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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-632
NDA 21-948

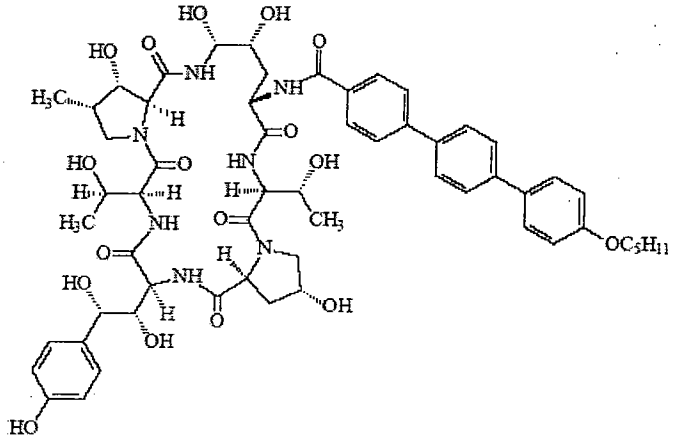
Medical Review(s)

CLINICAL REVIEW

Application Type	NDA 21-948
Submission Number	N 0 0 0
Submission Code	
Letter Date	Aug 18th, 2005
Stamp Date	
PDUFA Goal Date	Feb 18th, 2005
Reviewer Name	E. M. O'Shaughnessy, M.D.
Review Completion Date	January 31st, 2005
Established Name	Anidulafungin
(Proposed) Trade Name	Eraxis™
Therapeutic Class	Anti-fungal
Applicant	Vicuron/Pfizer
Priority Designation	S
Formulation	IV Solution
Dosing Regimen	200mg loading/100mg IV once daily
Indication	Invasive Candidiasis
Intended Population	Adults

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

Echinocandin B, 1-[(4R,5R)-4,5-dihydroxy-N_2-[[4"-(pentyloxy)[1,1',:4',1"-terphenyl]-4-yl]carbonyl]-L-ornithine]-(4R,5R)-4,5-Dihydroxy-N_2-[[4"-(pentyloxy)-p-terphenyl-4-yl]carbonyl]-L-ornithyl-L-threonyl*trans*-4-hydroxy-L-prolyl-(S)-4-hydroxy-(p-hydroxyphenyl)-L-threonyl-L-threonyl-(3S,4S)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide
Molecular formula: C58H73N7O17
Molecular weight: 1140.27



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1 EXECUTIVE SUMMARY

This document contains a clinical review of NDA 21-948. NDA 21-948 was submitted for review in August 18th, 2005 for the indication of candidemia, and other forms of invasive candidiasis. A six month priority review was granted for this indication. In this NDA, the applicant (Vicuron Pharmaceuticals Inc.) presents data to support their request for the indication of candidemia, and other forms of invasive candidiasis for an echinocandin antifungal drug, anidulafungin (Eraxis™).

The submission contains results from three clinical trials in patients with invasive candidiasis. Study VER002-9 is the pivotal study conducted in patients with invasive candidiasis, mostly candidemia. Study VER002-9b is an open-label extension study of study VER002-9. Study VER002-6 is an open-label, dose-ranging study in patients with candidemia that was previously reviewed as part of NDA 21-632.

Vicuron Pharmaceuticals Inc. submitted NDA 21-632 for anidulafungin injection for the indication of esophageal candidiasis on April 25, 2003. On May 21, 2004, the Division issued an approvable letter to Vicuron for this indication.The division had two main concerns regarding the original NDA 21-632, i.e. that a satisfactory risk- benefit ratio had not been shown for the use of anidulafungin as first-line therapy for esophageal candidiasis (study VER002-4) because of the higher relapse rate at two week follow-up in the anidulafungin treated patients compared to the fluconazole treated patients. From a safety standpoint, there may have been a signal for hepatoxicity based on one case in the anidulafungin treated group. Therefore, the division requested additional clinical data to further characterize the safety and efficacy of anidulafungin in invasive candidiasis.

In May 2005, Vicuron Pharmaceuticals Inc. submitted a complete response to the deficiencies cited in the approvable letter. Based on the data provided, anidulafungin could be approved for the treatment of esophageal candidiasis. However, an approvable letter was issued by the FDA in Nov 2005 because Pfizer Inc. was unable to complete labeling negotiations (Pfizer Inc. acquired Vicuron Pharmaceuticals Inc. during this review period).

1.1 Recommendation on Regulatory Action

From a clinical perspective, anidulafungin can be approved for the indication of candidemia, and other forms of *Candida* infection in non-neutropenic adults. Patients with meningitis, osteomyelitis and endocarditis were not studied. The overall risk-benefit balance favors approvability based on the efficacy and relative safety of anidulafungin in the treatment of patients with candidemia and other forms of *Candida* infection. The additional safety data provided in this NDA 21-948 (invasive candidiasis) is supportive of the data in the original NDA 21-362 (esophageal candidiasis).

1.2 Recommendation on Post marketing Actions

1.2.1 Risk Management Activity

Routine AERS surveillance

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are required

1.2.3 Other Phase 4 Requests

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Anidulafungin, a semisynthetic lipopeptide derived from the natural product echinocandin B, is an investigational echinocandin drug undergoing development for the treatment of fungal infections including candidemia and other forms of invasive candidiasis. Echinocandin antifungal agents are noncompetitive inhibitors of (1, 3)-beta-D-glucan synthase, a fungus-specific enzyme involved in the synthesis of glucan (Debono 1994). Glucan comprises the major portion of the cell wall of many pathogenic fungi and inhibition of its synthesis causes cell death of *Candida* spp. Mammalian cells do not have cell walls or glucan synthase.

Vicuron Pharmaceuticals Inc. submitted an application for the indication, esophageal candidiasis on April 25, 2003. The dose used in this study was 100mg loading followed by 50mg IV daily. The primary clinical reviewer for the phase 3 esophageal candidiasis study (NDA 21-632) concluded that at the end of therapy, anidulafungin met the protocol specified endpoint with 97.8% endoscopic success in the evaluable patients at the end of therapy compared to 98.7% for fluconazole. An approvable letter was issued in 2004 because further safety data was requested by the FDA because of concerns regarding hepatic safety. In May 2005, Vicuron submitted additional safety and efficacy data in a complete response to the deficiencies cited in the

approvable letter. The data presented in the complete response was adequate to support approval of anidulafungin for the indication of esophageal candidiasis. These data included results (safety and efficacy) from a randomized, double-blind, comparative study (VER002-9) of anidulafungin versus fluconazole in patients with invasive candidiasis, mostly candidemia. However, an approvable letter was issued by the FDA in Nov 2005 because Pfizer Inc. was unable to complete labeling negotiations (Pfizer Inc. acquired Vicuron Pharmaceuticals Inc. during the review period).

In this NDA 21-948, the applicant requests an indication for the treatment of candidemia and other forms of invasive candidiasis. The proposed therapeutic dose and regimen of anidulafungin for invasive candidiasis is a 200 mg intravenous (IV) loading dose on the first day, followed by 100 mg IV once daily thereafter. Both indications, i.e. esophageal candidiasis and candidemia/invasive candidiasis are included in the draft label submitted with NDA21-948.
The applicant submitted results from two new studies that employed a 200mg loading dose followed by the 100mg IV daily dose. The pivotal study, VER002-9 is a comparative, double blind study of anidulafungin compared to fluconazole IV in patients with invasive candidiasis, mostly candidemia. VER002-9b, is open-label study that was an extension of the pivotal study, VER002-9.The total number of patients exposed to anidulafungin in these two studies was 164 patients. The results from the two studies are not combined because VER002-9 is a randomized, comparative, double-blind study and study VER002-9b is a nonrandomized, noncomparative, open-label study. A review of the individual study is in Appendix A.

Overview of Invasive Candidiasis Study, VER002-9

This is a phase 3, randomized double-blind, non-inferiority multi-center study of the safety and efficacy of anidulafungin vs. fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis and prevention of complications.
Patients with candidemia and other forms of invasive candidiasis who met the inclusion and exclusion criteria were randomized (1:1 ratio) to treatment with either anidulafungin IV (200mg loading dose followed by 100mg daily maintenance dose) or fluconazole IV (800mg loading dose and 400mg maintenance dose).
The main criteria for inclusion were: *Documentation of Candida infection by:* 1) Candidemia: at least one blood culture positive for yeast (in the absence of other demonstrated foci of infection); OR 2) other forms of invasive candidiasis: positive culture for yeast from a specimen from a normally sterile site with or without a positive blood culture; positive yeast culture from a newly-placed drain in a normally sterile site; OR 3) any positive blood culture for yeast plus ophthalmic examination consistent with *Candida* endophthalmitis. AND *Clinical features by at least one of the following:*
fever; hypothermia; systolic blood pressure of less than 100 mmHg or a decrease in systolic blood pressure of at least 30 mmHg from baseline; signs or symptoms of candidemia/invasive

candidiasis; radiologic findings consistent with a diagnosis of invasive candidiasis. AND *expected hospitalization for at least 3 days.*
Main criteria for exclusion were: 1) Received > 48 hours of systemic antifungal therapy for the *Candida* infection for which they were enrolled. 2) Received prophylactic administration of fluconazole, itraconazole, or voriconazole for more than one week within 30 days prior to enrollment. 3) Known *Candida krusei* infection or suspected *Candida* osteomyelitis, endocarditis, or meningitis. 4) Had abnormal pre-specified liver tests: ALT or AST > 10 x ULN; total bilirubin > 5 x ULN. 5) Life expectancy ≤ 72 hours. Patients were stratified according to their APACHE II score (≤ 20 and > 20) and absolute neutrophil count (≤ 500 and > 500/mm^3). Study drug was to be administered for minimum treatment duration of 14 days. The maximum treatment duration of study drug was not to exceed 42 days. Qualifying patients in either group could be switched to oral fluconazole after at least 10 days of IV therapy.
Efficacy was evaluated based on clinical and microbiological responses. The primary efficacy endpoint was the global response (combined clinical and microbiological) in the microbiological intent-to-treat (Micro-ITT) population at the end of IV therapy. Safety was evaluated by the collection and analysis of data on adverse events (AEs), clinical laboratory tests, 12-lead ECGs, and temperature. An independent Data Safety Monitoring Board (DSMB) was formed to review safety data. Study VER002-9b was an open label, non comparative extension study of Study VER002-9.

