs had slight differences in patient populations and study definitions such as fever and neutropenia compared to Study 603. However, the studies in febrile neutropenic patients with both Ambisome and Sporanox used a similar composite endpoint as that used in Study 603. Both the Ambisome and Sporanox trials resulted in higher cure rates than the current study and both trials met their pre-specified statistical definitions of non-inferiority.

Prior to approval for empiric antifungal therapy in febrile neutropenic patients, a drug should have demonstrated efficacy against the most common pathogens in neutropenic hosts, namely *Aspergillus* and *Candida* species. The applicant has demonstrated efficacy in invasive aspergillosis, but the data in invasive candidiasis are still outstanding.

B. Recommendation for Further Studies

Subset analyses in a trial that fails the primary endpoint can be used to generate hypotheses for further studies. Although voriconazole failed to meet the primary endpoint in study 603, subset analyses did show a potential benefit in prevention of documented breakthrough fungal infections in high-risk neutropenic patients. Therefore, the medical officer recommends that the applicant conduct a further study in the indication of empiric antifungal therapy in neutropenic patients. Pfizer could perform such a study in patients at high risk for developing fungal infections, using the same definition of high risk as in Study 603 (see Efficacy Section below). This future study could utilize breakthrough infections as the primary endpoint. The analysis plan of the study should specify that patients who die or discontinue therapy would be considered failures of empiric therapy, as these patients may have either died of occult invasive fungal infections or potentially

gone on to develop breakthrough fungal infections if they had remained in the study. The applicant could use only the intravenous formulation of voriconazole in such a study. This would allow blinding of study therapy and eliminate problems with potential bias in ascertainment of outcomes and drug related adverse events, which may complicated the analysis of the non-blinded Study 603.

As stated above, although the applicant has demonstrated efficacy in invasive aspergillosis, the data in invasive candidiasis is still outstanding. The applicant could present the data from Study 608 in invasive candidiasis in support of the indication of empiric antifungal therapy in neutropenic patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Voriconazole is an antifungal compound that is a member of the triazole class. Pfizer is studying both the oral and intravenous formulations of voriconazole. The injectable form is a mixture of voriconazole with a cyclodextran to make voriconazole more water-soluble.

Pfizer conducted studies for voriconazole under INDs —— (intravenous formulation) and —— (oral formulation). Most of the Phase 2/3 trials of voriconazole used both the oral and intravenous form of the drug.

Pfizer is seeking approval of both the oral and intravenous formulations of voriconazole as empirical therapy of presumed fungal infections in febrile immunocompromised patients, for treatment of invasive aspergillosis, and for treatment of serious *Candida* infections, including esophageal and systemic candidiasis. The clinical trial for invasive candidiasis is still ongoing. Pfizer is seeking approval for treatment of serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp and for treatment of serious fungal infections in patients intolerant of, or refractory to, other therapies.

For invasive aspergillosis, Pfizer submitted one global comparative aspergillosis study comparing voriconazole to other licensed antifungal therapy (Study 307/602), as well as a non-comparative study (Study 304) and a historically controlled study (Study 1003). For candidiasis, the applicant submitted a randomized double-blind study comparing voriconazole with fluconazole in esophageal candidiasis (Study 305) and pooled efficacy data across other studies. Pfizer submitted an interim report for a randomized, open-label study comparing voriconazole to amphotericin B in patients with candidemia (Study 608). Approximately 10% of the total expected number of patients had been enrolled in this trial as of the November 2000 submission of the NDA. For *Scedosporium* and *Fusarium* infections and other rare and refractory fungal infections Pfizer provided pooled data across open label non-comparative studies (309 and 604). For the indication of empiric therapy of febrile neutropenia, Pfizer provided data from one comparative

study (603). There were 1493 patients enrolled in voriconazole therapeutic trials and a total of 2090 patients in total when considering non-comparative trials as well.

B. Efficacy

Pfizer performed one clinical trial (Study 603) in the indication of empiric antifungal therapy in neutropenic patients. Study 603 was designed as a prospective, centrally randomized, open label, comparative (non-inferiority), multicenter study. The applicant conducted the study from March 7, 1998 through September 9, 1999 at centers in the United States and Canada. Eligible subjects were male or female patients 12 years of age or older with neutropenia induced by cancer chemotherapy or bone marrow/ peripheral stem cell transplantation. Subjects had at least 96 hours of neutropenia (defined as a neutrophil count of <500 cells/mm^3 and <250 cells /mm^3 in the 24 hours preceding randomization), temperature of $\geq 38°C$, and at least 96 hours of systemic empirical antibacterial therapy prior to randomization. Subjects were randomized to receive either voriconazole or L-AMB in a 1:1 ratio. Randomization was stratified according to risk of fungal infection and previous systemic anti-fungal prophylaxis. The study defined high-risk patients as those with allogeneic transplants or relapsed leukemia.

This study was not blinded due to the differences in the physical natures of the intravenous formulations of voriconazole and L-AMB and the lack of a suitable oral formulation of L-AMB as reasons for conducting this as an open label trial. The absence of blinding in this trial could introduce potential bias. The toxicities of amphotericin B related products, both renal insufficiency and infusion related events, is well known and clinicians may have been more likely to discontinue therapy in patients receiving L-AMB. On the other hand, the efficacy of amphotericin B and related products has been well-established over years of use and clinicians may have been more likely to discontinue therapy with a new agent if they are concerned about it's efficacy.

Although the administration of study drug was not blinded, a blinded data review committee (DRC) evaluated all subjects with diagnoses of documented baseline and/or breakthrough deeply invasive fungal infections (DIFIs). Reviewers in the DRC were not provided with information on treatment allocation or dosage.

Subjects who were randomized to voriconazole received an intravenous loading dose of 6mg/kg q12h for the first two doses followed by 3mg/kg IV bid for a minimum of three days. After three days of intravenous voriconazole, further empirical treatment could be given using oral voriconazole (200mg bid for subjects $\geq$40 kg, 100mg bid for subjects $<$40 kg). Empirical oral therapy (or continued empirical intravenous therapy) was administered for a maximum of up to three days after recovery from neutropenia (RFN). Subjects diagnosed with baseline or breakthrough DIFI could receive a maximum of 12 weeks of therapy.

L-AMB was administered via intravenous infusion at a dose of 3mg/kg/day, the FDA approved dose for this indication. The protocol specified that L-AMB be infused at a

maximum rate of 3mg/kg per hour (i.e. at least 1 hour for a 3mg/kg dose, at least 2 hours for a 6mg/kg dose) if administered through a peripheral vein. Subjects randomized to L-AMB were treated with L-AMB until up to three days after RFN, or resolution of baseline or breakthrough DIFI for a maximum of 12 weeks of therapy, whichever came first.

The dosage of either treatment could be increased or decreased based on criteria specified in the protocol.

Investigators assessed the overall response to empirical therapy for patients without baseline of breakthrough DIFIs at least seven days after the last dose of study medication. There was no end of treatment (EOT) study assessment for subjects without baseline or breakthrough infections (the empirical therapy only group). The time point for assessment of the overall response for subjects with baseline or breakthrough documented DIFI was at least seven days after the last dose of study medication.

The primary endpoint for this study was the composite variable denoted as overall response. Investigators categorized the overall response as ***SUCCESS*** if <u>all</u> of the following five criteria were met (regardless of whether subjects were treated empirically or for a baseline DIFI):

1) Survival for at least seven days after discontinuation of study medication

2) Absence of breakthrough fungal infection during the period of neutropenia and for at least seven days after discontinuation of study medication

3) Defervescence during the period of neutropenia or prior to EOT, whichever occurred first

4) No discontinuation from randomized study medication due to toxicity or lack of efficacy prior to recovery from neutropenia

5) For subjects with baseline fungal infections only: global response assessed as complete or partial at EOT

Investigators categorized the overall response as ***FAILURE*** if <u>any one</u> of the following criteria was met:

1) Death within seven days after discontinuation of study medication

2) Documentation of breakthrough fungal infection during the period of neutropenia or within seven days after discontinuation of study medication

3) Persistent fever during the period of neutropenia or prior to EOT, whichever occurred first

4) Discontinuation of randomized study medication due to toxicity or lack of efficacy prior to recovery from neutropenia

5) For subjects with baseline fungal infections only: Global Response assessed as Stable or Failure at EOT

The definitions of the various components of the overall response to therapy as defined by the applicant were as follows:

- Recovery from neutropenia was defined as ANC >250 cells/mm^3.
- Time to recovery from neutropenia was defined as the date and time of the first sample with an ANC result of >250 cells/mm^3.
- Defervescence (resolution of fever) during neutropenia was defined as all temperatures of <38.0°C or 100.4°F (excluding those taken within one hour after the infusion of pyrogenic agents) for a continuous period of at least 48 hours preceding recovery from neutropenia (absolute neutrophil count >250 cells/mm^3).
- Time to defervescence was defined as the time from the first dose of study medication until the first time the oral temperature (or equivalent) measured <38.0°C or 100.4°F.
- Baseline infection was defined as any deeply invasive fungal infection that is diagnosed based on results of tests performed at baseline or up to 24 hours after study entry fungal infection.
- Breakthrough infection was defined as any deeply invasive fungal infection diagnosed based on results of tests performed from 24 hours after study entry up to seven days after discontinuation of study medication.

The primary analysis population for this study was the Modified Intent to Treat population (MITT) defined as all patients who had received as least one dose of the stud drug and who had sufficient clinical information available to confirm the investigator's assessment of overall response.

The overall response rate was 26% (108/415) in the voriconazole group and 30.6% (129/422) in the L-AMB group using a composite endpoint in a non-stratified analysis. The difference in the point estimates of the efficacy of the two therapies was -4.5% with a 95% confidence interval of -10.6% to +1.6%. The stratified results yielded an overall response rate using the same composite endpoint of 23.7% in the voriconazole group and 30.1% in the L-AMB group. The difference in the point estimates of the two therapies in the stratified analysis was –6.08% with a 95% confidence interval of –12.0% to –0.1%. The pre-specified lower bound of the 95% confidence interval used to define non-inferiority in this trial was –10%. Thus, in both the raw and stratified analyses, voriconazole did not meet the statistical definition of non-inferiority.

When a study does not meet the primary endpoint, one can attempt to explain that failure by looking at secondary and subset analyses. Pfizer presented subset analyses for each part of the 5 component endpoint in Study 603. The subset analysis looking at breakthrough infections showed a trend in favor of fewer breakthrough infections in the voriconazole arm (1.9%[8/415] for voriconazole and 5.0% [21/422] for L-AMB). However, the other 4 subset analyses trended in favor of L-AMB. There were more deaths in the voriconazole arm (8.0% [33/415 for voriconazole versus 5.9%[25/422] for L-AMB). There were more discontinuations in the voriconazole arm (9.9% [41/415] for voriconazole versus 6.6% [28/422] for L-AMB). There were fewer patients in the voriconazole arm who met the protocol definition of defervescence prior to recovery

from neutropenia (32.5% [135/415] for voriconazole and 36.5% [154/422] for L-AMB). Finally, the success rate in baseline infections was less in the voriconazole group (46%[6/13] for voriconazole versus 67% [4/6] for L-AMB) although the numbers in each group were quite small.

Several factors may account for the lower than expected overall success rate in Study 603. The applicant calculated the sample size for this trial based on expected success rate of approximately 50%, based on the success rates in the trial of empiric therapy of febrile neutropenic patients used to obtain FDA approval for Ambisome when compared to conventional amphotericin B deoxycholate (AMB-D). The lower than expected cure rates could have been one reason for the failure of voriconazole to meet the statistical definition of non-inferiority in this trial.

The main reason for failure in this trial was that many patients did not meet the protocol-specified definition for absence of fever prior to resolution of neutropenia. Only 33% (135/415) of voriconazole treated patients and 36%(154/422) of L-AMB treated patients fulfilled this criteria. This is lower than the rate of resolution of fever in previous trials of empiric antifungal therapy of febrile neutropenic patients with itraconazole compared to AMB-D or L-AMB compared to AMB-D. Part of the reason for the high numbers of failures in this part of the composite endpoint may be a more stringent criteria used to define defervescence in this trial. In Study 603, a patient was required to be afebrile for no less than 48 hours prior to recovery of neutropenia to have a successful outcome. In a previous trial of itraconazole versus AMB-D, their was no time requirement attached to resolution of fever i.e. a patient could be afebrile for less than 48 hours prior to recovery from neutropenia and still fulfill the criteria for a successful outcome. An FDA analysis applying the less restrictive definitions of resolution of fever to the data from Study 603 did result in an increase in the cure rate in both arms of the study (50.1% for voriconazole versus 56.2% for L-AMB). However, the difference in point estimates (-6.1%) between voriconazole and L-AMB still remained and voriconazole still did not meet the statistical definition of non-inferiority (95% CI –13.1%, 0.9%).