1.3.2 Efficacy

Efficacy results are presented for Study VER002-9. These results were not integrated with VER-002-9B because in contrast to VER002-9, studyVER002-9B is an open label, non-comparative, extension study of VER002-9.

Study VER002-9
There were 127 patients in the anidulafungin arm, and 118 patients in the fluconazole arm in the primary efficacy population, Micro-ITT population. The study population comprised of equal numbers of males and females. The average age of the anidulafungin-treated patients was 57 years compared with 59 years for the fluconazole-treated patients. Common co-morbid diseases for both treatment groups included endocrine/metabolic disorders (~50%), bacterial sepsis and recent surgical history (both ~40%), and neoplastic diseases (~20%).
The majority of patients in the study (>90%) of patients had candidemia. Approximately 50% of patients had candidemia related to a central venous catheter.
A global response to treatment was a combined clinical and microbiological response. Anidulafungin was found to be superior to fluconazole, 96/127 (75.6%) versus 71/118 (60.2%), (CI 15.42% (3.85-26.99)) for the treatment of candidemia and other *Candida* infections in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population. Anidulafungin-treated patients had higher rates of global, clinical, and microbiological success at all time points on therapy and at the end of therapy. There were more clinical failures than microbiological failures. In the anidulafungin arm, microbiological success (eradication or presumed eradication) occurred in 110/127 patients, and in 88/118(74.6%) in the fluconazole arm. At the end of IV therapy, 8/127 (6.3%) patients treated with anidulafungin had a documented persistent *Candida* infection compared with 17/118 (14.4%) of patients treated

with fluconazole. In all secondary efficacy analyses, anidulafungin was superior to (end of IV therapy, end of all therapy and 2-week FU time points), or at least as effective as (end of oral therapy and 6-week FU time points), fluconazole consistent with the primary efficacy analysis. This study provided satisfactory additional evidence of the efficacy of anidulafungin for the treatment of another invasive *Candida* infection, i.e. candidemia.

It must be emphasized that statistical superiority for anidulafungin over fluconazole was demonstrated in a single study. Further statistical analysis demonstrated that the results from one study site (site 41 in Canada) was significantly contributing to the statistical differences in outcome between anidulafungin and fluconazole. Exclusion of this site from statistical analysis of the MITT population shows that anidulafungin is non-inferior to fluconazole. See statistics review of by C. Dixon, Ph.D. for a more detailed analysis.

GLOBAL RESPONSE AT END OF IV THERAPY (MICRO-ITT POPULATION)

Response Outcome	Anidulafungin (N = 127) n (%)	Fluconazole (N = 118) n (%)	Between-Group Difference[a]	(95% CI)
Success	96 (75.6)	71 (60.2)	15.42%	(3.85 , 26.99)
Failure	31 (24.4)	47 (39.8)		

a: Anidulafungin minus fluconazole. Source: Data from study report VER002-9, Section 14.2, Table 2.1.1

1.3.3 Safety

Anidulafungin was generally well tolerated in this group of critically ill patients with invasive candidiasis, mostly candidemia. The major safety concern was hepatic safety. Other safety issues included gastrointestinal and infusion-related reactions. No clinically significant cardiac effects were attributable to anidulafungin. The treatment-associated adverse events that were reported have been previously reported for the echinocandin class of antifungal agents. There were no adverse events uniquely associated with anidulafungin.

The results of an integrated safety analysis is presented that includes 204 patients with candidemia who received the proposed anidulafungin IV dosing regimen of 200mg/100mg; VER002-6 (n=40), VER002-9 (n=131), and VER002-9B (n=33). The database included 125 fluconazole-treated patients from study VER002-9.

No cases of hepatic failure, anaphylaxis, or QT prolongation occurred in either treatment group. Adverse events were reported by 130 (99.2%) patients in the anidulafungin arm and 122 (97.6%) patients in the fluconazole arm. The proportion of patients with related adverse events was similar, approximately 25%, in the two treatment groups.

Deaths: Fewer anidulafungin-treated patients 48/204(23.5%) than fluconazole-treated patients 39/125(31.2%) died. Case reports for deaths were reviewed, and none of the deaths could be attributed to study drugs.

The most common adverse events (drug-related and unrelated) reported in the anidulafungin group were nausea (22%), hypokalemia (20%), and diarrhea (18%). The most common reported

events for fluconazole patients were hypokalemia (19%), bacteremia (18%), pyrexia (18%), and diarrhea (18%).
In the anidulafungin group, treatment related-adverse events in ≥ 2% were hypokalemia and diarrhea and increased ALT levels, and raised alkaline phosphatase levels. Diarrhea was categorized as mild to moderate, and was twice as common in the anidulafungin treated patients, 8/204(3.9%) versus 2/125 (1.6%). Hypokalemia was present in 6/204(2.4%) anidulafungin-treated patients, and 3/125(2.9%) fluconazole-treated patients. ALT was increased in 5(2.5%) and 4 (3.2%) in the anidulafungin group and fluconazole group, respectively. Hepatic enzyme elevation required discontinuation of anidulafungin in one patient with candidemia.
Among patients in the integrated safety database, 102 (50.0%) anidulafungin-treated patients and 71 (56.8%) fluconazole-treated patients had at least one serious adverse event, (SAE). SAEs were considered related to treatment for two patients in each study arm. In the largest of the three studies, VER002-9, the three most common SAEs for patients treated with anidulafungin were cardiac arrest, multi-organ failure, and respiratory arrest. The three most common SAEs for patients treated with fluconazole were cardiac arrest, sepsis, and septic shock. A causal relationship to study drug was not established for these events.
A total of 3/204 (1.5%) patients in the total anidulafungin group and 4/125 (3.2%) in the total fluconazole group had at least 1 treatment-related AE that led to discontinuation of study medication. One patient in study VER002-9 had increased hepatic enzymes, one patient in study VER002-9B had increased creatinine, and one patient in VER002-6 had a convulsion. None of these events could be definitively related to study drug. The only treatment-related AE that led to study withdrawal for more than 1 patient in any treatment group was hepatic enzyme increased, reported by two (1.6%) patients in the total fluconazole group (VER002-9).

Infusion/Hypersensitivity reactions:
Possible infusion related reactions included local reactions such as phlebitis, and systemic reactions such as flushing of the skin, rash and dyspnea. There were no cases of anaphylaxis in the integrated analysis of safety or in the entire clinical program. Infusion reactions were generally mild. In the integrated analysis of safety for this NDA, 28(13.2%) and 9(7%) patients experienced infusion-related reactions. Flushing of the skin associated with infusion occurred in approximately 2% of anidulafungin- and fluconazole- treated patients. Flushing of the skin has been observed during infusion with other approved echinocandins. In the majority of patients, flushing lasted for 24 hours and then resolved.

Dyspnea: In an integrated safety database in 329 patients with candidemia, a total of 23 (10.8 %) of anidulafungin-treated patients and 4 (3.2%) of fluconazole-treated patients had dyspnea reported as an adverse event. None of the 23 anidulafungin treated patients were considered drug related and a temporal relation to infusion for 14 patients was not reported. The remaining 9 patients (all in comparative study VER002-9) who had dyspnea during treatment, and are tabulated below.