Another reason for the lower than expected rate of patients becoming afebrile prior to recovery of neutropenia was that the duration of neutropenia after randomization to study drug was shorter in this trial compared to previous trials. This may reflect changes in clinical practice in oncology. In the trial of itraconazole vs. AMB-D and the trial of L-AMB versus AMB-D, the median duration of neutropenia after randomization was approximately 10 days in both the test and control arms of these trials. In Study 603, the median duration of neutropenia after randomization to study drug was 5.5 days in each treatment arm.

C. Safety

In the indication of empiric antifungal therapy in febrile neutropenic patients, many patients may receive therapy who in fact do not have a fungal infection. This is due to the inadequacies of current methods in diagnosing invasive fungal infections. A drug for

empiric antifungal therapy in this population should posses a good safety profile as patients who do not have occult fungal infections will receive no benefit from therapy but still be subject to potential toxicities.

Dr. Rosemary Tiernan presents the overall analysis of safety for voriconazole in the Integrated Summary of Safety Review. This section of the Executive Summary will present highlights from Study 603 that are relevant to the indication of empiric antifungal therapy in neutropenic patients.

There were 421 patients and 428 patients in the safety population for voriconazole and L-AMB respectively. All patients who received at least one dose of study drug were included in the safety population.

Study 603 utilized a composite endpoint that included deaths and discontinuations due to toxicity or lack of efficacy as part of the primary endpoint. Therefore, the data on deaths and discontinuations are presented in the section on efficacy above. To summarize, there were more deaths in the voriconazole arm of the trial. Overall, there were more discontinuations in the voriconazole arm of the trial as well. In evaluating the reasons for discontinuation from the study, there were more discontinuations due to toxicity in the L-AMB arm (4.6% [19/415] for voriconazole versus 5.5% [32/422] for L-AMB), but more discontinuations due to lack of efficacy in the voriconazole arm (5.3% [22/415] for voriconazole versus 1.2% [5/422] for L-AMB). An analysis of the discontinuations is complicated by the non-blinded nature of the study.

The most concerning adverse events in the voriconazole studies as a whole were visual disturbances, rash, hepatic abnormalities, cardiac issues and drug interactions. In study 603, the incidence of abnormal vision (all causality) in the voriconazole group was 26.1% (110/421) versus 4.9% in the L-AMB group (21/428). Rash (all causality) was equally common in both groups, occurring in 22.8% (96/421) of voriconazole treated patients compared to 24.5% (105/428) L-AMB treated patients. There was one case of anaphylactoid reaction in the voriconazole group compared to 10 such cases in the L-AMB group. The incidence of abnormal liver tests was similar in both arm of Study 603 (see Safety section of this review for more details) with the exception of a slightly higher rate of alkaline phosphatase abnormalities in the L-AMB group (3.2% [10/137] and 4.3% [14/426] for voriconazole and L-AMB respectively). There were two cases of heart arrest attributed to study drug in the voriconazole group. One death occurred due to presumed cardiac arrhythmia and the investigator and sponsor concluded that this was possibly related to voriconazole. This patient is discussed in more detail in Dr. Tiernan's overall review of safety.

Vasodilatation was more common in the L-AMB group (5.9% [25/421] for voriconazole and 13.6% [58/428] for L-AMB). Fewer voriconazole subjects discontinued due to treatment related infusion related reactions compared to L-AMB subjects (2.1% ([9/421] and 20/428 [4.7%], respectively) or had dose reduced or temporarily discontinued due to treatment related infusion related reactions (1.2% [5/421] and 7.7% [33/428] respectively).

A unique finding in Study 603 compared to the voriconazole database as a whole was the incidence of hallucinations. Hallucinations occurred in 13.3% (56/421) of voriconazole treated subjects and 4.2% (18/428) L-AMB treated subjects. Many of these patients were on concomitant medication that could have caused hallucinations (e.g. opiates). Most of the cases of hallucinations were mild to moderate in severity.

There were no major differences in the incidence of renal insufficiency in either arm of the trial. In the voriconazole group, 16.4% (57/348) of subjects went from a normal to abnormal blood urea nitrogen compared to 20.5% (73/356) in the L-AMB group. There were similar numbers of patients in each arm whose serum creatinine concentrations became abnormal over the course of the study (8.6% [33/384] for voriconazole and 9.8% [37/376] for L-AMB).

In summary, voriconazole appears to have fewer infusional related adverse events than L-AMB. Renal toxicity in this trial was similar in the two arms. The incidence of visual disturbances was higher in the voriconazole arm of the trial. Although the safety profile of voriconazole appears comparable to L-AMB, approval of the drug should await further clarification of the efficacy of voriconazole in empiric therapy of febrile neutropenic patients.

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Marc Cavaille Coll
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6/12/02 10:50:04 AM
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NDA	21266 and 21267
Applicant:	Pfizer Global Research & Development
Drug:	Voriconazole (Intravenous Injection and Oral Tablets)
Study Reviewed:	Study 608

REVIEW OF INTERIM STUDY REPORT

Medical Reviewer:	Rosemary Johann-Liang, M.D.
Finish Date:	September 5, 2001
Team Leader Concurrence:	September 10, 2001 (Rigoberto Roca, M.D.)

PROTOCOL 150-608: A Randomized, Open Label, Comparative Multicenter Study of Voriconazole Versus Conventional Amphotericin B Followed by Fluconazole in the Treatment of Candidemia in Non-Neutropenic Subjects

SUMMARY

This document reviews the interim report on the above protocol submitted by the applicant on November 2000 as part of NDA 21266. The interim report presented the results of an administrative interim analysis for the regulatory submission, descriptively summarizing data after approximately 10% of the total number of subjects to be enrolled had completed the study. Forty-five subjects in voriconazole arm and 22 in amphotericin B-to-fluconazole arm were treated after 2:1 ratio randomization. Baseline characteristincs in the 2 arms were similar. Thirty-one (69%) in voriconazole arm and 15 (68%) in amphotericin B-to-fluconazole were evaluated for efficacy by modified intent to treat analysis. The outcome assessment at 12 weeks follow-up was comparable between the two arms with 41.9% cure for voriconazole treated subjects and 40% for amphotericin B-to-fluconazole treated. The voriconazole arm had a poorer safety profile than amphotericin B-to-fluconazole. There were 8 discontinuations from the study in the voriconazole arm due to adverse events versus none in the amphotericin B-to-fluconazole arm. The concerning safety issues were liver function test elevations, visual symptoms, and a patient with blistering rash.

COMMENT / RECOMMENDATION

In this interim analysis of voriconazole for the treatment of candidemia in non-neutropenic patients, the safety risk concerns outweigh the comparable efficacy results when compared to amphotericin B-to-fluconazole exposure. Continued monitoring is needed for safety issues (especially in regards to liver, vision, and skin) as the protocol proceeds forward. The interim results reviewed do not favorably add to the safety profile of completed voriconazole trials seeking candida treatment indications.

PROTOCOL SPECIFICS

Objectives

Primary: To compare the efficacy and safety of voriconazole and amphotericin B followed by fluconazole (amphotericin B→fluconazole) in the treatment of candidemia in non-neutropenic patients.

Secondary: To examine the health-care resource utilization in subjects treated with voriconazole as compared to amphotericin B→fluconazole. To examine the population pharmacokinetics of voriconazole.

Study Design

This is an open-label, comparative, multicenter, randomized study to compare voriconazole and conventional amphotericin B followed by fluconazole in the treatment of non-neutropenic subjects with candidemia. Randomization is 2 (voriconazole):1 (amphotericin B-to-fluconazole) ratio. Subjects received the study treatment for at least two weeks following the complete resolution of all clinical findings of an active infection or at least two weeks after the last positive culture was collected, whichever was later. The total maximum duration of therapy for the two treatment arms was to be eight weeks.

Inclusion Criteria Subjects were required to have had a diagnosis of Candida or Torulopsis infection, based on blood cultures within 96 hours of study entry, and clinical evidence of infection within 48 hours prior to study entry.

Drug Administration Intravenous voriconazole was administered at a loading dose of 6mg/kg Q12 hrs for the first 24 hours, with a maintenance dose thereafter of 3mg/kg Q12 hrs. The maximum rate of infusion was 3mg/kg/h. Oral voriconazole treatment was initiated at 200mg BID (or 100 mg BID for subjects weighing less than 40kg). For subjects who failed to demonstrate prompt improvement, the voriconazole dose could be escalated to 4mg/kg Q12 hrs for the IV formulation and 300mg BID for the oral formulation (or to 150 mg BID for subjects weighing less than 40 kg). Subjects whose doses were escalated but who were unable to tolerate the increased dose could be considered for dose reduction. Voriconazole was administered intravenously for a minimum of three days. Amphotericin B was to be administered at a minimum average daily dose of 0.7mg/kg. Amphotericin B was to be administered for a minimim of three days and a maximum of seven days. Subjects who could not tolerate amphotericin B or had baseline isolates that, based upon the available data, were thought to be more appropriately treated by extended amphotericin B therapy or fluconazole therapy beginning earlier than Day 4 were permitted to deviate from this regimen.

Study Evaluations

Clinical (Blood pressure, pulse, temperature, signs and symptoms of infection) assessment were made by the investigator daily during therapy, at the end of therapy (EOT), as well as at two, six, and 12 weeks following EOT.

Mycological (blood cultures, other cultures, histopathology) assessments were as follows. Blood cultures were performed on Days 1 through 4, and Day 7, at EOT, two weeks following EOT, and if clinically indicated, at 6 and 12 weeks following EOT. Histopathology was performed if clinically indicated.

Imaging tests (i.e. Radiographic, sonographic, MRI) were also conducted if clinically indicated.

Safety monitoring Adverse events, including serious adverse events, were recorded on the Case Report Form (CRF) at each evaluation during therapy and the 12 week follow-up period. Clinical laboratory tests were performed twice weekly during therapy, at EOT, and at the two-week follow-up evaluation. Visual acuity and visual fields data were collected at EOT and the six-week follow-up evaluation. Dilated funduscopic examinations were performed at Day 7, at the two-week and six-week follow-up evaluations, and if clinically indicated, at the 12-week follow-up evaluation. In addition, serious adverse events occurring between the time of randomization and the last follow-up visit required by the protocol or 30 days following EOT, whichever was later, were required to be reported to the sponsor by telephone.

Data Review Committee (DRC) In addition to the investigator's assessment, a DRC assessed each completed subject's response to antifungal therapy. To make the assessment, the DRC was provided with a blinded, monitored, and corrected copy of the CRF of each subject as well as other relevant documentation. The possible classifications were cured, improved, failed, indeterminate, withdrew from study, relapsed, or not a study subject. Subjects with a DRC assessment of cured or improved at the 12-week follow-up visit were cured or improved in the primary analysis; all other subjects were considered to have failed.

Methods of Analysis

The primary efficacy endpoint was derived from the DRC assessment of each subject's response to antifungal therapy as follows. Subjects with a DRC assessment of cured or improved at the 12-week follow-up visit were cured or improved in the analysis; all other subjects were considered to have failed.

The sponsor clearly states that this data represents an administrative interim analysis for the regulatory submission, summarizing data after approximately 10% of the total number of subjects to be enrolled had completed the study. No formal statistical analyses were carried out. The primary efficacy endpoint analysis is summarized descriptively only.

Safety analysis included subjects who had received at least one dose of the study medication and, in addition, had either completed the study by the data collection cut-off date (September 20, 1999) or had a baseline visit and had their data in-house by that date. Efficacy analysis (modified intent-to-treat: MITT) included only patients who based on the study design could have completed the study by the cut-off date (so efficacy cut-off date became May 30, 1999). To be included in the MITT analysis, subjects were required to have 1) a positive blood culture of a *Candida* or *Torulopsis spp.* Within 96 hours prior to study entry; 2) have received at least one dose of randomized study medication; and 3) have not previously participated in this study.

MO Comment: *The need for efficacious and safe antifungal medications to treat very ill patients with systemic candidal infections is present since resistance and toxicity concerns regarding current available therapies continue to trouble us. This study attempts to examine the test drug against the current standard of initial therapy for systemic candidiasis, i.e. Amphotericin B intravenously followed by fluconazole orally. The test drug, voriconazole, is proposed to be particularly attractive due to it's activity against resistant strains and the*

convenience of switching from intravenous formulation to oral drug. I like the design of this study and the comparison of these two arms in a randomized fashion. The problem is that it is an open-label study. This can introduce bias when reporting clinical efficacy and adverse events. The independent assessment by a DRC group is a good practice when evaluating results from complicated patients with fungal infection. The proposed methods of efficacy analysis and safety monitoring are adequate.