Summary of anidulafungin–treated patients with dyspnea in the pivotal comparative study, VER002-9

Patient ID	Underlying illness	Respiratory signs and symptoms at baseline	Day of event on therapy	Drug discontinued	Clinical reviewer attribution	Investigator attribution
09-001-001	Renal failure/ intubated at baseline	Yes	3	No	Unrelated	Unrelated
09-002-008	Diabetic/renal failure/IHD	Yes	2	No	Unlikley related	Unlikley related
09-003-004	Pulm embolus/pleural effusions	Yes	3	No	Unlikley related	Unlikley related
09-019-001	Pneumonia/pleural effusions/renal failure	Yes	5	No	Unlikley related	Unlikley related
09-032-001	Small bowel obstruction/peritonitis	Yes	3	No	Unlikley related	Unlikley related
09-041-004	Metastatic cancer/pleural effusions	Yes	5	No	Unrelated	Unrelated
09-040-001	Peritonitis/pleural effusions	Yes	5	No	Unrelated	Unrelated
09-041-005	Metastatic cancer/COPD	Yes	2	No	Unrelated	Unrelated
09-068-001	Colon cancer/sleep apnea/pl. effusions	Yes	11	No	Unrelated	Unrelated

Medical officer comment: All nine patients reported with dyspnea in this study had significant underlying respiratory illnesses, including pneumonia, pleural effusions, COPD and pulmonary embolus. The interval between the start of anidulafungin therapy and the event varied from 2 to 11 days, and did not appear to be consistently related to the time of infusion. All these patients continued to receive anidulafungin daily and no doses of anidulafungin were prematurely terminated. The medical officer concluded that these events were unrelated to study drug.

Hypotension

Hypotension as an adverse event as an adverse event was reported for 19 (14%) and 18 (14%) patients in the anidulafungin and fluconazole arms respectively, of study VER002-9. None were judged to be related to infusion or attributable to study drug. Patients with this adverse event had significant underlying illness such as heart transplant, respiratory failure on a ventilator, and cardiac failure.

On further examination of the entire NDA database, no specific reports of hypotension related to infusion were found in all phase 1, 2 and 3 studies of anidulafungin.

While histamine-like reactions characteristically incorporate a variety of symptoms including flushing, a sensation of feeling hot, nausea, tachycardia, dyspnea and hypotension, the hypotension component was not reported for patients in these studies.

In seven phase 1 studies among 118 healthy volunteers, infrequent histamine-like reactions were related to infusion rates of anidulafungin greater than 1.1mg per minute. These consisted of flushing, dyspnea and nausea. Similar reactions were seen with infusions of the vehicle alone although these were milder.

The medical officer concluded that hypotension was not documented as a drug related adverse event for anidulafungin.

Anaphylaxis

There were no cases of anaphylaxis in this integrated analysis of safety or in the entire clinical program for anidulafungin.

Medical officer's comment

Though there were no reports of anaphylaxis in the anidulafungin database, an anaphylactic reaction may possibly occur with more widespread use.

Anaphylaxis has been reported for the other approved echinocandins, caspofungin and micafungin. The AERS database was searched for reports of anaphylaxis or anaphylactic shock for caspofungin and micafungin; 6 and 3 reports were found for caspofungin and micafungin, respectively. The reports for micafungin were from Japan. In the database, a total of 609 and 65 adverse event reports of any type were found for caspofungin and micafungin, respectively.

Convulsions: Five (2.5%) anidulafungin-treated patients and 2 (1.6%) fluconazole-treated patients experienced convulsions. Following a review of the case narratives, the seizure activity reported in patients receiving anidulafungin does not appear to be related to study drug. Across the clinical program, the 929 subjects who received intravenous anidulafungin across the 20 studies in the anidulafungin clinical development program, there were 11 reports of seizures occurring in 10 (1.5%) of 672 subjects receiving anidulafungin in Phase 2 and 3 studies, either during (0.9%) or after (0.7%) treatment. Seizures occurring after therapy occurred 6, 15, 20, 21 and 29 days following the last dose. The frequency of seizures on therapy (0.7%) was similar in the 426 patients treated with fluconazole in the comparative studies. No case of seizure was reported in healthy subjects (n=202), including 10 healthy volunteers receiving anidulafungin 130mg IV daily. Based on the information provided, the cases of convulsion could not be attributed to study drug. Convulsion is listed in the micafungin (Mycamine™) label as a clinically significant event that has been reported in their overall safety database. Convulsion has been reported for caspofungin and micafungin in the AERS database.

Hepatic Safety

Hepatic Safety was extensively reviewed. Hepatic safety across the entire clinical program has been previously reviewed in the clinical review of the complete response to NDA21-632. There were more Hy's rule cases in the fluconazole group, seven versus four cases. Of the 690 patients with representative exposure to anidulafungin, the reviewer identified two cases of significant hepatic injury possibly related to anidulafungin. Both cases were confounded by inter-current illness and drugs with potential for hepatotoxicity. The hepatic chemistry abnormalities resolved

slowly after drug discontinuation. Of the 426 fluconazole-treated patients, one case of hepatic injury were considered possibly related to study drug by the clinical reviewer. The frequency of liver injury was slightly less with anidulafungin- than fluconazole-treated patients.
Overall, a few cases of significant hepatic dysfunction and hepatitis were reported in patients receiving anidulafungin in studies completed since the original NDA 21-632 submission. However, a causal relationship to anidulafungin was not established. In the two comparative studies (esophageal candidiasis and invasive candidiasis) with fluconazole, both sets of data were confounded by co-morbid conditions and concomitant medications with potential for hepatotoxicity. No hepatic safety concerns emerged when compared to fluconazole.
As with other FDA approved echinocandins, monitoring of hepatic function should be done at baseline and during anidulafungin therapy. Significant elevations in hepatic chemistry should prompt an assessment of the risks and benefits of continuing therapy. The proposed label has a section describing the hepatic effects of anidulafungin that is similar to hepatic effects section in the FDA approved labels for caspofungin and micafungin.
In summary, the safety data show that anidulafungin at a dose of 100 mg IV daily (for approximately two weeks) has a favorable safety profile compared to fluconazole 400 mg IV daily in patients with candidemia.

Risk-Benefit Assessment

Anidulafungin has a favorable risk/benefit ratio in the treatment of candidemia and some forms of invasive candidiasis. This echinocandin antifungal has shown efficacy in esophageal candidiasis, and in candidemia. Safety concerns are mainly related to hepatic effects. Information on the hepatic safety of anidulafungin from a review of Vicuron's complete response, including 292 new patients treated with anidulafungin who were not included in the original NDA, did not reveal any cases of significant hepatic dysfunction where a causal relationship to anidulafungin could be established. These cases were confounded by co-morbid conditions and concomitant medications. Anidulafungin appears to be similar to other echinocandins in its hepatic and overall safety profile.
Anidulafungin has an advantage over some other echinocandins in that it does not interact with a number of immunosuppressive drugs commonly used in clinical oncology and organ transplant medicine. For example, concomitant use of caspofungin and cyclosporine is not recommended. Monitoring of tacrolimus levels and appropriate tacrolimus dose adjustments are required for patients receiving caspofungin and tacrolimus. Monitoring of sirolimus levels is recommended for patients receiving sirolimus and micafungin. In drug interaction studies, there were no interactions between anidulafungin was combined with tacrolimus or cyclosporine. No drug interactions have been demonstrated between anidulafungin and voriconazole. In the era of combination antifungal therapy, this lack of interaction with a commonly prescribed triazole such as voriconazole is advantageous. Please refer to the original review of NDA 21-632 for additional information on risk/benefit analyses in HIV patients with esophageal candidiasis.
Higher relapse rates off anidulafungin seen in the original submission remain a concern. Consideration of the relapse rates off-therapy should be taken into account when considering anidulafungin as initial therapy for the treatment of esophageal candidiasis. The relapse rates off anidulafungin therapy can be adequately addressed in the proposed label.

1.3.4 Dosing Regimen and Administration

The proposed dose of anidulafungin is 200mg IV loading dose followed by 100mg IV daily maintenance dose.
The dose of anidulafungin (200mg loading dose/100mg daily) selected was determined by phase 1 dose-ranging studies in healthy subjects, and by a phase 2, dose-ranging study (VER002-6) of anidulafungin in patients with invasive candidiasis, Table 2. The dose of fluconazole (400mg IV daily) is the highest approved dose for invasive fungal infections.

GLOBAL SUCCESS IN VER002-6 (NDA21-632)

		Anidulafungin Dose		
Population	50 mg/day	75 mg/day	100 mg/day	All Patients
Time point	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Micro-ITT				
End of Therapy	25/37 (68)	30/40 (75)	27/39 (69)	82/116 (71)
2-week Follow-up	14/37 (38)	23/40 (58)	20/39 (51)	57/116 (49)
Efficacy Evaluable				
End of therapy	21/25 (84)	27/30 (90)	25/28 (89)	73/83 (88)
2-week Follow-up	13/18 (72)	22/26 (85)	20/24 (83)	55/68 (81)

Source: Data from VER002-6 Clinical Study Report Appendix 14 and Appendix 18

The dose of anidulafungin (200mg IV loading dose followed by 100mg IV daily) in this study is twice the dose (100mg IV loading dose followed by 50mg daily) used in the original esophageal candidiasis study, VER002-4. One could speculate that the dose (50mg IV daily) of anidulafungin in the esophageal candidiasis trial may have been low in light of subsequent dose ranging studies, VER002-6.

1.3.5 Drug-Drug Interactions

Based on the *in vitro* results, anidulafungin is unlikely to inhibit or induce the metabolism of drugs dependent on cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Also, anidulafungin is not a substrate of cytochrome P450 isoforms.
No clinically relevant drug-drug interactions were observed in human subjects receiving tacrolimus, cyclosporine, voriconazole, liposomal amphotericin B, and rifampin (a potent inducer of CYP450). Another member of the echinocandin class, caspofungin, is known to interact with cyclosporine and tacrolimus.
The lack of interaction with immunosuppressive agents and anti-fungal drugs, commonly used in clinical practice, is advantageous.
See the clinical pharmacology/biopharmaceutics review by D. Chilukuri, Ph.D.

1.3.6 Special Populations

Dosage adjustment is not required based on gender, age, race, HIV status, hepatic insufficiency, or renal insufficiency.
Dosage adjustment is not required for patients receiving anti-retroviral therapy.

Pediatrics
The pharmacokinetics of anidulafungin after daily dosing was investigated in 25 immunocompromised pediatric (2 through 11 years) and adolescent (12 through 17 years) patients with neutropenia. The steady state was achieved on the first day after loading dose (twice the maintenance dose), and the C_{max} and AUC_{ss} increased in a dose-proportional manner. Systemic exposures following 0.75 and 1.5 mg/kg/day in patients aged 2 to 17 years old were comparable to those observed in adults following 50 and 100 mg/day, respectively. No child developed invasive fungal infection during treatment with anidulafungin. The safety and efficacy of anidulafungin in children with invasive candidiasis remains to be elucidated.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Anidulafungin is a semisynthetic antifungal lipopeptide (cyclic hexapeptide with lipophilic acyl side chain) derived from the natural product echinocandin B. The chemical formula is (1-[(4R,5R)-4,5-dihydroxy-N(2)-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]carbonyl]-L-ornithine]echinocandin B); the empirical formula for anidulafungin is C58H73N7O17. Similar to other echinocandins, anidulafungin is a non-competitive inhibitor of (1,3)-β-D-glucan synthase. Glucan is the major component of the fungal cell wall and the proportion of this polysaccharide in the walls of different fungi varies. Glucan is not found in mammalian cells. To date, glucan synthase inhibition is the only documented mode of antifungal action of anidulafungin. It is believed that echinocandin antifungal activity requires the rigid cyclopeptide structure to position key fatty acid and amino acid fragments into proper alignment for biological activity.

2.2 Currently Available Treatment for Indications

Antifungal drugs that are commonly used in clinical practice for the treatment of invasive *Candida* infection include, triazoles i.e. fluconazole, voriconazole, and itraconazole, and echinocandins i.e. caspofungin and micafungin, and polyenes i.e. amphotericin B formulations. Caspofungin is the only echinocandin drug approved for treatment of candidemia in the USA. Micafungin is approved by the FDA for the treatment of esophageal candidiasis, and for anti-fungal prophylaxis of patients undergoing hematopoietic stem cell transplantation.

The IDSA 2004 guidelines for treatment of candidemia in different patient populations are summarized in table 1. CID 2004:38 161-189, Pappas *et al.*

Table 1. IDSA 2004 guidelines for treatment of candidemia

Comment: Number tables

	Therapy			
Condition	Primary	Alternative	Duration	Comments
Candidemia				
Nonneutropenic adults	AmB 0.6–1.0 mg/kg per day iv; or Flu 400–800 mg/day iv or po; or Caspofungin	AmB 0.7 mg/kg per day plus Flu 800 mg/day for 4–7 day, then Flu 800 mg/day	14 days after last positive blood culture and resolution of signs and symptoms	Remove all intravascular catheters, if possible
Children	AmB 0.6–1.0 mg/kg per day iv; or Flu 6 mg/kg q12h iv or po	Caspofungin	14–21 days after resolution of signs and symptoms and negative repeat blood cultures	PK data in children for Caspo are not available
Neonates	AmB 0.6–1.0 mg/kg per day iv; or Flu 5–12 mg/kg per day iv	Caspofungin	14–21 days after resolution of signs and symptoms and negative repeat blood cultures	PK data in neonates for Caspo are not available
Neutropenia	AmB 0.7–1.0 mg/kg per day iv; or LFAmB 3.0–6.0 mg/kg per day; or Caspofungin	Flu 6–12 mg/kg per day iv or po	14 days after last positive blood cultures and resolution of signs and symptoms and resolved neutropenia	Removal of all intravascular catheters is controversial in neutropenic patients; gastrointestinal source is common

NOTE. AmB, conventional deoxycholate amphotericin B; Caspo, caspofungin; Clo, clotrimazole; Flu, fluconazole; Itr, itraconazole; LF, lipid formulation; Nys, nystatin; PK, pharmacological; Vor, voriconazole; 5-FC, 5-flucytosine.
a Caspofungin dosing in adults consists of 70-mg loading dose followed by 50 mg iv.

2.3 Availability of Proposed Active Ingredient in the United States

Please refer to the chemistry review by M. R. Seggel, Ph. D.

Comment: Add info re class

2.4 Important Issues With Pharmacologically Related Products

2.5 Presubmission Regulatory Activity

NDA 21-948 was submitted for review in August 18th, 2005 for the indication of candidemia, and other forms of invasive candidiasis. A six month priority review was granted for this indication.

Vicuron submitted NDA 21-632 for anidulafungin injection for the indication of esophageal candidiasis on April 25, 2003. On May 21, 2004, the Division issued an approvable letter to Vicuron for NDA 21-632.
The division had two main concerns regarding the original NDA 21-632, i.e. that a satisfactory risk- benefit ratio had not been shown for the use of anidulafungin as first-line therapy for esophageal candidiasis (study VER002-4) because of the higher relapse rate at two week follow-up in the anidulafungin treated patients compared to the fluconazole treated patients. From a safety standpoint, there may have been a signal for hepatoxicity based on one case in the anidulafungin treated group. Therefore, the division requested additional clinical data to further characterize the safety and efficacy of anidulafungin in invasive candidiasis.

Brief Overview of pre NDA 21-948 Meetings

Comment: Make a table like Maureen's

On December 22, 2004, Vicuron requested a face to face meeting to discuss the future submission plans for anidulafungin for the indications of esophageal candidiasis (EC) and invasive candidiasis (IC).
On February 16, 2005, a briefing package was submitted to the Division in preparation for this meeting. On March 17, 2005, the Division responded by fax to the questions in Vicuron's background package.
On March 28, 2005, the Review Team provided the following response:
The Division acknowledged the pediatric waiver granted for anidulafungin for the indication of esophageal candidiasis. Following resubmission, this waiver will remain in effect for the indication of esophageal candidiasis. The Division agreed with Vicuron's plan to submit a deferral for the pediatric requirement for the invasive candidiasis indication.
On May 27th, 2005, a complete response to the FDA action letter of May 2004 was submitted by Vicuron Pharmaceuticals Inc. Concurrent with the submission of the complete response, Vicuron was acquired by Pfizer Inc.
To address the FDA's concerns, the applicant submitted data from a large, adequate and well-controlled clinical trial in patients with invasive candidiasis as the pivotal study in the complete response submission. A hepatologist's safety report and an integrated summary of safety across the entire clinical program were also submitted. The applicant addressed the concern regarding relapse rates off- therapy by requesting a second-line indication for anidulafungin in esophageal candidiasis.
From a clinical perspective, anidulafungin can be approved for the indication of esophageal candidiasis. Pfizer Inc. indicated that they were not able to negotiate the label for this indication in a timely manner. On November 25th, 2005, an approvable letter was issued pending labeling negotiations. In December 2005, Pfizer submitted a new trade name for anidulafungin, i.e.

Eraxis™ instead of [ ] The new trade name, ERAXIS™ was reviewed by DDMAC and DMETS and was found to be acceptable.

2.6 Other Relevant Background Information

Anidulafungin is not approved in countries outside the USA at this time.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The application is recommended for approval from the chemistry, manufacturing and controls perspective. See the chemistry review by M.R. Seggel, Ph. D. for a detailed discussion.

3.2 Animal Pharmacology/Toxicology

There are no animal pharmacology or toxicology findings that preclude the approval of anidulafungin. Liver toxicity, including single cell hepatocellular necrosis, hepatocellular hypertrophy and increased liver weights were observed in monkeys and rats at doses equivalent to approximately eight times the human exposure for 3 months. Skeletal abnormalities in rat fetuses and reduction in litter weights in rabbits were observed in animal studies. Anidulafungin has been found in the milk of lactating rats. Long term carcinogenicity studies have not been conducted in animals. See Dr. Owen McMaster's animal pharmacology/toxicology review for a detailed analysis. The following is an excerpt from Dr. Owen McMaster's animal pharmacology/toxicology review.

"Toxicology studies of ANIDULAFUNGIN have mostly been conducted in rats and monkeys and include intravenous studies of up to 13 weeks. These are supported by additional studies in mice and dogs.

In repeat dose studies, the principal clinical finding was a transient infusion reaction consisting of swollen snout, red ears and hypoactivity. These signs were only observed for the first few days of dosing. These effects were not listed among the common adverse events in the clinical trial.