STUDY SUBJECTS AND TREATMENT

Table 1 (below) summarizes the subject disposition by treatment group for the 10 % interim analysis. One randomized patient (to voriconazole) did not receive any study treatment and was therefore not included in any analyses.

Table 1: Study Evaluation Groups

Study Evaluation Group	Voriconazole	Amphotericin B-to-fluconazole
Randomized to Treatment	N = 46	N = 22
Treated	N = 45	N = 22
Completed Study	N = 15 (33%)	N = 8 (36%)
Discontinued from Study	N = 27 (60%)	N = 11 (50%)
Ongoing	N = 3	N = 3
Evaluated for Efficacy (MITT)	N = 31 (69%)	N = 15 (68%)

Table 2 (below) summarizes the baseline patient characteristics. The subjects in the voriconazole treatment group were on average slightly older and heavier. There was a higher proportion of white subjects in the voriconazole group (77.8%) than in the amphotericin B-to-fluconazole group (54.5%). Half of the patients in both treatment groups had surgery as their predisposing factor to candidemia with the majority of surgeries being abdominal surgery. Abdominal surgeries included procedures such as emergency laporatomy for gunshot wound, drainage of infected pancreatic cyst, and Whipple procedure. Some non-abdominal surgeries were tumor mass removals from lung, neck, and rectum, kidney drainage, and wound debridement. Non-surgical diagnoses included pneumonia, pancreatitis, endocarditis, urosepsis, and others. Two subjects in the voriconazole treated group did not have candidemia based upon blood culture results prior to initiation of treatment. The most common fungal pathogen isolated from blood of subjects in both treatment groups within 96 hours prior to study entry was *C. albicans*. More *C. glabrata* was isolated from the amphotericin B-to-fluconazole group while more *C. parasilosis* was cultured from the voriconazole treated group.

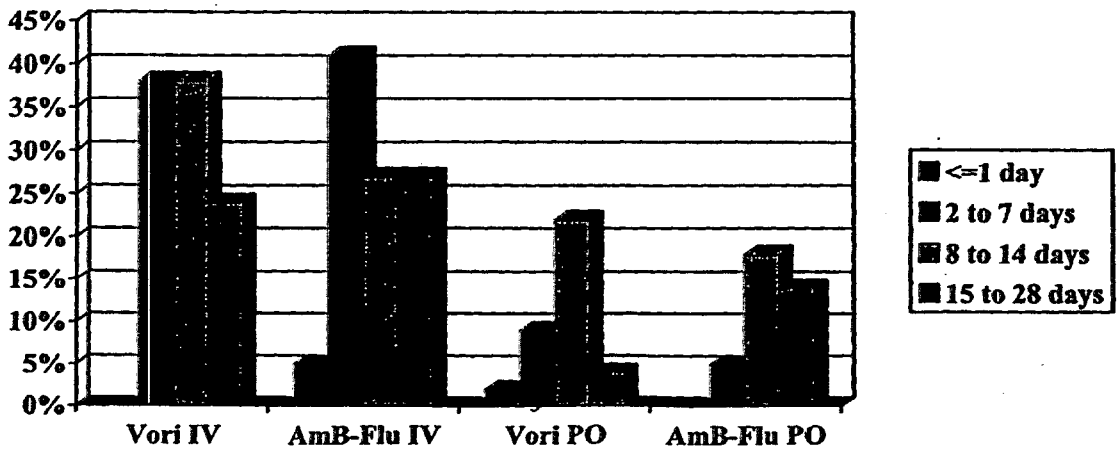
Subjects in the two treatment groups were roughly comparable with respect to rate of past and present diseases/syndromes. Present diseases/syndromes that differed in frequency by more than 20% between treatment groups were "neurotic/personality/nonpsychotic mental disorders" at 40% for Voriconazole versus 13.6% for amphotericin B-to-fluconazole, "other diseases of intestines and peritoneum" at 28.9% for voriconazole versus 4.5 % for amphotericin B-to-fluconazole, and "noninfectious enteritis and colitis" at 31.8 % amphotericin B-to-fluconazole verses 8.9% for voriconazole.

Table 2: Baseline Study Subject Characteristics

Baseline Subject Characteristics	Voriconazole (N=45)	Amphotericin B-to-fluconazole (N=22)
Mean Age (range)	55.3 years (26-85)	49.8 years (16-79)
Gender	26 males / 19 females	10 males /12 females
Race	35 W / 9 B / 1 Other	12 W / 6 B / 1 A / 3 O
Mean Weight (range)	73.8 kg (35 – 128.8)	67.5 kg (41 – 130)
Predisposing factor		
Abdominal surgery	N = 14 (31%)	N = 9 (41%)
Non-abdominal surgery	N = 7 (16%)	N = 2 (9%)
Non-surgical	N = 24 (53%)	N = 11 (50%)
Pretreatment Isolated Fungus		
C. albicans	N = 21 (46.7%)	N = 13 (59.1%)
C. glabrata	N = 3 (6.7%)	N = 5 (22.7%)
C. tropicalis	N = 7 (15.6%)	N = 3 (13.6%)
C. parasilopsis	N = 9 (20%)	N = 1 (4.5%)
C. pelliculosa	N = 1 (2.2%)	N = 0
Hansenula anomola	N = 1 (2.2%)	N = 0
Neg. blood cx for Candida spp.	N = 3 (6.7%)	N = 0
Medical History		
Past diseases/symptoms	N = 36 (80%)	N = 18 (81.8%)
Present diseases/symptoms	N = 45 (100%)	N = 21 (95.5%)

The duration of therapy of subjects in both treatment groups are shown in Figure 1 (below). The mean duration in days ± SD (range) for voriconazole group was 10 days ± 5 (3 –22) for IV therapy and 9 days ± 5 (1 – 15) for oral therapy. The mean duration in days ± SD (range) for amphotericin B-to-fluconazole group was 9 ± 6 (1-21) for IV and 13 ± 6 (5 – 22) for oral therapy. It is notable that 28 (62%) subjects remained on IV voriconazole for the total duration of treatment. On the other hand, only five (23%) subjects remained on amphotericin B and did not switch to fluconazole. In other words, this study does not compare IV voriconazole head to head with IV Amphotericin B in duration of treatment.

Figure 1: Number of patients (shown by percent of total treated in each group) receiving IV or PO therapy by duration ranges in days.



All subjects in both treatment groups received at least one concomitant medication during the study. Antibacterial drugs were the most common concomitant medications administered to subjects (100% of subjects in both treatment groups). The next most common concominant medications/therapy taken were electrolyte/water replacement (87% for voriconazole and 86% for amphotericin B-to-fluconazole), hypnotics/sedatives/anxiolytics (71% for voriconazole and 73% for amphotericin B-to-fluconazole), analgesics (82% for voriconazole and 86% for amphotericin B-to-fluconazole), ulcer-healing drugs (76% for voriconazole and 73% for amphotericin B-to-fluconazole), anticoagulants (69% for voriconazole and 68% for amphotericin B-to-fluconazole), and blood preparations (67% for voriconazole and 55% for amphotericin B-to-fluconazole).

MO Comment: *We are comparing very small numbers of patients from the two arms at this juncture. Nevertheless, the baseline patient characteristics for this small group of patients were roughly similar between the two treatment arms. One issues is worthy to note. There were no C. krusei isolated at all in both arms and only 3 isolates for C. glabrata in the voriconazole arm. The sponsor's view that voriconazole is superior in efficacy over fluconazole for resistant candidal isolates cannot be tested when the isolates are not available for comparison. We hope that as this study progresses more sizable numbers of subjects with different candidal isolates will be studied.*

EFFICACY EVALUATION

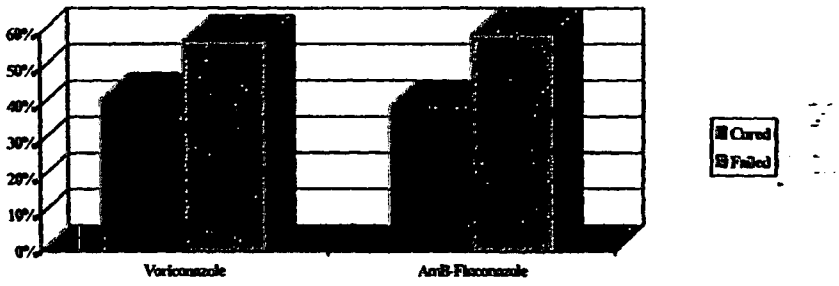
The sponsors state that no formal statistical analysis were carried out since this interim report represents a descriptive summary of data after 10% of the subjects to be enrolled had completed study. Nevertheless, for the purposes of fair comparison between the two treatment groups, MITT population was used as described previously. Table 3 (below) summarizes the reasons for exclusion from MITT analysis and the efficacy outcome at 12 week follow-up evaluation.

Table 3: Efficacy Evaluation Groups

Subject Evaluation Groups	Voriconazole	Amphotericin B-to-fluconazole
Treated patients	N = 45	N = 22
Excluded from MITT	N = 14	N = 7
Entered study post-efficacy cut-off	N = 11	N = 6
No positive blood culture	N = 3	N = 0
No DRC assessment	N = 0	N = 1
Included in MITT analysis	N = 31	N = 15
CURED outcome at 12 wk f/u	N = 13	N = 6
FAILED outcome at 12 wk f/u	N = 18	N = 9

The results of the MITT analysis show that the responses to antifungal therapy in the two treatment groups were equivalent. Figure 2 (below) depicts the 12 week outcome of 41.9% of voriconazole subjects and 40% of amphotericin B-to-fluconazole subjects classified as cured by the DRC's assessment.

Figure 2: Outcome assessment at Twelve weeks follow-up



The sponsor states that the difference between the cure rates reported here and those in other studies of non-neutropenic subjects with candidemia are attributable to the more conservative outcome criteria used in the current study.

MO Comment: It is noted that this interim efficacy analysis is descriptive only. Given that, the modified intent-to-treat analysis that the sponsor uses to give the cure response comparison appears to be reasonable. In the end, the two arms are almost identical in efficacy at this juncture. The safety profile becomes even more important in the consideration of risk-benefit analysis if the two arms in this study end with equivalent efficacy.

Table 4: MITT population – Response by Pathogen

	Voriconazole: 31 subjects Isolates (N=36 total) **Clinical Response**			Amphotericin B-to-fluconazole: 15 subjects Isolates (N=17 total) **Clinical Response**		
	Cured	Failed	% response	Cured	Failed	% response
C. albicans	8	9	8/17 (47%)	4	4	4/8 (50%)
C. tropicalis	1	4	1/5 (20%)	0	3	0/3
C. parasilopsis	6	2	6/8 (75%)	0	1	0/1
C. glabrata	0	4	0/4	2	3	2/5 (40%)
C. pelliculosa	0	1	0/1			
H. anomala	0	1	0/1			
Totals	**15**	**21**	**15/36 (41.7%)**	**6**	**11**	**6/17 (35.3%)**

MO Comment: The table above was generated to take a closer look at the available isolates from the MITT population. There are several points to note. As mentioned previously, no C. Krusei has been isolated in this study thus far. All four patients with the isolate of C. glabrata failed with voriconazole treatment in comparison to 3 out of 5 patients in the amphotericin B-to-fluconazole arm failing treatment. Voriconazole treated patients with C. parasilopsis did well (6/8 patients cured). The number of isolates are very small and the MIC data on these isolates incomplete in the database. The data generated from these isolates may be more meaningful if combined with other systemic candidal treatment protocols at this juncture, or be analyzed in more detail when the full database is submitted.

SAFETY RESULTS

Table 5: Adverse Events - Clinical

Subjects Assessed for AE	Voriconazole N = 45	Amphotericin B-to-fluconazole N = 22
Subjects with AE (all causes)	N = 45 (100%)	N = 21 (95.5%)
Listing of most frequent events	N (%)	N (%)
Sepsis	11 (24.4)	3 (13.6)
Hypotension	8 (17.8)	4 (18.2)
Elevated creatinine	0	4 (18.2)
Peripheral edema	8 (17.8)	1 (4.5)
Diarrhea	7 (15.6)	2 (9.1)
Anemia	7 (15.6)	2 (9.1)
Respiratory Disorder	6 (13.3)	0
Urinary Tract Infection	5 (11.1)	4 (18.2)
Vomiting	5 (11.1)	0
Hypokalemia	4 (8.9)	2 (9.1)
Hypernatremia	4 (8.9)	0
Pneumothorax	4 (8.9)	1 (4.5)
Subjects with AE (body systems)	N (%)	N (%)
Body as a whole	29 (64.4)	12 (54.5)
Cardiovascular	21 (46.7)	7 (31.8)
Digestive	21 (46.7)	7 (31.8)
Hemic/lymphatic	13 (28.9)	4 (18.2)
Metabolic/nutritional	20 (44.4)	9 (40.9)
Musculoskeletal	2 (4.4)	0
Nervous	9 (20.0)	5 (22.7)
Respiratory	21 (46.7)	9 (40.9)
Skin/appendages	13 (28.9)	5 (22.7)
Special senses	7 (15.6)	3 (13.6)
Urogenital	17 (37.8)	10 (45.5)
Subjects with AE (drug-related)	N = 22 (48.9%)	N = 8 (36.4%)
Serious AE	N = 5 (11.1%)	N = 2 (9.1%)
Severe AE	N = 8 (17.8)	N = 3 (13.6%)

Adverse events (all causalities) that occurred from Day 1 to seven days following the end of treatment were reported in all treated patients except one. The 45 voriconazole subjects experienced a total of 260 adverse events and the 21 amphotericin B-to-fluconazole subjects experienced a total of 109 adverse events. The rates of adverse events reported for metabolic and nutritional body system, for respiratory system, for skin and appendages, and for special senses were comparable. A greater proportion of voriconazole subjects than amphotericin B-to-

fluconazole subjects experienced adverse events coded to the body as a whole, cardiovascular, and digestive body systems. A greater proportion of amphotericin B-to-fluconazole subjects than voriconazole subjects experienced adverse events coded to the urogenital body system.

The all-causality adverse events that occurred more frequently in the voriconazole group and for which the inter-group difference in the rate was greater than 10% were sepsis, peripheral edema, respiratory disorder, and vomiting. The sponsor reports that upon review of the individual cases of sepsis, no clear association with the study drug treatment was observed. (*MO agrees with this statement by the sponsor upon review of the brief narratives provided by in this submission; however, a more detailed review is warranted when the complete safety databases are submitted for full concurrence*). One adverse event, elevated creatinine, occurred more frequently in the amphotericin B-to-fluconazole group with an inter-group difference of more than 10% in the rates of the event (*This is in keeping with the known nephrotoxicity profile of amphotericin B*).

For treatment-related adverse events, 22 voriconazole subjects and eight amphotericin B-to-fluconazole subjects experienced a total of 42 and 18 treatment-related adverse events. The most frequent treatment-related adverse events in voriconazole group were abnormal vision (n=3, 6.7%) and rash (n=3, 6.7%). The most frequent treatment-related adverse events in the amphotericin B-to-fluconazole group included elevated creatinine (n=3, 13.6%), hypotension (n=2, 9.1%), and hypokalemia (n=2, 9,1%). Eight (17.8%) voriconazole subjects and three (13.6%) amphotericin B-to-fluconazole subjects reported treatment-related severe adverse events. Within both treatment groups, the severe treatment-related adverse events were also serious, or led to the subject's discontinuation, or both. The events in the voriconazole group were pancytopenia; leukopenia; cholestatic jaundice (2 subjects); rash; grand mal convulsion and abnormal vision; elevated alkaline phosphatase; and moniliasis and abnormal liver function tests. The events in amphotericin B-to-fluconazole group were respiratory distress syndrome; asthma; allergic reaction; hypotension; hypokalemia; and unspecified drug reaction.

Table 6: Study Discontinuations

Reasons Discontinued	Voriconazole (N= 45 treated)	Amphotericin B-to-fluconazole (N = 22 treated)
Subject Died	N = 15 (33.3%)	N = 7 (31.8%)
Related to Study Drug	N = 8 (17.8%)	N = 1 (4.5%)
Insufficient clinical response	0	1 (4.5%)
Adverse Event	4 (8.9)	0
Laboratory abnormality	4 (8.9)	0
Not Related to Study Drug	N = 4 (8.9%)	N = 3 (13.6%)
Protocol Violation	1 (2.2)	1 (4.5)
Lost to follow-up	1 (2.2)	0
Withdrawn consent	0	1 (4.5)
Other	2 (4.4)	1 (4.5)
TOTAL Discontinued	N = 27 (60%)	N = 11 (50%)

A similar proportion of subjects in both treatment groups died during therapy or within 30 days of the end of therapy. For subjects in both treatment groups, the most common causes of death given by the investigators were multi-organ failure, sepsis, septic shock, and septicemia. No deaths in either group were considered causally related to the study treatment. (*MO agrees with this statement by the sponsor upon review of the brief narratives provided by in this submission;*

however, a more detailed review is warranted when the complete safety databases are submitted for full concurrence).

Adverse Events - Laboratory

Forty-five (100%) voriconazole subjects and 20 (90.9%) amphotericin B-to-fluconazole subjects had one or more on-treatment laboratory tests performed. However, not all laboratory tests were performed for all subjects, and for many of the tests, the number of subjects in each group who had available data for this interim analysis was small. As a consequence, the sponsor stated that no firm conclusions can be drawn at this juncture with respect to laboratory safety. Nevertheless, with what was available, the median changes observed with selected laboratory tests from baseline to end-of-treatment were as follows.

Table 7: Lab Values: % Median Change from Baseline to End-of-Treatment

Laboratory Variable	Voriconazole	Amphotericin B-to-fluconazole
SGOT	Increased 2.9%	Decreased
SGPT	Increased 10.3%	Decreased
Alkaline Phosphatase	Increased 19.1%	Decreased
Total Bilirubin	No change	Decreased 15.4%
Creatinine	Increased 7.7%	Increased 9.6%

Eight subjects in the voriconazole group discontinued study due to study drug related reason (4 for adverse events and 4 for laboratory abnormality) verses none in the amphotericin B-to-fluconazole group. In order to look at this discrepancy in more detail, the following table was generated summarizing each of the eight subject profiles. Three study-drug related vision adverse events were reported with the voriconazole group. All were photopsia type of events. All four permanent discontinuations were due to some level of abnormal liver function tests (LFT) in the voriconazole group. Two other subjects also in the voriconazole group had dose recuntion or temporary discontinuation due to LFT elevations. No discontinuations due to LFT abnormalities were reported for the comparator group.

Table 8: Closeup of 8 patients on voriconazole arm discontinuing due to AE

Subject ID/ Demographic	Treatment Discontinuing Day	Reason for Discontinuation (Investigator entry)	Coded Severity	Coded as Serious AE	Comments
03860051 80 y/o w male	Day 4 (Had received all IV)	-Leukopenia ADVERSE EVENT	Severe	Yes	COPD and baseline blood isolate of C. tropicalis, admitted 17 days prior to study with respiratory distress. Day one of treatment WBC = 7,170/mm^3 and on day 4 = 2,920/mm^3.

Subject ID/ Demographic	Treatment Discontinuing Day	Reason for Discontinuation (Investigator entry)	Coded Severity	Coded as Serious AE	Comments
50390029 47 y/o w male	Day 14 (Had received all IV)	-Recurrent Candidemia ADVERSE EVENT	Severe	no	C. albicans was isolated from blood on Day 12. The nomiliasis was present on Days 12 to 24.
50920036 45 y/o w male	Day 10 (Had received all IV)	-Rash ADVERSE EVENT	Severe	Yes	Patient with primary necrotizing pancreatitis and C. albicans in blood developed rash on Day 8 of study treatment. On Day 11, the rash had developed into blisters on arms, legs, chest, and back and diagnosed as superficial perivascular dermatitis. Began to heal by Day 15.
80500062 46 y/o w female	Day 9 (Had received 6 days IV and 3 days PO)	-Grand mal seizure ADVERSE EVENT	Severe	Yes	Bloodstream isolate of C. parapsilosis, on Day 4 of study had a dilated funduscopic erxam done with Atropine 1%. Patient experienced pain, loss of close vision, and audiovisual hallucinations. On Day 9, patient had the seizure. Patient has a history of seixures with visual disturbances. The investigator thorught that it is possible that voriconazole cuased the photopsia, which then induced the seizure.
ADDITIONAL COMMENT ON VISION: Three (6.7%) voriconazole subjects experienced one treatment-related visual adverse event each. No amphotericin B-to-fluconazole subjects experienced treatment-related visual adverse events. The three eventw in the voriconazole group were coded to the enhance/altered visual perception category. Two were coded as mild in severity. The third AE was reported as severe and is the patient described above.					
04030005 63 y/o w male	Day 9 (Had received 7 days IV and 2 days PO)	-Cholestasis LABORATORY ABNORMALITY ↑Alkaline Phosphatase	Severe	Yes	Baseline bloodstream isolate of C. parapsilosis. Had undergone surgery for aortic and right iliac aneurysm, additional revascularization surgeries of lower extremities prior to study entry. Was in ICU for acute renal failure secondary to rhabdomyolysis. On day 8 of the study developed cholestasis with Day 1 Alkaline Phosphatase Value at 312 U/L climbing up to 1352 U/L on Day 8 and climbing back down to 238 U/L after discontinuation.

Subject ID/ Demographic	Treatment Discontinuing Day	Reason for Discontinuation (Investigator entry)	Coded Severity	Coded as Serious AE	Comments
50320055 76 y/o w female	Day 7 (Had received all IV)	-Elevated Liver - Enzymes LABORATORY ABNORMALITY ↑Bili and GGT	Moderate	No	Patient with history of cholecystits s/p cholecystectomy 8 weeks prior to study entry. Bili on Day 2 at 1.3 mg/dL rose to 1.8 mg/dL on Day 7. GGT was 122 at Day 1 and rose to 163 on Day 7. Bili came down to 1.2 after discontinuation
50390059 45 y/o w male	Day 9 (Had received all IV)	-Cholestatic jaundice LABORATORY ABNORMALITY ↑Bili, OT/PT/APhos	Severe	No	LFT Day 1 Day 9 Day 23 Bili normal 2.2 mg/dL normal SGOT normal 81 U/L normal SGPT 50 U/L 102U/L normal Aphos 179 634 320 U/L
50940011 69 y/o w female	Day 10 (Had received 9 days IV and 1 day PO)	-Elevated Alkaline Phosphatase LABORATORY ABNORMALITY ↑ APhos	Severe	No	Baseline alkaline phosphatase was 363 U/L, and increased until reaching a peak of 1378 U/L on Day 10. Following discontinuation, the alkaline phosphatase decreased, and dropped to 257 U/L on Day 53.
ADDITIONAL COMMENT ON LIVER ENZYME ABNORMALITIES: There were 4 additional patients who dose reduced or temporarily discontinued due to adverse events with one patient in the amphotericin B-to-fluconazole arm and 3 patients in the voriconazole arm. 2/3 who dose reduced/temporarily discontinued were due to elevated liver function tests. One patient had increased lab values to Total bili of 3.9 mg/dL, SGOT/PT to 97/79 on day 11 of therapy (this was considered severe) and the other patient had lab values increased on day 6 of therapy to Total bili of 5.1 mg/dL, SGOT/PT to 167/96 U/L (this was considered moderate).					

MO COMMENT: *The evaluation of the safety profile at this 10% interim analysis is concerning. The amphotericin B-to-fluconazole group had more renal adverse events (increase in creatinine) than the voriconazole group which is not unexpected. Other than that, the voriconazole group had comparable or higher AE over the comparator. This is particularly highlighted by the discrepancy in the number of discontinuations due to study drug adverse events. Eight (18%) patients in the voriconazole group discontinued voriconazole (drug withdrawn by the investigator) due to adverse events compared to none in the amphotericin B-to-fluconazole group. Furthermore, the three safety issues we are particularly concerned about with voriconazole, namely vision issues, skin issues, and liver issues, were all highlighted by the patients discontinuing on the voriconazole arm. One patient developed a "blistering" rash on IV voriconazole which started to resolve when the medication was discontinued. Another patient had vision changes associated with a seizure although she was a patient with a history of siezures. Lastly four discontinuations due to laboratory abnormalities were all due to some elevation in LFTs. All four patient's offending abnormality improved or resolved when voriconazole was discontinued.*

It is possible since this was an open-label study, the investigators did have a bias toward stopping the "investigating" medication more readily than the current standard of therapy (comparator).

However, the elevations in LFTs did occur more frequently in the voriconazole arm over the comparator when available laboratory data were reviewed. The sponsor states "the disparity in the discontinuation rates due to adverse events may be attributable to the fact that subjects in the active-control group were required, as per the protocol, to switch from amphotericin B to fluconazole early in the study and had less exposure to amphotericin B than subjects randomized to voriconazole". This logic is not adequate since half of the discontinuing adverse events seen in voriconazole group were LFT abnormalities and this adverse event would be expected more with fluconazole rather than amphotericin B.