Rats treated with ANIDULAFUNGIN exhibited a regenerative anemia which the sponsor ascribes to excessive blood sampling. No hemolysis was observed in monkeys. In vitro exposure of rat or human blood cells to ANIDULAFUNGIN showed that rat erythrocytes were more sensitive than human erythrocytes to the hemolytic effects of ANIDULAFUNGIN (0.7 % hemolysis in humans versus 17 % in rat cells at 8.78 mg/mL ANIDULAFUNGIN). This

hemolysis seen in rats seems to be a species specific finding.
In four- and thirteen week studies in rats and monkeys, liver toxicity was observed, including increased liver weights, hepatocellular hypertrophy, increased activity of AST and ALT and liver necrosis. These changes were beginning at doses around 8 fold higher than recommended clinical doses based on AUC comparisons. Animals allowed a one month recovery period after the end of dosing still showed microscopic changes in the liver. Increased liver enzymes have been observed in patients that received high doses of ANIDULAFUNGIN (see Overdose section of the label). Other signs observed in high dose animals included kidney tubular vacuolation, skeletal muscle atrophy and increased spleen, kidney, and lung weight.
ANIDULAFUNGIN injections resulted in skeletal changes in rat fetuses including incomplete ossification of various bones and wavy, misaligned or misshapen ribs. These bone changes occurred at maternal doses at or above 2 mg/kg/day, a dose equivalent to 0.4 times the recommended clinical maintenance dose (based on body surface area comparisons).
In rabbits at higher doses, (4 to 8 times the recommended dose) there was a reduction in litter weight and increased late resorptions. There was an increase in the number of fetuses and litters with an extra aortic arch at doses two times the recommended dose. Drug was detected in the blood of pups and in the milk of drug-treated rats."

Microbiology

No new information was submitted regarding preclinical microbiology. *In vitro* studies of anidulafungin have shown fungicidal activity against *Candida* species. Across the clinical program (11 studies), anidulafungin demonstrated activity against *C. albicans, C. glabrata, C. parapsilosis, and C. tropicalis*. Anidulafungin also demonstrated activity against other *Candida* species such as *C. krusei*, and *C. guilliermondii* but the numbers of infected patients were too low to make a definitive conclusion regarding activity. In the pivotal candidemia study, VER002-9, the distribution of baseline pathogens is similar between the two treatment arms.

The relative proportion of isolates is consistent with the *Candida* species found in hospitalized patients. See medical officer's review of pivotal study, VER002-9 on pages 96, 97 and 103. The following is an excerpt from L. Steele-Moore's microbiology review (October 2005) of studies VER002-9, and VER002-9B.
"In the VER002-9 study at the end of intravenous (IV) therapy there were 194 patients evaluable (103 patients in the anidulafungin treatment group and 91 in the fluconazole group). Of these, a majority were infected with C. albicans (n=108), and the remaining with Candida species other than C. albicans (28 C. glabrata, 20 C. parapsilosis, 16 C. tropicalis, 2 C. guilliermondii, 2 C. lusitaniae, and 1 C. famata) in both treatment arms. Mixed infections were seen in both groups.
Global success (combined clinical and microbiological) at end of treatment (EOT) in the MITT population was seen in 90 patients (87%) in the anidulafungin arm and 68 patients (75%) in the fluconazole arm. At the follow up (FU) visit, overall global success in the anidulafungin arm was seen in 71 out of 88 patients (80.7%) vs. 51/76 (67.1%) in the fluconazole arm. Baseline pathogen of a Candida species other than C. albicans was observed in 32 patients in the anidulafungin arm and 29 patients in the fluconazole arm. Anidulafungin treated patients had higher proportions of global success at EOT and at FU. Overall, there was no correlation between clinical outcome and anidulafungin or fluconazole MICs.

In the VER002-9B study (a noncomparative study) at the end of IV therapy there were 17 patients evaluable. C. albicans (n=8) and C. glabrata (n=7) were the most frequently isolated baseline pathogens. Global success at EOT in the MITT population was observed in 21 of 31 patients (67.7%). There was no correlation between clinical outcome and anidulafungin MICs. Microbiological success at the pathogen level was comparable to those in study VER002-9 at EOT (88% for all species). Global, clinical, and microbiological success was sustained at the same level (64.3%, 61.3%, 61.3% respectively) at the 2 and 6 week follow up visits."

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of data for the efficacy analysis was from Study VER002-9, a phase 3, randomized, comparative, non-inferiority study of anidulafungin versus fluconazole in invasive candidiasis, mostly candidemia. The results of three clinical studies were submitted for review and data from these studied were integrated in the safety analysis - two clinical studies VER002-9 and VER002-9b and a phase 2, open label dose ranging study in invasive candidiasis (VER002-6). Study VER002-6 was previously reviewed in NDA21-632.
Other sources of information used in the review process included:
The clinical review of NDA21-632 from 2004 by E. Ibia, M.D.
Diflucan™ (Fluconazole) product labeling
Cancidas™ (Caspofungin) medical officer review and product labeling
Micafungin™ (Micafungin) medical officer review and product labeling
Vfend™ (Voriconazole) product labeling
Prior hepatology consultations from Dr. J. Senior (FDA) for anidulafungin, and micafungin
In addition to the submitted data, the Infectious Diseases Society of America (IDSA) guidelines for the management of invasive candidiasis were reviewed as well as a Pub-Med search of published literature regarding the safety and efficacy of echinocandin antifungal drugs.
Note: The majority of tabular and graphical information is from the applicant's submission as referenced in the footnotes of the tables and graphics.

4.2 Tables of Clinical Studies

Table 2. CLINICAL STUDIES

CLINICAL STUDIES	
VER002-9	A Phase 3, Double-Blind, Randomized, Multi-Center, Study of the Safety and Efficacy of Anidulafungin vs. Fluconazole in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications
VER002-9B	A Phase 3, Open Label, Non-Comparative, Multi-Center, Study of the Safety and Efficacy of Anidulafungin in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications
VER002-6*	A Phase 2, Open-Label, Randomized, Dose-Ranging Study of the Safety and Efficacy of Intravenous Anidulafungin (VER002) in the Treatment of Patients with Invasive Candidiasis

*VER002-6 has been previously reviewed as part of NDA21-632

4.3 Review Strategy

1) Review of study reports for VER002-9, VER002-9b and VER002-6.
2) Review of CRTs and case summaries of efficacy studies for adherence to inclusion/exclusion criteria, case and outcome definition
3) Review of case summaries of deaths, serious adverse events, and adverse events of concern including but not limited to hepatic safety, cardiac safety, neurological safety and infusion-related adverse events.

4) An integrated analysis of safety for all trials submitted in NDA 21-948

4.4 Data Quality and Integrity

A routine DSI inspection of site 41 in Canada was satisfactory.

Data Integrity, VER002-9

A total of seven patients in the fluconazole arm were unblinded. None of the patients in the anidulafungin arm were unblinded. Five were unblinded by investigator request and two were accidentally unblinded. Two patients were not protocol evaluable.

Table 3. Unblinded Patients

Reason for the Unblinding Patient ID	Treatment	Efficacy Evaluable Status
Randomization fax accidentally sent to study coordinator		
25-001	FLU	Yes, study coordinator not involved in efficacy assessment*
73-001	FLU	Yes, study coordinator not involved in efficacy assessment*
Per Investigator request for patients with clinical failure		
02-012	FLU	Yes, not a protocol violation
39-001	FLU	Yes, not a protocol violation
71-001	FLU	Yes, not a protocol violation
Per Investigator request for patients with serious adverse events		
10-002	FLU	No, received only 1 dose of study drug
31-002	FLU	No, received only 1 dose of study drug

* Both study coordinators were removed from care of unblinded patients
Source:Data from Section 16.2.3, Listing 1.5

4.5 Compliance with Good Clinical Practices

The applicant stated that studies complied with good clinical practices based ICH "Good Clinical Practice-Consolidated Guideline," published 9 May1997; and/or with the applicable FDA regulations (21 CFR Parts 50, 56, and 312) or other applicable foreign regulations.

4.6 Financial Disclosures

The applicant submitted signed documentation that it has not entered into financial arrangements with any of the clinical investigators.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The bulk of the pharmacokinetic (PK) data and the metabolism, distribution, excretion of anidulafungin have been previously reviewed in NDA 21-632.
The only new PK data provided in this NDA21-948 was a pediatric study conducted in 25 immunocompromised children, and PK drug interaction studies with tacrolimus and voriconazole.
There was no PK drug-drug interaction observed when anidulafungin was administered with voriconazole or tacrolimus in healthy male subjects. Five of the 36 subjects enrolled in this study experienced adverse events of elevated ALT on Day 12 or 16. The subjects experiencing these events were asymptomatic, and the elevations were mild and transient.

In the pediatric study, the pharmacokinetics of anidulafungin after daily dosing was investigated in 25 immunocompromised pediatric (2 through 11 years) and adolescent (12 through 17 years) patients with neutropenia. The steady state was achieved on the first day after loading dose (twice the maintenance dose), and the C_{max} and AUC_{ss} increased in a dose-proportional manner. Systemic exposures following 0.75 and 1.5 mg/kg/day in patients aged 2 to 17 years old were comparable to those observed in adults following 50 and 100 mg/day, respectively. No child developed invasive fungal infection during treatment with anidulafungin. The safety and efficacy of anidulafungin in children remains to be elucidated.
This is an excerpt from Dr Chilukuri's clinical pharmacology review of NDA 21-632:
PK of anidulafungin were examined in healthy subjects and those with mild, moderate, or severe hepatic impairment [Child-Pugh scores 5 to 6 (mild), 7 to 9 (moderate), and 10 to 15 (severe)] in an open-label study (VER002-2). Anidulafungin concentrations were not increased because of hepatic impairment. C_{max}, AUC, V_{ss}, and CL were similar for healthy subjects, subjects with mild, moderate and severe hepatic impairment.