CONCLUSIONS/RECOMMENDATIONS

The sponsor has submitted this interim report of study 608 after 10% patient completion in order to support the global voriconazole NDA application and in particular the treatment of "serious candida" indications. The patient population for this study was an assortment of subjects (many surgical patients after multiple trauma, prolonged central line with total parenteral nutrition, elderly with severe pneumonia) who were non-neutropenic with candidemia. The comparison of treatment was open-label, but randomized arms of either voriconazole (IV first, then to PO at the investigator's discretion) or amphotericin B (short duration: 3 to 7 days IV) followed by fluconazole (IV or PO). Evaluation of efficacy by the MITT population at 12 weeks outcome resulted in the two arms having equivalent results (41.9% cured for voriconazole subjects and 40% cured for amphotericin B-to-fluconazole subjects. The numbers for different candidal isolates were quite small, but the breakdown from this study suggests equivalent results between the two arms for *C. albicans* and *C. tropicalis*, better response against *C. parasilopsis* for voriconazole, and poorer response against *C. glabrata* for voriconazole. There were no *C. krusei* isolated.

The safety results on the other hand were not similar between the two arms. Except for kidney/urological adverse events which occurred more frequently in the amphotericin B-to-fluconazole arm, all the other body systems adverse events were either same or more occurring in the voriconazole group. Of particular concern was the discrepancy in numbers of patients discontinuing study due to adverse events. Eight subjects in the voriconazole group discontinued study due to study drug-related reasons (4 for adverse events and 4 for laboratory abnormality) verses none in the amphotericin B-to-fluconazole group. The three safety issues we are particularly concerned about with voriconazole, mainly vision issues, skin issues, and liver issues, were all highlighted by the patients discontinuing on the voriconazole arm.

In this interim analysis of voriconazole for the treatment of candidemia in non-neutropenic patients, the safety risk concerns outweigh the comparable efficacy results when compared to amphotericin B-to-fluconazole exposure. Continued monitoring is needed for safety issues (especially in regards to liver, vision, and skin) as the protocol proceeds forward. The interim results reviewed do not favorably add to the safety profile of completed voriconazole trials seeking candida treatment indications.

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EXECUTIVE SUMMARY
VORICONAZOLE NDAs 21-266 and 21-267

Indication: Refractory Candidiasis

Background:

Pfizer submitted 2 new drug applications (NDA) 21-266 and 21-267 for the use of the intravenous and oral solution formulations of voriconazole in the treatment of a variety of fungal infections including serious fungal infections caused by *Candida* spp. in patients intolerant of, or refractory to, other therapy.
The proposed dosing schedule can be seen in the applicant's table below.

	Intravenous	Oral	
		Patients 40 kg and above	**Patients less than 40 kg**
Loading Dose Regimen	Two doses of 6 mg/kg separated by 12hour interval in first day	Two doses of 400 mg separated by 12-hour interval on first day	Two doses of 200 mg separated by 12-hour interval on first day
Maintenance Dose	3 mg/kg every 12 hours***	200 mg BID**	100 mg BID*
Dosage Adjustment: If inadequate patient response, increase dose up to: *** 4 mg/kg every 12 hours ** 300 mg BID * 150 mg BID If subjects are unable to tolerate treatment at these higher doses, reduce dose by 1 mg/kg IV or 50 mg oral steps to original dose.			

The indication(s) as it appears in the proposed label is as follows:
VFEND™ is indicated in the treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy.

VFEND™ is indicated in the treatment of serious *Candida* infections (including *C. krusei*), including esophageal and systemic *Candida* infections (hepatosplenic candidiasis, disseminated candidiasis, candidemia).
Background:

Clinical Studies:

The clinical data in the applicant's NDA submission pertinent to the refractory candidiasis indication were derived from 3 phase 2/3 open, multicenter, non-comparative studies (150-303, , 150-309, and 150-604) as well as from 3 compassionate use studies (150-301, 150-312, and 150-606). Studies 150-309 and 150-604 (open, non-comparative trials in subjects intolerant have or failing other therapies or with infections for which there is no approved therapy (interim analyses) were the primary studies from which data were collected.

The CRFs of all cases identified by the applicant as having a refractory *Candida* were reviewed by the MO. Subjects were assessed for key elements including (i) primary underlying condition, (ii) hematological risk factor, (iii) previous antifungal treatment, (iv) infection details with pathogen, site, and certainty of infection, and (v) outcome.

43 subjects with 64 isolates were included in the FDA database. The primary efficacy variable was the global response (complete, partial, stable, or failure) evaluated by the investigator at EOT/week 16 (for subjects continuing with voriconazole therapy), based on their overall clinical, mycological, radiological, and serological responses. Global response was also assessed 4 weeks after EOT (and compared with EOT) in subjects who stopped voriconazole therapy at or before week 16 and whose global response at EOT was complete, partial, or stable disease. Clinical, radiological, mycological, and serological responses were evaluated at weeks 2, 8, 12, or EOT/week 16 (for those subjects continuing therapy). Clinical response was also evaluated at weeks 1 and 4. When available the applicant's VERA assessments took precedence over the investigators. Those subjects who were in compassionate use protocols did not undergo VERA. Subjects with complete or partial successes were determined to have satisfactory response or a success.

The primary population assessed by the MO was the MITT, defined as subjects that received at least one dose of voriconazole, had a definite or probable diagnosis of systemic or invasive fungal infection at baseline as confirmed by the review of culture or histology reports by the MO, and were recruited on or before 26 May, 1999 (Study 150-604) or May 31, 1999 (Study 150-309). An additional 10 subjects who were treated after the original cut-off date were also included.

The applicant's and the FDA's MITT populations were the same. Relapses were counted as failures by the MO but not by the applicant.

Table 1
Complete and Partial Success Rates by Pathogen and by Subject

Complete and Partial Success Rate by Pathogenic Organism	Pathogen	Subjects
Candida albicans	5/14 (36%)* 4/14 ((29%) excluding relapses	5/12 (42%)* 4/12 (33%) excluding relapses
Candida tropicalis	4/7 (57%)	3/6 (50%)
Candida krusei	7/13 (54%)	6/10 (60%)
Candida glabrata	6/17 (35%)	4/12 (34%)
Candida parapsilosis	2/2 (100%)	2/2 (100%)
***Candida* spp.**	6/10 (60%)	6/8 (75%)*
Yeast Unspecified	0/1	0/1
ALL	30/64 (47%)	22/43 (51%)

* = Relapse (1 *Candida albicans*, 1 *Candida* spp.)

Table 2
Complete and Partial Success Rate By Patient and By Pathogen

Complete and Partial Success Rate	By Patient	By Pathogen
FDA	22/43 (51%)	30/64 (47%)

NOTE 2 relapses: 20/43 (47%), 1each *Candida* spp. and *Candida albicans*

Voriconazole appeared relatively effective as salvage therapy in the treatment of refractory *Candida* infections due to *Candida albicans* and *Candida krusei*. Success rates were 5/12 (42%) or 4/12 with relapse (33%) in a by patient analysis of *Candida albicans* (by pathogen: 5/14 (36%) or 4/14 (29%) with relapses) and 6/10 (60%) in a by patient analysis for *Candida krusei* (by pathogen 7/13 (54%). Although the success rates are not high especially for *Candida albicans* spp. infections, the mortality associated with these infections can be very high and thus the success rates obtained with voriconazole are of significance for patients with these refractory infections.

Voriconazole was marginally effective in the treatment of infections due to *Candida glabrata* with a large number of failures in patients with candidemia (success by patient 4/12 (33%) and by pathogen 6/17 (35%). As the success rates versus *Candida glabrata* are similar to those attained versus *Candida albicans*, a final decision regarding approval can only be made based on the bulk of the evidence of voriconazole's effectiveness versus this pathogen in a population with non-refractory but with disseminated disease.

Conclusions regarding the efficacy of voriconazole in the treatment of infections due to *Candida tropicalis* and *Candida parapsilosis* could not be drawn due to the small number of isolates.

The total sample size of 43 subjects was too small to draw valid conclusions regarding the efficacy of voriconazole depending on the underlying disease process. It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

20/43 (47%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. 3/8 (38%) of subjects with profound neutropenia including 2 with *Candida krusei* and 19/35 (54%) without neutropenia including 4 subjects with *Candida krusei* were treated successfully with voriconazole.

Total by patient success rate was 22/43 (51%) or 20/43 (46.5%) excluding relapses. Total by pathogen rate was 30/64 (47%) or 28/64 (44%) excluding relapses.

The sample size was too small to allow for valid conclusions regarding the outcome of refractory *Candida* infections by site of infection. 2/6 subjects with hepatosplenic candidiasis, 10/24(17%) with candidemia, 4/6 (67%) with skin infections, 2/6 (33%) with pulmonary infections, and 9/15 (60%) subjects with other sites of infection were treated successfully with voriconazole. All subjects with cerebral disease failed.

Special Populations:

Efficacy:

The sample size was too small to allow for the observation of differences in the efficacy rates with respect to race, gender, age, or ethnic group.

Recommendations:

The MO recommends approval for use of voriconazole in the treatment of serious fungal infections caused by *Candia albicans* and *Candia krusei* in subjects intolerant of or refractory to other therapy. The MO does NOT recommend approval for other *Candida* species as requested by the applicant as the sample size studied was small and the outcomes inconclusive. The recommendation for approval for *Candida albicans* is based on the bulk of evidence within the NDA that supports the activity of voriconazole versus *Candida albicans* and on the fact there is no other currently approved oral antifungal with a refractory candidiasis indication and that the severity of the infections as well as the underlying diseases in the patients studied indicate the medical need for an oral antifungal for this indication.

Serious *Candida* Infections:

In pooled analyses of patients enrolled across the development program, voriconazole was shown to be effective in the treatment of 5 of 12 (42%) refractory infections due to *Candida albicans* and in 6 of 10 (60%) cases due to *Candida krusei.*

Medical Officer's Clinical Review of NDAs 21-266 and 21-267

Indication: Refractory Candidiasis

I. Introduction and Background

A. Applicant, Drug Established and Proposed Trade Names, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Applicant: Pfizer Global Research and Development
Eastern Point Road
Groton, CT 06340

Date of Submission: November 17, 2000
CDER Stamp Date: November 22, 2000
Date Assigned to MO: August 12, 2001
Date Review completed: August 31, 2001

Drug Name: Voriconazole

Proprietary Name:
VFENDTM (voriconazole) Film-Coated Tablets
VFENDTM I.V. (voriconazole) for Infusion

Pharmacologic Category: Triazole antifungal

Chemical Name: (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)- 1-(1H - 1,2,4-triazol-1-yl)-2-butanol with an empirical formula of C, H, F, N, O and a molecular weight of 349.3.

Dosage Form: Film-coated tablets for oral administration, and a lyophilized powder for solution for intravenous infusion.

Route of Administration: Intravenous and oral

Strengths: 50 or 200 mg tablets and 200 mg voriconazole in a 30 ml Type I clear glass vial.

Proposed Indications and Usage: VFEND™ is indicated in the treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy.

VFEND™ is indicated in the treatment of serious *Candida* infections (including *C. krusei*), including esophageal and systemic *Candida* infections (hepatosplenic candidiasis, disseminated candidiasis, candidemia).
NOTE: ***On August 15, 2001, the MO requested that the applicant clarify the requested indication including delineation of the requested patient populations and or isolates for which voriconazole would be indicated. In an email received on 8/21/01 the sponsor stated that***

"They considered that the indication for voriconazole as "treatment of serious *Candida* infections" was inclusive of primary and salvage therapy. We also considered the indication for "treatment of other serious pathogens inpatients intolerant of, or refractory to, other therapies" to be inclusive of voriconazole as salvage therapy.

Materials Reviewed:

NDA volumes 1.1, 1.3 120, 148, 149, 131- 134, 142, 138, 139
JMP datasets submitted 11/17/2000
CDROM with CRFs submitted 8/13/2001
CDROM with CRFs submitted 8/17/2001
CDROM with JMP datasets submitted 8/20/2001
CDROM with WORD version of ISE submitted 6/8/2001
CDROM with CRFs submitted 8/18/2001
EMAIL with sponsor's analysis submitted 8/21/01
EMAIL with additional refractory candidiasis patients submitted 8/31/01
EMAIL with JMP datasets submitted 8/31/01

Abbreviations:

CRF = Case Report Form
AMPB = Amphotericin B
ITR = Itraconazole
FLU = Fluconazole
ABLC = Abelcet
BMT = Bone Marrow Transplants
CRF = Case Report Form
AE = Adverse Event
EOT = End of Therapy
MITT = Modified Intent to Treat
CGD = Chronic Granulomatous Disease
GVHD = Craft versus Host Disease
OPC = Oropharyngeal Candidiasis

Note on fonts: This review is written in Times New Roman 12. Arial is used for direct quotes from the applicant's submission.

B. State of Armamentarium for Indication(s):

Invasive fungal infections continue to present a major problem in immunocompromised subjects, especially in those with hematologic malignancies (during induction or at the peak of granulocytopenia), those with immunosuppression due to organ transplantation, and in those with AIDS. Many of these subjects die from these infections (mortality ranging from 50 – 80%, Mandell, Douglas, Bennett, "Principles and Practice of Infectious Diseases", Chapter 259, 2000) depending on the causative fungal pathogen. Most common are infections due to *Candida* spp., followed by *Aspergillus* spp. Candida spp. are the fourth most common organisms isolated from

the blood of US hospitalized patients. There are over 150 species of Candida, but 9 are human pathogens *including Candida albicans, Candida lusitaniae, Candida parapsilosis, Candida glabrata, Candida tropicalis, Candida pseudotropicalis, Candida krusei,* and others.

AMP B remains the cornerstone of treatment for *Candida* spp. associated serious or invasive infections. Azoles such as fluconazole may also be effective in deep-seated and//or disseminated candidiasis depending on the site of infection and the infecting species. ABELCET® and AMBISOME® are approved as second line agents for the treatment of "invasive fungal infections in patients who are intolerant of or refractory to conventional antifungal therapy."

ABELCET® was approved in May 1996 for the treatment of refractory infections due to *Candida* spp. The approval was based on the evaluation of 556 cases of serious invasive fungal infections treated through an open label, emergency use trial. 291 cases were mycologically confirmed and there was a complete or partial response to ABLC in 28/42 (67%) of cases of disseminated candidiasis. This total included complete or partial response in 15/20 (75%) subjects with candidemia and 22/29 (76%) of subjects with single organ involvement. These response rates are to be expected as compared to the more dismal rates found in patients with infections due to filamentous fungi and are indicative of the more varied population that develop disseminated infections due to *Candida* spp. including a wider range of hosts. (ABLC for Invasive Fungal Infections: Analysis and Efficacy in 556 cases; Walsh t. J. et all, Clinical Infectious diseases 1998; 26:1383 – 96).

The current ABELCET® label states that "For evaluable patients, the following fungal infections were treated (n=282): aspergillosis (n=111), candidiasis (n=87), zygomycosis (n=25), cryptococcosis (n=16), and fusariosis (n=11). There were fewer than 10 evaluable patients for each of several other fungal species treated. For each type of fungal infection listed above there were some patients successfully treated. However, in the absence of controlled studies it is unknown how response would have compared to either continuing conventional amphotericin B therapy or the use of alternative antifungal agents."

AMBISOME® was approved in August, 1997 and is indicated for the "treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate".

The approval was based on an open, multicenter, compassionate use study in hospitalized patients with systemic fungal infections. These patients either had fungal infections refractory to AMP B, were intolerant to the use of AMP B, or had pre-existing renal insufficiency. There were 140 infectious episodes in 133 patients, with 29 FDA clinically evaluable infections due to *Candida* spp. 17/29 (59%) were cured and 2/29 (7%) were improved in the FDA analysis. The current label states that "clinical success and mycological eradication occurred in some patients with documented aspergillosis, candidiasis, and cryptococcus".

NOTE: The ABELCET® and Ambisome® labels do not provide for mycologic identification of isolates beyond the species level. However both were alternative formulations of AMP B as opposed to a new molecular entity and therefore there was no need to further identify species.

This brief review of the current status of available antifungal agents approved for the treatment refractory *Candida* infections revealed that there is a need to increase the therapeutic options available to physicians in the treatment of subjects who develop such refractory infections as the current armamentarium is primarily limited to intravenous AMP B or liposomal products. An example is the need for alternatives to this for the treatment of deep seated candidal infections such as hepatosplenic candidiasis that require prolonged duration of treatment. The availability of an oral agent with acceptable toxicity would be of extreme benefit.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Microbiology

Voriconazole like other azole antifungal agents acts by inhibiting fungal cytochrome P450-dependent 1a-sterol demethylase (P450 DM), an essential enzyme in ergosterol biosynthesis. It is more selective than other azoles for fungal sterol and steroid biosynthesis and has fungicidal as opposed to fungistatic activity. The overall profile of voriconazole indicates that its potent, broad-spectrum antifungal activity *in vitro* translates to excellent efficacy *in vivo* against aspergillosis, candidiasis, cryptococcosis, and scedosporiosis, irrespective of the immune status of the animal.

In vitro, voriconazole demonstrates potent activity against fluconazole-resistant strains of *Candida albicans*, as well as other *Candida* spp. including *Candida krusei* and *Candida glabrata*).

As per the sponsor:

Voriconazole has shown high *in vitro* potency across a wide range of *Candida* species. In the following table are the available susceptibility data from 309 and 604 for subjects from the submission.

Table 1
MIC Range, MIC_{50} and MIC_{90} for *Candida* Isolates. *
Studies 309 and 604.

Species	N of Isolates	Range (µg/mL)	MIC_{50}	MIC_{90}
Candida albicans	61	[redacted]	0.5	8.0
Candida dublinensis	1	[redacted]		
Candida glabrata	45	[redacted]	2.0	4.0
Candida keyfir	1	[redacted]		
Candida krusei	4	[redacted]		
Candida parapsilosis	4	[redacted]		
Candida tropicalis	8	[redacted]	0.12	16.0

* NCCLS M27A Method

Recently published comparative *in vitro* data can be found in the following table.

Table 2
In vitro* Activity (MIC90) of Selected Antifungal Agents Against Yeasts

Organism	Number of Isolates	Antifungal Agent	MIC_{90} Range (µg/mL)
Candida species	3,664	Voriconazole	
		Fluconazole	
		Amphotericin B	
		Itraconazole	
		Ketoconazole	
		Flucytosine	

- NCCLS M27A Method

The *in vitro* data summarized in Tables 1 and 2 and additional data provided within the filing includes over 4000 isolates and confirms that voriconazole has high potency against all clinically important *Candida* spp.

B. Pharmacokinetics and Pharmacodynamics

The following were copied from the applicant's PK/PD summary:

- The bioavailability of voriconazole was estimated from the population analysis to be 96% and the estimate of inter subject variability (CV) was 13%.

- Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1 to 2 hours after dosing.

For further detailed information, Please refer to the appropriate review.

III. Description of Clinical Data and Sources

A. Overall Data

Subjects assessed for the indication of rare fungal infections were obtained from Phase 2/3 non-comparative studies: 150-303, 150-304, 150-309, and 150-604

- **Study 150-303**: Open, non-comparative, multicenter study assessing the efficacy of orally administered voriconazole in the treatment of chronic invasive infections caused by *Aspergillus* spp. or *Candida* spp.

- **Studies 150-309 and 150-604:** Open, non-comparative trials in subjects intolerant have or failing other therapies or with infections for which there is no approved therapy (interim analyses).

- Additionally patients were obtained from the following compassionate use studies: 150-301, 150-303a, 150-304a, 150-312, and 150-606

B. Table Listing the Clinical Trials

Table 3
List of Clinical Trials

Study Number	Indication	Main Region	Study Status	Design
150 - 303	Chronic Aspergillosis and Candidiasis	Europe	Complete	Non-comparative
150 - 309	Rare and Refractory Fungal Infections	Europe	Interim Analysis	Non-comparative
150 - 604	Rare and Refractory Fungal Infections	US	Interim Analysis	Non-comparative
150 – 301	Compassionate Use	Europe	Complete	Non-comparative
150 – 312	Compassionate Use	Europe	Complete	Non-comparative
150 - 606	Compassionate Use	US	Interim Analysis	Non-comparative

C. Postmarketing Experience

This drug is not marketed at present.

D. Literature Review

NOTE: There is minimal current literature available regarding the treatment of *Candida* infections in subjects who have failed prior treatments (refractory). Most literature deals with the primary treatment of candidemia, thus highlighting the potential limited capacity for treating refractory infections with the currently available agents.

1) Practice Guidelines for the Treatment of Candidiasis; Rex J. et al, CID 2000:30 (April) 662 - 678

Infections due to *Candida* spp are the most common of the fungal infections and can range in severity from non life-threatening mucocutaneous disease to invasive processes. Both AMP B and the azoles play a role in the treatment of these infections and the choice may be guided by weighing the greater activity of AMP B for some non-*albicans* species against the toxicities of other agents. Infections due to non-*albicans* species are increasing in frequency. AMP B resistance appears uncommon among isolates of *Candida albicans, Candida tropical is,* and *Candida parapsilosis*. Isolates of *Candida lusitaniae* most often demonstrate resistance and a non-trivial propostion of *Candida glabrata* and *Candida krusei* isolates may be resistant to AMP B. Thus when AMP B is used to treat these infections, very high doses are used. Similar concerns apply to the lipid-based compounds that are approved for refractory Candida infections. Recommendations for the empirical therapy of infections due

to *Candida glabrata* remain divided, as these isolates have reduced susceptibility to both AMP B and the azoles. At present very high doses of fluconazole are recommended for these infections.

2) Risk Factors for Death Among Cancer Patients with Fungemia,
Nucci M et al, CID 1998; 27:107 – 11

An 18 month survey of patients with fungemia in 3 Brazilian hospitals. 54 episodes of fungemia were identified. 43 were due to Candida (38 non-*albicans*). Death rate was 48%.

3) Current and future antifungal therapy: new targets for antifungal agents,
Andriole, V. T., Journal of Antimicrobial Chemotherapy (1999) 44, 151 – 162

The incidence of invasive fungal infections in immunosuppressed patients continues to increase and they are significant causes of morbidity and mortality. Approximately half the patients who die with malignancies are infected with *Candida* spp. AMP B has excellent activity against most but not all *Candida* spp. and is recommended as the primary treatment of disseminated candidiasis, serious Candida infections, and deep-seated infections. The currently available azoles primarily have activity versus *Candida albicans* and of the class, fluconazole is effective in disseminated candidiasis including hepatosplenic candidiasis.

4) Fungal Infections in Patients with Neutropenia, Herbrecht R et al,
Drugs and Aging 2000 Nov; 17(5), 339 –351

Candidiasis and aspergillosis account for most invasive fungal infections and are a leading cause of mortality. Candidiasis often presents as invasive disease in severely immunocompromised hosts and there are 2 patterns of infections, the acute with positive blood cultures and the more chronic or chronic disseminated candidiasis. *Candida albicans* used to be the cause of 66% of candidemias but this is no longer the case. *Candida glabrata* and *Candida krusei* have been more common and are often resistant to fluconazole. Fluconazole is the best choice for acute candidiasis in stable patients; AMP B should be used in unstable disease. The use of fluconazole is restricted by the existence of resistant strains (*Candida krusei* and to a lesser extent *Candida glabrata*). Mortality is approximately 40% and worse in non-albicans infections.

5) Fungal infections in neutropenia: current problems and chemotherapeutic control
Warnock D, Journal of Antimicrobial Chemotherapy (1998) 41, Suppl. D, 95 – 105

Candidiasis is the most common invasive fungal infection in patients with malignant hematologic disorders and BMT recipients. Additionally, chronic disseminated candidiasis, a distinct clinical entity only occurs in leukemic patients and BMT recipients. *Candida albicans* remains the predominant etiologic pathogen of both the superficial and the deep-seated forms of candidiasis but infections attributable to other species are increasing. In the 1970s, *Candida tropicalis* emerged as an important pathogen. More recently the spectrum has continued to change, primarily due to prophylactic treatment with fluconazole that has reduced the number of *Candida albicans* and *Candida tropicalis* infections and has led to

increased rates of colonization and infection with *Candida krusei*. Both *Candida krusei* and *Candida glabrata* are less susceptible to fluconazole. As per the author, AMP B remains the drug of choice for candidal infections.

IV. Clinical Review Methods

A. How the Review was conducted including overview of materials reviewed and methods used to evaluate data quality and integrity

CRFs of all cases identified by the applicant as having an infection with a refractory *Candida* spp. isolate were reviewed. Subjects included in the applicant's database from studies other than 309 and 604, often did not have baseline culture or histopathological information to document the presence of an infection and were included in the database based only on investigators comments made when requesting voriconazole for compassionate use. A review of these protocols (301, 303, 312, 606) revealed that the submission of culture (or other) evidence was not an inclusion criterion, that these studies were not monitored, and that the verification of cases was difficult in the absence of culture (or other) information. Therefore, the MO determined to exclude any case from the analyses where culture or histopathological evidence of an invasive refractory *Candida* infection was not provided. For studies 309 and 604, where the submission of cultures was an inclusion criterion and where the subjects were monitored, the MO accepted all cases. Additionally, the MO excluded from the database those subjects with refractory esophageal candidiasis and requested that the sponsor develop a separate database of such patients from all studies to be reviewed by the primary reviewer. Finally, the MO accepted only those cases of definite or probable infection for inclusion into the FDA MITT.