The results of the renal impairment study indicated that there were no changes in anidulafungin PK due to renal impairment. Also, anidulafungin PK parameters were not affected by whether the drug was given before or after dialysis, nor was anidulafungin found in any dialysate samples.
See Dr. D. Chilukuri's clinical pharmacology/biopharmaceutics reviews for NDA21-632 and NDA21-948 for a detailed discussion of pharmacokinetics.

5.2 Pharmacodynamics

See section 5.1 above.
See Dr. D. Chilukuri's clinical pharmacology/biopharmaceutics reviews for NDA21-632 for a detailed discussion of pharmacodynamics

5.3 Exposure-Response Relationships

See section 5.1 above. See Dr. D. Chilukuri's clinical pharmacology and biopharmaceutics review for a detailed discussion of exposure-response relationships.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is the treatment of patients with candidemia and other forms of invasive candidiasis ; [ ] More than 90% of patients studied had candidemia. Less than 20 patients had *Candida* infection at other sites. Patients with meningitis, osteomyelitis, and endocarditis were excluded.

6.1.1 Methods

Review of study reports for VER002-9, VER002-9b and VER002-6.
Clinical, safety, and laboratory data was reviewed as well as individual case reports were reviewed.
Review of case summaries of deaths, serious adverse events, and adverse events of concern including but not limited to hepatic safety, cardiac safety, neurological safety and infusion-related adverse events.
An integrated analysis of safety was performed for all trials submitted in NDA 21-948

The majority of tables and some text in the review are taken directly from the applicant's study report.

6.1.2 General Discussion of Endpoints

Primary Endpoint

The primary efficacy endpoint was the global response (based on the clinical and microbiological responses) at the end of IV therapy in the Micro-ITT population.

Patients were assigned a global response in the Micro-ITT population as follows:

Success: required both a clinical and microbiological success as described below

Clinical Success

- Cure: Resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or oral fluconazole required to complete the course of therapy. OR
- Improvement: Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or additional oral fluconazole required.

AND

Microbiological success

- Eradication (documented or presumed): Culture was negative for all *Candida* species present at baseline (documented), or culture data were not available for a patient with a successful clinical response (presumed).

Failure:

Clinical failure

- No significant improvement in signs and symptoms, or death due to the *Candida* infection.

Microbiological failure

- Documented or presumed persistence or recurrence of baseline *Candida* infection; super-infection with a new *Candida* species while on study medication; emergence of a new *Candida* species at an original site of infection or at distant, sterile site after study medication completion.
- The sponsor considered the following patients "indeterminate" and evaluated them as failures,
    - patients who received fewer than 3 doses of study medication
    - death not due to the *Candida* infection;
    - withdrawal from study medication for reasons other than failure

Medical officer's comment
In the efficacy evaluable population, the same criteria of success and failure were applied, except that patients with an "indeterminate" response were excluded from the evaluation. Indeterminate results that were listed as deaths were included in the efficacy evaluable population in the FDS statistical analysis. See statistical review by Cheryl Dixon, Ph.D.

Microbiological Response at the Baseline Pathogen Level

Success:

- Eradication (documented or presumed): Culture was negative for the *Candida* species present at baseline (documented), or culture data were not available for a patient with a successful clinical response (presumed).

Failure:

- Persistence (documented or presumed): The baseline *Candida* species was present in repeat cultures (documented), or culture data were not available for a patient with a clinical response of failure (presumed).
- Recurrence (documented or presumed): The baseline *Candida* species isolated following eradication (documented), or culture data were not available for a patient with a clinical response of failure after a previous response of success (presumed).
- Indeterminate: culture data were not available for a patient with a clinical response of indeterminate.

Secondary Endpoints

Global response at all secondary time points in the Micro-ITT population
Global response at the end of IV therapy in the modified Micro-ITT population
Global response at all time points in the efficacy evaluable population
Clinical response at all time points in the Micro-ITT and efficacy evaluable populations
Patient level microbiological response at all time points in the Micro-ITT and efficacy evaluable populations
Pathogen level microbiological response in the Micro-ITT and efficacy- evaluable populations at the end of IV therapy and 2 week FU time points only.
Death directly attributable to candidemia/ invasive candidiasis and all cause mortality

Prevention of Late Complications

The number of patients who developed endophthalmitis and the number of patients who had global success at the 2-week FU and then had a positive *Candida* culture (blood or other

normally sterile site) by the time of the 6-week FU were summarized. No statistical comparisons were done.

6.1.3 Study Design

Study VER002-9 is a phase 3, double-blind, randomized, multi-center, non-inferiority study of the safety and efficacy of anidulafungin versus fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis. All patients were to receive the study medication for minimum treatment duration of 14 days from the time of the last negative culture and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Total treatment duration was not to exceed 42 days.
Patients in either group were permitted to switch to oral fluconazole (400 mg/daily) after at least 10 days of IV treatment if the following criteria were met,

- the patient was afebrile for at least 24 hours;
- the patient was able to tolerate oral medications;
- the last blood culture was negative for *Candida* species;
- reduction of signs and symptoms of the *Candida* infection such that the investigator felt it was appropriate to switch to oral fluconazole (oral fluconazole was not to be given as prophylaxis).

The patients were followed for safety through the 6-week follow-up (FU) visit.
The duration of therapy and of follow-up was adequate to determine outcome.

Study Sites: Study sites were located in six countries: 33 in the United States, 8 in Canada and 4 in Europe. Forty-seven of 70 investigators enrolled patients. The majority of patients were enrolled in the United States. The number of treated patients by country was USA (185), Canada (59), Belgium (2), Germany (3) and Italy (6) and Netherlands (1). The largest number of patients (25) was enrolled at a single site in Canada.

Patients with candidemia and other forms of *Candida* infection who met the inclusion and exclusion criteria were randomized (1:1 ratio) to treatment with either anidulafungin IV (200mg loading dose followed by 100mg daily maintenance dose) or fluconazole IV (800mg loading dose and 400mg maintenance dose).
The main criteria for inclusion were: *Documentation of Candida infection by:* 1) Candidemia: at least one blood culture positive for yeast (in the absence of other demonstrated foci of infection); OR 2) other forms of invasive candidiasis: positive culture for yeast from a specimen from a normally sterile site with or without a positive blood culture; positive yeast culture from a newly-placed drain in a normally sterile site; OR 3) any positive blood culture for yeast plus ophthalmic examination consistent with *Candida* endophthalmitis. AND *Clinical features by at least one of the following:*
fever; hypothermia; systolic blood pressure of less than 100 mmHg or a decrease in systolic blood pressure of at least 30 mmHg from baseline; signs or symptoms of candidemia/invasive

candidiasis; radiologic findings consistent with a diagnosis of invasive candidiasis, AND *expected hospitalization for at least 3 days.*
Main criteria for exclusion were: 1) Received > 48 hours of systemic antifungal therapy for the *Candida* infection for which they were enrolled. 2) Received prophylactic administration of fluconazole, itraconazole, or voriconazole for more than one week within 30 days prior to enrollment. 3) Known *Candida krusei* infection or suspected *Candida* osteomyelitis, endocarditis, or meningitis. 4) Had abnormal pre-specified liver tests: ALT or AST > 10 x ULN; total bilirubin > 5 x ULN. 5) Life expectancy ≤ 72 hours.
Patients were stratified according to their APACHE II score (≤ 20 and > 20) and absolute neutrophil count (≤ 500 and > 500/mm^3). Study drug was to be administered for minimum treatment duration of 14 days. The maximum treatment duration of study drug was not to exceed 42 days. Qualifying patients in either group could be switched to oral fluconazole after at least 10 days of IV therapy.
Efficacy was evaluated based on clinical and microbiological responses. The primary efficacy endpoint was the global response (combined clinical and microbiological) in the microbiological intent-to-treat (Micro-ITT) population at the end of IV therapy. Safety was evaluated by the collection and analysis of data on adverse events (AEs), clinical laboratory tests, 12-lead ECGs, and temperature. An independent Data Safety Monitoring Board (DSMB) was formed to review safety data.