Multiple JUMP datasets were merged and a final FDA population dataset was constructed. Demographics and basic descriptive statistics were performed on this dataset.

The applicant's analyses are presented in brief as the MO accepted the applicant's definitions of response as well as the individual patient responses. This information was in the original 11/2000 submission and included in the 309 and 604 interim study reports as well as in the ISE.

The MO performed a literature search utilizing MEDLINE and EMBASE of all articles within the last 5 years pertinent to the indications. The references generated provided a baseline "success" rate for the infections under review.

B. Were Trials Conducted in Accordance with Accepted Ethical Standards

It appeared as if all trials were conducted ethically and after IRB approval. In all CRFs reviewed, the consent forms were signed.

C. Evaluation of Financial Disclosure

There was no conflict of interest with regards to the indications under review,

V. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Voriconazole appeared relatively effective as salvage therapy in the treatment of refractory Candida infections due to *Candida albicans* and *Candida krusei*. Success rates were 5/12 (42%) or 4/12 with relapse (33%) in a by patient analysis of *Candida albicans* (by pathogen: 5/14 (36%) or 4/14 (29%) with relapses) and 6/10 (60%) in a by patient analysis for *Candida krusei* (by pathogen 7/13 (54%). Although the success rates are not high especially for *Candida albicans* spp. infections, the mortality associated with these infections can be very high and thus the success rates obtained with voriconazole are of significance for patients with these refractory infections.

Voriconazole was marginally effective in the treatment of infections due to *Candida glabrata* with a large number of failure in patients with candidemia (success by patient 4/12 (33%) and by pathogen 6/17 (35%). As the success rates versus *Candida glabrata* are similar to those attained versus *Candida albicans*, a final decision regarding approval can only be made based on the bulk of the evidence of voriconazole's effectiveness versus this pathogen in a population with non-refractory but with disseminated disease.

Conclusions regarding the efficacy of voriconazole in the treatment of infections due to *Candida tropicalis* and *Candida parapsilosis* could not be drawn due to the small number of isolates.

Total by patient success rate was 22/43 (51%) or 20/43 (46.5%) excluding relapses. Total by pathogen rate was 30/64 (47%) or 28/64 (44%) excluding relapses.

The total sample size of 43 subjects was too small to draw valid conclusions regarding the efficacy of voriconazole depending on the underlying disease process. It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

20/43 (47%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. 3/8 (38%) of subjects with profound neutropenia including 2 with *Candida krusei* and 19/35 (54%) without neutropenia including 4 subjects with *Candida krusei* were treated successfully with voriconazole.

Regarding outcome by site of infection, 2/6 subjects with hepatosplenic candidiasis, 10/24(17%) with candidemia, 4/6 (67%) with skin infections, 2/6 (33%) with pulmonary infections, and 9/15 (60%) subjects with other sites of infection were treated successfully with voriconazole. All subjects with cerebral disease failed. Again, the sample size was too small to allow for valid conclusions regarding the outcome of refractory *Candida* infections by site of infection.

20/43 (47%) subjects had a documented risk factor. This number was too small to allow for valid conclusions.

B. Detailed Review of Trials by Indication

Studies 150-309 (An open label, non-comparative, multicenter, phase III trial of the efficacy, safety, and toleration of voriconazole in the primary or secondary treatment of invasive fungal infections) and 150-604 (An Open Label, Non-comparative, Multicenter, Phase III Trial of the Efficacy, Safety and Toleration of Voriconazole in the Primary or Secondary Treatment of Invasive Fungal Infections) are identical ongoing protocols conducted in Europe and the US respectively. For a detailed description of these studies including definitions of response, please see the MOR of rare and refractory fungal infections.

Briefly, both studies were open label, non-comparative in which all subjects were allocated to receive voriconazole. The investigators used their clinical judgement as to whether initial therapy should be by the intravenous or oral route (oral and intravenous doses of 200mg and 4mg/kg twice daily, respectively). The maximum total duration of voriconazole treatment (intravenous and oral) for any subject was expected to be 12 weeks. The actual total duration of treatment in each subject was determined by the investigator depending on the subject's response. For subjects who continued voriconazole for more than 12 weeks, the end of therapy (EOT) assessments were carried out at week 16 or EOT whichever was sooner. With the agreement of the sponsor, any subject requiring more than 16 weeks of treatment received further voriconazole therapy in continuation protocol 150-311. Subjects who continued in this way had their final assessment recorded as a Week 16 assessment rather than an EOT assessment. The follow up visit took place 4 weeks after EOT for all subjects who completed voriconazole therapy in this study.

The primary efficacy variable in these studies was the global response (complete, partial, stable, or failure) evaluated by the investigator at EOT/Week 16 (for subjects continuing with voriconazole therapy), based on their overall clinical, mycological, radiological, and serological responses. Global response was also assessed 4 weeks after EOT (and compared with EOT) in subjects who stopped voriconazole therapy at or before week 16 and whose global response at EOT was complete, partial or stable disease. Clinical, radiological, mycological, and serological responses were evaluated at weeks 2, 8, 12, or EOT/week 16 (for those subjects continuing therapy). Clinical response was also evaluated at weeks 1 and 4. If no response for any of the clinical, mycological, serological or radiological responses at EOT was recorded the assessment was set to 'missing' by the applicant and "unknown by the MO".

Table 4
Schedule of Assessments

Assessment	When Assessed	Grading
Clinical Response	Weeks 1, 2, 4, 8, 12, 16, and EOT	Complete, partial, stable, failure
Mycology	Weeks 2, 8, 12, 16, and EOT	Eradication, presumed eradication, persistence, indeterminate
Radiology	Weeks 2, 8, 12, 16, and EOT	Complete, partial, stable, failure
Serology	Weeks 2, 8, 12, 16, and EOT	Normalized, improved, unchanged, worsened, indeterminate
Global Response	EOT or Week 16	Complete, partial, stable, failure
Global Response follow-up	4 weeks after EOT	Cured, improved, stable, relapsed

Included were subjects at least 12 years of age, with a diagnosis at baseline and documented within four weeks preceding study entry of a systemic or invasive fungal infection for which there was no licensed therapy or a systemic or invasive fungal infection with evidence of failure and/or intolerance to approved treatments. For the indication under review, a diagnosis of failure was made when there was a lack of clinical response after at least 7 days of systemic antifungal treatment at an adequate dose

Applicant's Pooled Analyses:

The applicant provided 2 types of efficacy analyses. One set of analyses was based on the results of each clinical study conducted and analyzed in accordance with the protocol for that study. The second set of analyses was based on a pooled database containing subjects with documented fungal infections from the 13 Phase 2/3 studies using standardized criteria (VERA). For the indication of refractory Candida infections, the MO determined that because patients were collected from a number of studies, the presentation of efficacy results from each study was not useful. Therefore, only the applicant's pooled results are presented."

Subjects were reviewed for key elements including (i) primary underlying condition, (ii) hematological risk factor, (iii) previous antifungal treatment, (iv) infection details with pathogen, site and certainty of infection, and (v) outcome. Where available, the DRC/expert assessments took precedence over any other assessment. For those studies where an expert or DRC was not employed, outcome at End of Therapy (EOT) used the investigator assessment, within the context of other available pertinent information. The sponsor was allowed only to downgrade and never upgrade an investigator outcome assessment.

NOTE: VERA was utilized in a portion but not all subjects with refractory *Candida* infections. Those subjects who were in compassionate use protocols did not undergo VERA.

MO Comment: *The applicant's efficacy analyses were performed on a modified intent-to-treat (MITT) population defined as subjects that received at least one dose of voriconazole, had a definite or probable diagnosis of invasive refractory Candida infection at baseline, and were recruited on or before 26 May, 1999 (Study 150-604) or May 31, 1999 (Study 150-309). The interim analysis includes all data collected from visits before September 20, 1999.*

The applicant also collected a number of cases of refractory candidal infections from other studies 301, 303, 312, and 606 and included them in the analyses if they met the MITT population definition. 20 of the applicant's subjects were from studies 309 and 604, the remaining 23 subjects received voriconazole as salvage therapy in a variety of compassionate use protocols.

Outcome as per the sponsor, can be seen in the following table:

Table 5

Serious Systemic *Candida* Infections Outcomes--Salvage Therapy	
	Voriconazole N = 43
Salvage therapy	
Success	22 (51.2)
Failure	21 (48.8)

As per the sponsor, "the success rate in the pooled population was less when voriconazole was used as salvage therapy (51%) compared to primary therapy (65%).

Applicant's Conclusions for the Treatment of Refractory Infections due to Candida spp. with Voriconazole:

NOTE: *The sponsor did not provide demographics of the patient population with refractory infections due to Candida spp. isolates or a further breakdown of the isolates. Additional efficacy analyses by isolate were also not provided. The MO requested that the sponsor provide such an analysis on 8/14/01. This was submitted via email on 8/21 and the sponsor's conclusions can be seen below:*

Overall, the data supporting the efficacy of voriconazole as salvage therapy for *Candida* infections, while limited in number, are encouraging for both neutropenic and non-neutropenic patients. These salvage patients, for whom there has traditionally been only a dim prospect of response to antifungal therapy, have shown promising responses to voriconazole. In those patients without neutropenia, there was a great deal of pretreatment, and yet 54.3% responded successfully to voriconazole.

Even in the primary treatment of candidemia the rates for successful therapy are only 70-80%. In non-neutropenic patients, Rex *et al.* demonstrated that 70% of patients (72/103) treated with fluconazole (400 mg/day) had successful outcomes, while amphotericin B deoxycholate, ($\geq$ 0.5 mg/kg/day), was successful in 79% of patients (81/103). In a survey across available therapies, Anaissie *et al.* reported that the best available therapy for candidemia was successful in 186/257 patients (72%). A smaller

Canadian study of candidemia compared outcomes for patients treated with fluconazole (400 mg/day) with those for patients given amphotericin B deoxycholate (0.6 mg/kg/day). Fluconazole was effective in 25/50 (50%) of patients, while amphotericin B deoxycholate was successful in 31/53 patients (58%). In a comparable primary therapy setting, voriconazole has a success rate of 70% (28 of 40 non-neutropenic candidemia patients with candidemia in the pooled efficacy population).

In neutropenic patients, as expected, success rates are lower. Anaissie *et al.* showed that the best current primary therapy was successful in 44 % of neutropenic patients (96/217) with candidemia. Experience with voriconazole in this clinical setting, while limited, is promising. Of the neutropenic candidemia patients treated with voriconazole, four of 13 (31%) had successful outcomes, as summarized in the pooled efficacy database.

The Sponsor believes that, given the literature data for outcome of primary or salvage therapy in invasive *Candida* infection, voriconazole represents an appropriate salvage therapy option.

1. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. N Engl J Med 1994; 331:1325-1330.
2. Espinel-Ingroff A. In vitro fungicidal activities of voriconazole, itraconazole, and amphotericin B against opportunistic moniliaceous and dematiaceous fungi. Journal of Clinical Microbiology 2001; 39: 954-958
3. Anaissie EJ, Rex JH, Uzun Ö, Vartivarian S. Predictors of adverse outcome in cancer patients with candidemia. Am J Med 1998; 104:238-245.
4. Phillips P, Shafran S, Garber G, et al. Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. Eur J Clin Microbiol Infect Dis 1997; 16:337-345.

FDA Analysis:

In study 150-604 there were a total of 156 subjects, 49 (31.4%) had candidiasis. Of these, 32 were included in the applicant's MITT population. The MO excluded an additional 9 subjects with esophageal disease (60410336059, 60110346184, 60460446210, 60460446208, 60410016196, 60410336059, 60410626032, 60410666138, 60410666141) and 5 with primary R/x (60410716020, 60410496010, 60410366024, 60410016196. 60410326022)

In study 150-309, there were a total of 74 subjects 21 subjects (28.4%) had candidiasis. Of these, 10 were included in the sponsor MITT population. MO excluded an additional 7 with esophageal disease (30900141010, 30900141014, 30902691182, 30903531600, 30903541610, 3094321735, 30920051418) and 1 with primary R/x (30903001140)

The FDA database also included 10 subjects from study 301, 5 from study 303, 2 from study 312, and 6 from study 606.

The sponsor and the MO agreed to assess only those subjects and isolates that met the definitions of definite or probable infections. This determination led to the exclusion of 7 possible isolates from 5 subjects. (60410366166: *Candida tropical is*, hepatosplenic; 60410366192: *Candida tropical is,* urine; 30102930001: *Candida krusei,* bone, hepatosplenic; 60410496106: *Candida*

glabrata, urine; 60650200030: *Candida tropicalis* urine and unspecified yeast from tracheal secretions).

In addition, there were 5 subjects with mixed infections (60410186170: *Aspergillus fumigatus* lung and definite *Candida glabrata* of the sinus; 60410336058: fungemia with *Candida albicans* and *Rhodotorula glutinis*; 30104780001: pulmonary infection with *Candida albicans, Candida glabrata,* definite *Aspergillus fumigatus*, and possible *Saccharomyces cerevisiae*; 31201110001: definite blood and cerebral infection with *Candida krusei,* definite cerebral infection with *Candida albicans*, *Candida glabrata*, and *Rhizopus*; 31202030001: probable mediastinal infection with *Candida albicans* and definite lung *Aspergillus fumigatus*) however, the MO considered on the *Candida* spp. isolates in the current review.

The MO accepted the applicant's determinations of efficacy in all cases. In the final analyses the MO as opposed to the applicant calculated success rates including subjects who relapsed as failures.

The FDA population consisted of 43 subjects with 64 isolates. There were 17 subjects that had more than 1 isolate. 37 subjects were white, 3 were black and the remaining 3 were 1 each Hispanic, Asian, and Indian. 27 subjects were male and 16 female. The mean age was 40.8 (standard deviation 19.8), the median age was 43 and the range was 2, 73. There were 4 subjects ≤ 15 (9%) and 5 subjects ≥ 65 (12%).

21/43 (49%) of subjects had underlying hematologic malignancies, 2 each had aplastic anemia, other disorders, and other hematologic disorders (5%), 5 had transplants (12%), and 5 had other malignancies (5%). The remaining subjects had 1 each HIV, CGD, unknown, and surgery.

Documentation of underlying neutropenia as a risk factor was poor. In 24 subjects this factor was "unknown" and in 19 was listed as > 1000 cells/mm'3. It should be noted however, that 8 subjects were assessed as having profound neutropenia as a risk factor (19%).

Mean duration of treatment was 61.6 days (standard deviation 74.2), the median was 27 days and the range was 2, 315. The mean duration of IV voriconazole was 18.4 days (standard deviation 22.4) and the median was 10.5 days (2, 109). The mean duration of PO voriconazole was 73.7 days (standard deviation 74.7) and the median was 45 days (2, 271).

Mean duration of previous antifungal therapy was 22 days (standard deviation 9.3), the median was 26 days and the range was 0, 31.

36 of the subjects were prior efficacy failures, 4 were intolerant, and 3 received salvage treatment for unknown reasons. 26 of the 36 subjects who failed prior treatment, were fluconazole failures, 18 of whom had also received AMP B.

35 subjects had definite infections (81%) and 8 (19%) had probable infections. Of the 64 isolates, 24 were from blood, 6 were pulmonary, 6 were hepatosplenic, 2 were from the sinus, 6 from skin, 1 was from bone, 3 were cerebral, 1 was esophageal, 4 were from the biliary tree, and

3 were from the UT. In addition, there were 12 "other" isolates that included 1 each from the oropharynx, mediastinum, UT, muscle, prosthetic valve. There were also 2 isolates from tonsils.

12 subjects had *Candida albicans*, 9 *Candida glabrata*, 8 *Candida krusei*, 2 *Candida parapsilosis*, 6 *Candida* spp., 5 *Candida tropicalis*, and 1 had unspecified yeast. NOTE: 17 subjects had more than 1 isolate but these infections were not mixed.

Overall success was 22/43(51%), of whom 2 relapsed for a final success rate of 20/43 (47%). 15 subjects were failures due to insufficient response, 3 due to intolerance, 2 were failure/stable, and 1 was deemed unevaluable.

Of those subjects who were prior efficacy failures, 16/36 (44%) were successes.

Relapses are described below:

- **30301370396**: 60 YO female with AML received voriconazole for 6 months as treatment for a definite hepatosplenic infection with *Candida* spp. Previous antifungal treatment for 26 days included fluconazole. Patient was classified as a complete success followed by relapse with *Candida tropicalis* in bone.

- **30300250004**: 34 YO male with AIDS received voriconazole for 30 days as treatment for probable oropharyngeal infection with *Candida albicans* (mouth swab with severe clinical picture). Previous antifungal treatment for 27 days included AMP B, ITR, and 5FC. Patient was classified as a partial success followed by relapse.

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Other Documented Risk Factors							
Prolonged Neutropenia	8	-	2	2	3	4	-
Autologous BMT	1	-	-	1	-	-	-
Allogeneic BMT	5	2	1	-	1	3	-
GVHD	4	1	3	-	-	-	-
None Known	23	9	6	5	1	3	1
Malignancy Relapse	1	-	-	-	1	-	-
Post BMT	1	-	-	-		-	1

NOTE: Some subjects had more than 1 species of *Candida* isolated.

Table 7
FDA MITT Populations and Isolates

Pathogenic Organism	Isolates N = 64	Subjects N = 43
Candida albicans	14 (22%)	12 (28%)
Candida tropicalis	7 (11%)	6 (14%)
Candida krusei	13 (20%)	10 (23%)
Candida glabrata	17 (27%)	12 (28%)
Candida parapsilosis	2 (3%)	2 (5%)
***Candida* spp.**	10 (16%)	8 (19%)
Yeast Unspecified	1 (2%)	1 (2%)
Total	64	43

Table 8
Complete and Partial Success Rates by Subject and Isolate

Complete and Partial Success Rate by Pathogenic Organism	Isolates	Subjects
Candida albicans	5/14 (36%)	5/12 (42%)
Candida tropicalis	4/7 (57%)	3/6 (50%)
Candida krusei	7/13 (54%)	6/10 (60%)
Candida glabrata	6/17 (35%)	4/12 (34%)
Candida parapsilosis	2/2 (100%)	2/2 (100%)
***Candida* spp.**	6/10 (60%)	6/8 (75%)
Yeast Unspecified	0/1	0/1
ALL	30/64 (47%)	22/43 (51%)

Demographics:

Table 6
Demographics of FDA MITT Population

Demographic factor	ALL N = 43	*C. albicans* N = 12	*C. glabrata* N = 12	C. spp. N = 8	*C. trop.* N = 6	*C. krusei* N = 10	*C. paraps* N = 2
Sex							
Male	27	9	8	4	2	7	2
Female	16	3	4	4	4	3	-
Age							
0 – 15	4	1	-	1	1	1	-
16 – 65	34	10	10	7	4	9	2
> 65	5	1	2	-	1	-	-
Mean (sd)	40.8 (19.8)	44.2 (18.3)	52 (14.4)	44.8 (20.5)	45.6 (22.5)	32.4 (18.3)	17.5 (2.1)
Median	43	48	53.5	50.5	51.5	29	17.5
Min., max.	2, 73	4, 73	24, 73	2, 65	9, 70	12, 69	16, 19
Race							
White	37	12	9	7	5	8	2
Other	1	-	-	-	1	1	-
Black	3	-	2	1	-	-	-
Hispanic	1	-	1	-	-	-	-
Asian	1	-	-	-	-	1	-
Underlying disease							
Hematologic Malignancy	21	3	5	6	5	6	-
Other malignancy	5	2	1	1	1	1	1
Transplant	4	2	3	-	-	-	-
Immunosuppression	3	2	-	1	-	-	-
Surgery	1	-	1	-	-	-	-
CGD	1	-	1	-	-	-	-
AIDS	1	1	-	-	-	-	-
Aplastic Anemia	2	-	1	-	-	1	-
Chronic Hepatitis B	-	-	-	-	-		-
Other	4	2	-	-	-	1	1
Unknown	1	-	-	-	-	1	-
Neutropenia							
Unknown	24	7	7	5	3	8	
Yes	-	-	-	-	-	-	
NO	19	5	5	3	3	2	
EOT Duration							
Mean (sd)	61.6 (74.2)	91.4 (108.4)	22.8 (27.7)	84.2 (71.3)	64 (56.1)	37.3 (40.9)	60 (74.9)
Median	27	44.5	16	66.5	62.5	19.5	60
Min., Max.							

Table 9
Outcome by patient
FDA Population

	Candida albicans N = 12	*Candida krusei* N = 10	*Candida glabrata* N = 12	*Candida tropicalis* N = 6	*Candida spp.* N = 8	*Candida paraps.* N = 2
Complete success	1	3	4	-	1*	2
Partial success	4*	3	-	3	5	-
Failure ALL	7	4	8	3	2	-
Death	-	1	-	-	-	-
Unevaluable	1	-	-	-	-	-
Insufficient response	4	2	6	2	2	-
Stable	2	-	-	-	-	-
Intolerance	-	1	2	1	-	-

* = Relapse (1 *Candida albicans*, 1 *Candida* spp.)

Table 10
Complete and Partial Success Rate By Patient and By Pathogen

Complete and Partial Success Rate	By Patient	By Pathogen
FDA	22/43 (51%)	30/64 (47%)

NOTE 2 relapses: 20/43 (47%), 1each *Candida* spp. and *Candida albicans*

Candida albicans:
(N = 14 isolates from 12 patients):

Subjects with *Candida albicans infections* had a variety of underlying diseases. 8 subjects had definite infection and 4 had probable. 1 subject with a definite blood infection also had a probable esophageal and pulmonary infection. All subjects received prior antifungal treatment with a mean duration of prior treatment of 22.4 days and a median of 29 (range 6, 31).

Mean age of the subjects was 44.2 (median 48, range 4 – 73) and there 9 males and 3 females.

1 subject had 3 isolates each and the remaining 9 subjects had 1 *Candida* isolate each. 3 of these subjects however had a mixed infection and their outcomes are in the following table:

Subject Number	Baseline Pathogens	Site(s)	Outcome
301-04780001 (salvage)	*A. fumigatus* *C. albicans* *C. glabrata*	All pulmonary	Complete success
312-01110001 (salvage)	*C. albicans* *C. glabrata* *C. krusei* *Rhizopus* spp.	Brain Brain Brain and blood Brain	Failure
604-10336058 (salvage)	*C. albicans* *Rhodotorula glutinis*	Both blood	Failure (unevaluable)

3 subjects had pulmonary isolates, 2 had blood isolates and there was 1 each bone, cerebral, skin, esophageal, oropharyngeal, tonsil, peritoneal, biliary, and hepatosplenic.

Mean duration of voriconazole treatment was 91.4 days (median 44.5 days).

Overall per patient success rate was 5/12 or 42% at the EOT. There was 1 relapse, therefore the complete and partial success rate was 4/12 (33%) at follow-up. As can be seen from the above mixed infection table, 2 of the failures were in mixed infection patients.

The most common cause of failure was insufficient response (4), followed by failure/stable in 2 subjects and failure due to protocol violations in 1.

Global response was assessed as complete in 1/12 (8%) and partial in 3/12 (25%). Global response was assessed as failure in 2 subjects (16%), as stable in 2 (16%) and was not assigned in 4 (33%).

Mycologic response was unknown in 6 subjects because it was not a protocol requirement, indeterminate in 3, presumed eradication in 1, eradication in 1, and persistence in 1.

Of 3 subjects with a documented risk factor, 2 had allogeneic BMT. One had cerebral candidiasis as part of a mixed infection and was a failure and the other had definite candidemia and probable lung and esophageal infection and was a partial success. One subject with GVHD and underlying hematologic malignancy was a stable/failure and had hepatosplenic candidiasis.

A total of 6 subjects died during the study period or follow-up, and death was due to underlying disease.

3 cases had a follow-up assessment (30300250004, 30300510401, and 30300790605). These subjects were followed for 104. 95, and 29 days post-treatment respectively. The first subject had probable oropharyngeal candidiasis and was a partial success followed by relapse, the second had bone involvement and was a partial success, and the third with probable tonsil disease was a partial success. The latter had a relapse after 4 weeks, whereas the former continued to do well.

Mean calculated survival day from the start of treatment was 128.3 days (sd 128.0), median 99.5, (range 7, 365).

In conclusion, voriconazole appeared marginally effective in the treatment of refractory infections due to *Candida albicans*. It should be noted however that there is no other currently approved oral antifungal with a refractory candidiasis indication and that the severity of the infections as well as the underlying diseases in the patients studied, makes the anticipation of a better outcome highly unlikely. The MO recommends approval for the use of voriconazole in the treatment of such infections in subjects who have failed or are intolerant of other conventional antifungal therapies if the risk/benefit analysis supports this usage and if the bulk of evidence in the NDA support the activity of voriconazole versus *Candida albicans*.