Protocol Objectives

Primary objective:

- to determine if anidulafungin is at least as effective as fluconazole with respect to the global response (combined clinical and microbiological response at the end of IV therapy) for the treatment of patients with a diagnosis of candidemia and/or other forms of invasive candidiasis

Secondary objectives:

- to compare anidulafungin with fluconazole in this patient population for safety profile, the prevention of late infections and the clinical and microbiological efficacy at various time points

6.1.4 Efficacy Findings

There were 127 patients in the anidulafungin arm, and 118 patients in the fluconazole arm in the primary efficacy population, Micro-ITT population. The study population comprised of equal numbers of males and females. The average age of the anidulafungin-treated patients was 57 years compared with 59 years for the fluconazole-treated patients. Common co-morbid diseases for both treatment groups included endocrine/metabolic disorders (~50%), bacterial sepsis and recent surgical history (both ~40%), and neoplastic diseases (~20%).
The majority of patients in the study (>90%) of patients had candidemia. Approximately 50% of patients had candidemia related to a central venous catheter; the global success rates were higher

in the anidulafungin arm compared to the fluconazole arm, 74 (85.1%) versus 50(73.5%), respectively, in those patients who had a central IV catheter and had it removed. Three patients in each arm had a central IV catheter and it was not removed

A global response to treatment was a combined clinical and microbiological response. Anidulafungin was found to be superior to fluconazole (75.6% versus 60.2%), (CI 15.42% (3.85-26.99) for the treatment of invasive candidiasis/candidemia in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population. Anidulafungin-treated patients had higher rates of global, clinical, and microbiological success at all time points on therapy and at the end of therapy. In all secondary efficacy analyses, anidulafungin was superior to (end of IV therapy, end of all therapy and 2-week FU time points), or at least as effective as (end of oral therapy and 6-week FU time points), fluconazole consistent with the primary efficacy analysis. This study provided satisfactory evidence of the efficacy of anidulafungin for invasive *Candida* infection.

It must be emphasized that statistical superiority was demonstrated in a single study. Further statistical analysis demonstrated that the results from one study site (site 41 in Canada) was significantly contributing to the statistical differences in outcome between anidulafungin and fluconazole. Exclusion of this site from statistical analysis shows that anidulafungin is non-inferior to fluconazole.

See review by Dr. C. Dixon, Ph. D. for a detailed statistical analysis.

GLOBAL RESPONSE AT END OF IV THERAPY (MICRO-ITT POPULATION)

	Anidulafungin	Fluconazole		
Response	(N = 127)	(N = 118)	Between-Group	
Outcome	n (%)	n (%)	Difference[a]	(95% CI)
Success	96 (75.6)	71 (60.2)	15.42%	(3.85 , 26.99)
Failure	31 (24.4)	47 (39.8)		

a: Anidulafungin minus fluconazole. Source: Data from study report VER002-9, Section 14.2, Table 2.1.1

6.1.5 Clinical Microbiology

Global success (combined clinical and microbiological) at end of treatment (EOT) in the MITT population was seen in 90 patients (87%) in the anidulafungin arm and 68 patients (75%) in the fluconazole arm.

See excerpt from Microbiology review by L. Steele-Moore, M.Sc.

"In the VER002-9 study at the end of intravenous (IV) therapy there were 194 patients evaluable (103 patients in the anidulafungin treatment group and 91 in the fluconazole group). Of these, a majority were infected with Candida albicans (n=108), and the remaining with Candida species other than C. albicans (28 C. glabrata, 20 C. parapsilosis, 16 C. tropicalis, 2 C. guilliermondii, 2 C. lusitaniae, and 1 C. famata) in both treatment arms. Mixed infections were seen in both groups. Global success (combined clinical and microbiological) at end of treatment (EOT) in the MITT population was seen in 90 patients (87%) in the anidulafungin arm and 68 patients (75%) in the fluconazole arm. At the follow up (FU) visit, overall global success in the anidulafungin arm was seen in 71 out of 88 patients (80.7%) vs. 51/76 (67.1%) in the fluconazole arm. Baseline pathogen of a Candida species other than C. albicans was observed in

32 patients in the anidulafungin arm and 29 patients in the fluconazole arm. Anidulafungin treated patients had higher proportions of global success at EOT and at FU. Overall, there was no correlation between clinical outcome and anidulafungin or fluconazole MICs."

6.1.6 Efficacy Conclusions

In study VER002-9, anidulafungin was superior to fluconazole for the treatment of invasive candidiasis/candidemia in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population. In all secondary efficacy analyses, results were comparable with the primary efficacy analysis. Anidulafungin-treated patients had higher rates of global, clinical, and microbiological success at all time points on therapy and at the end of therapy. Candidemia was present in more than 90% of patients in both study arms. Approximately half of all patients had invasive candidiasis related to an IV catheter. Most patients had a single baseline pathogen; *C. albicans* and *C. glabrata* were the baseline pathogens most frequently isolated.

- Anidulafungin (96/127, 75.6%) was superior to fluconazole (71/118, 60.2%) for the treatment of invasive candidiasis/candidemia in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population. It must be emphasized that the result of superiority is from one study.
- At the end of IV therapy, 6.3% of patients treated with anidulafungin had a documented persistent *Candida* infection compared with 14.4% of patients treated with fluconazole.
- In all secondary efficacy analyses anidulafungin (end of IV therapy, end of all therapy and 2-week FU time points), (end of oral therapy and 6-week FU time points), results were comparable with the primary efficacy analysis.
- The results of the study may not be applicable to neutropenic patients due to the low numbers of patients with neutropenia in the study. Neutropenic patients accounted for 3 (2.4%), and 4 (3.4%) in the anidulafungin and fluconazole arms, respectively.

7 INTEGRATED REVIEW OF SAFETY

Safety data from the three trials conducted in patients with invasive candidiasis are summarized. There were no adverse events that were specifically related to anidulafungin. No major safety concerns emerged during the review of the pivotal invasive candidiasis study, VER002-9.

The integrated safety database consisted of data from 329 treated patients with candidemia/invasive candidiasis who participated in two phase 3 clinical studies (VER002-9 and VER002-9b) and one phase 2 study (VER002-6) in which anidulafungin maintenance dosages of 100 mg IV per day were administered.

Patient Disposition

There were 204 patients in the ITT population who received 100mg IV anidulafungin, and 125 patients who received 400mg IV fluconazole. The 204 patients include 131 patients from VER002-9, 33 patients from Study VER002-9B, and 40 patients from one arm of study VER002-6.

The disposition of patients in the integrated safety database is summarized in Table 4. In studies VER002-9 and VER002-9b only, the investigators recorded whether patients received the full course of study medication. A total of 164 patients from study VER002-9 and VER002-9B received 100mg IV anidulafungin. More patients in the anidulafungin group completed study drug, 122/204 (74.4%) versus 77/125 (61.6%). This difference was largely caused by more discontinuations (from study medication) due to AEs and worsening clinical status in the fluconazole-treated patients.

A total of 42 (25.6%) in the anidulafungin group and 48 (38.4%) fluconazole patients discontinued study medication; 16(9.8%) of anidulafungin-patients and 21(16.8%) fluconazole-treated patients discontinued study medication due to an adverse events. A total of 67(32.8%) versus 45(36.0%) did not complete the study. The main reasons for not completing the study were deaths and lost to follow up.

Table 4. Patient Disposition, Phase 2-3 Integrated Database

	Anidulafungin			Fluconazole		
	≤14 days	>14 days	Total	≤14 days	>14 days	Total
Total enrolled/randomized	128	76	206	90	35	129
Study VER002-6	21	19	41	0	0	0
Study VER002-9	86	45	132	90	35	129
Study VER002-9b	21	12	33	0	0	0
Total treated (ITT)	**128**	**76**	**204**	**90**	**35**	**125**
Total ITT in VER002-9 and VER002-9b	107	57	164	90	35	125
Completed study medication[a]	69 (64.5)	53 (93.0)	122 (74.4)	46 (51.1)	31 (88.6)	77 (61.6)
Did not complete study medication[a]	38 (35.5)	4 (7.0)	42 (25.6)	44 (48.9)	4 (11.4)	48 (38.4)
Reason study medication discontinued						
Adverse event	14 (13.1)	2 (3.5)	16 (9.8)	17 (18.9)	4 (11.4)	21 (16.8)
Patient withdrew consent	6 (5.6)	0	6 (3.7)	4 (4.4)	0	4 (3.2)
Patient non-compliance	1 (0.9)	0	1 (0.6)	0	0	0
Worsening clinical status	11 (10.3)	2 (3.5)	13 (7.9)	16 (17.8)	0	16 (12.8)
Investigator discretion	6 (5.6)	0	6 (3.7)	5 (5.6)	0	5 (4.0)
Vicuron's request	0	0	0	1 (1.1)	0	1 (0.8)
Patient lost to follow-up	0	0	0	1 (1.1)	0	1 (0.8)
Completed study[b]	81 (63.3)	56 (73.7)	137 (67.2)	56 (62.2)	24 (68.6)	80 (64.0)
Did not complete study[b]	47 (36.7)	20 (26.3)	67 (32.8)	34 (37.8)	11 (31.4)	45 (36.0)
Reason study discontinued						
Adverse event[c]	7 (5.5)	1 (1.3)	8 (3.9)	0	0	0
Patient or investigator request[c]	5 (3.9)	1 (1.3)	6 (2.9)	0	0	0
Patient died	24 (18.8)	12 (15.8)	36 (17.6)	28 (31.1)	10 (28.6)	38 (30.4)
Patient lost to follow-up	7 (5.5)	5 (6.6)	12 (5.9)	6 (6.7)	1 (2.9)	7 (5.6)
Other[c]	4 (3.1)	1 (1.3)	5 (2.5)	0	0	0

Source: Appendix A, Table 1-1. Includes data from VER002-6, VER002-9, and VER002-9b
Note: Only patients in one arm (200 mg loading dose followed by 100 mg daily dose) of the VER002-6 study were integrated in the ISS database.
a Only patients in study VER002-9 and VER002-9b had this information collected. Percentages are based on the number of ITT patients in studies VER002-9 and VER002-9b.
b This information was collected for all studies in the integrated safety database. Percentages are based on the total ITT population.
c This reason was only collected for VER002-6.

Exposure to Study Drug

The median duration of IV study drug was 14 and 11 days for anidulafungin and fluconazole, respectively. The median exposure to oral fluconazole following IV therapy was 7 and 5 days for anidulafungin- and fluconazole-treated patients, respectively.

Table 5. Exposure to Study Drug

	Anidulafungin			Fluconazole		
	≤14 days (N=128)	>14 days (N=76)	Total (N=204)	≤14 days (N=90)	>14 days (N=35)	Total (N=125)
Number of IV Doses						
N	128	76	204	90	35	125
Mean	10	18.8	13.3	9.1	19.6	12.0
SD	3.97	5.07	6.16	4.02	5.02	6.40
Median	11	17.0	14.0	10.0	18.0	11.0
Minimum - Maximum	1-15	12 -38	1 - 38	1 - 14	14 -36	1 - 36
Duration of IV treatment (days)						
N	128	76	204	90	35	125
Mean	10.0	19.2	13.5	9.1	19.9	12.2
SD	3.99	5.05	6.25	3.99	5.16	6.51
Median	11.0	17.0	14.0	10.0	18.0	11.0
Minimum - Maximum	1 - 14	15 -38	1 - 38	1 - 14	15 -37	1 - 37
Duration of oral treatment (days)a						
N	37	4	41	30	6	36
Mean	9.5	11.0	9.7	8.7	9.2	8.8
SD	6.99	10.83	7.27	8.41	3.60	7.78
Median	7.0	7.0	7.0	4.5	8.5	5.0
Minimum - Maximum	1 - 32	3 - 27	1 - 32	1 - 33	5 - 15	1 - 33

Source: Appendix A, Table 3-1. Includes data from VER002-6, VER002-9, and VER002-9b
a Only patients in VER002-9 and VER002-9b could continue treatment with oral fluconazole.

Baseline Characteristics

The anidulafungin and fluconazole treatment groups were well matched with respect to demographic characteristics. The majority (67%) of patients were white. There were 106 (52%) men and 98 (48%) women in the anidulafungin group, and 69 (34%) were age ≥ 65yrs. Approximately 40% of patients had impaired renal function with baseline creatinine clearance values <50 mL/min. Baseline hepatobiliary status was elevated for approximately one-third of patients in each treatment group. The mean Apache II score among anidulafungin- and fluconazole-treated patients was 14.7 and 14.4, respectively. The percentage of patients with a baseline APACHE II score >20 was 20.6% in the anidulafungin group and 17.6% in the fluconazole group. Within each treatment group, there were no major differences in demographic characteristics among patients treated for ≤14 days or >14 days. No pregnancies were reported in the clinical studies of anidulafungin.

7.1 Methods and Findings

7.1.1 Deaths

A greater percentage of patients in the total fluconazole group 39/125 (31.2%) than the total anidulafungin group 48/204 (23.5%) had at least one AE with the outcome of death. In both the total anidulafungin and total fluconazole groups, cardiac arrest (2.9% anidulafungin, 5.6% fluconazole) was the most common AE resulting in death. Deaths were not found to be related to study drug. One patient ID # 011-001 from study VER002-6 has been previously reviewed. This patient had a complex medical history including hereditary cystinosis, renal transplant and iatrogenic immunosuppression; he was unresponsive to verbal stimuli and was minimally responsive to pain (following a cardiac arrest) on entry into the study. The patient experienced convulsions on anidulafungin therapy. The cause of death was metabolic acidosis and respiratory failure. The underlying cause of the patient's seizures was most likely to be multi-factorial including anoxia secondary to cardiac arrest, metabolic acidosis and concomitant medications.

Table 6. Adverse Events with the Outcome of Death: Phase 2-3 Integrated Database [Number (%) of Patients]

	Anidulafungin			Fluconazole		
AE Preferred Term	**≤14 days (N=128)**	**>14 days (N=76)**	**Total (N=204)**	**≤14 days (N=90)**	**>14 days (N=35)**	**Total (N=125)**
Patients with at least 1 AE with outcome of death	33 (25.8)	15 (19.7)	48 (23.5)	29 (32.2)	10 (28.6)	39 (31.2)
Cardiac arrest	4 (3.1)	2 (2.6)	6 (2.9)	7 (7.8)	0	7 (5.6)
Cardio-respiratory arrest	3 (2.3)	2 (2.6)	5 (2.5)	1 (1.1)	0	1 (0.8)
Multi-organ failure	2 (1.6)	2 (2.6)	4 (2.0)	3 (3.3)	2 (5.7)	5 (4.0)
Respiratory failure	1 (0.8)	3 (3.9)	4 (2.0)	4 (4.4)	0	4 (3.2)
Sepsis	3 (2.3)	0	3 (1.5)	2 (2.2)	1 (2.9)	3 (2.4)
Renal failure	2 (1.6)	1 (1.3)	3 (1.5)	2 (2.2)	0	2 (1.6)
Cardiac failure	1 (0.8)	1 (1.3)	2 (1.0)	0	1 (2.9)	1 (0.8)
Respiratory arrest	1 (0.8)	1 (1.3)	2 (1.0)	1 (1.1)	0	1 (0.8)
Respiratory distress	2 (1.6)	0	2 (1.0)	0	0	0
Septic shock	1 (0.8)	0	1 (0.5)	2 (2.2)	2 (5.7)	4 (3.2)
Renal failure acute	0	1 (1.3)	1 (0.5)	1 (1.1)	1 (2.9)	2 (1.6)
Gastrointestinal hemorrhage	1 (0.8)	0	1 (0.5)	1 (1.1)	0	1 (0.8)
Acute respiratory distress syndrome	1 (0.8)	0	1 (0.5)	0	0	0
Adult T-cell lymphoma/leukemia	1 (0.8)	0	1 (0.5)	0	0	0
Bacteremia	1 (0.8)	0	1 (0.5)	0	0	0
Candida sepsis	1 (0.8)	0	1 (0.5)	0	0	0
Cerebral hemorrhage	0	1 (1.3)	1 (0.5)	0	0	0
Cervix carcinoma	0	1 (1.3)	1 (0.5)	0	0	0
Convulsion	1 (0.8)	0	1 (0.5)	0	0	0
Lung disorder	0	1 (1.3)	1 (0.5)	0	0	0
Myocardial infarction	1 (0.8)	0	1 (0.5)	0	0	0
Non-Hodgkin's lymphoma	1 (0.8)	0	1 (0.5)	0	0	0
Pancreatic carcinoma	1 (0.8)	0	1 (0.5)	0	0	0
Pancreatic carcinoma metastatic	1 (0.8)	0	1 (0.5)	0	0	0
Pseudomonal sepsis	1 (0.8)	0	1 (0.5)	0	0	0
Pulmonary hemorrhage	1 (0.8)	0	1 (0.5)	0	0	0
Subarachnoid hemorrhage	1 (0.8)	0	1 (0.5)	0	0	0
Bradycardia	0	0	0	2 (2.2)	0	2 (1.6)
Aspiration	0	0	0	0	1 (2.9)	1 (0.8)
Bacterial sepsis	0	0	0	1 (1.1)	0	1 (0.8)
Bile duct cancer	0	0	0	1 (1.1)	0	1 (0.8)
Injury	0	0	0	0	1 (2.9)	1 (0.8)
Lung neoplasm malignant	0	0	0	0	1 (2.9)	1 (0.8)
Metastases to lung	0	0	0	1 (1.1)	0	1 (0.8)

Source: Appendix A, Table 16. Includes data from Studies VER002-6, VER002-9, and VER002-9b.
Note: Patients are only counted once at each level of summarization.

Adverse Events
Greater than 97% of patients in both groups had a least one adverse event.
More patients in the total fluconazole group (21.6%) than the total anidulafungin group (10.3%) had adverse events leading to discontinuation of study drug. Treatment-related serious adverse events occurred in 1 (1.1%) and 2 (1.6%) patients, respectively in anidulafungin versus fluconazole. There were no notable differences in the frequencies of AEs, SAEs, or deaths when analyzed by treatment duration (≤14 days, >14 days).

7.1.2 Other Serious Adverse Events

The most frequently occurring SAEs in the total anidulafungin group were respiratory distress and cardiac arrest (3.4%); cardio respiratory arrest (2.5%); respiratory failure, respiratory arrest, sepsis, multi-organ failure, convulsion, and renal failure (2.0% each).
In the total fluconazole group, the most frequently occurring SAEs were cardiac arrest (8.8% of patients); sepsis and septic shock (6.4% each); respiratory failure and renal failure acute (4.8% each); multi-organ failure (4.0%); bacteremia (3.2%); pulmonary embolism, hyperkalemia, renal failure, and deep vein thrombosis (2.4% each).

Table 7. Treatment Related Serious Adverse Events: Phase 2-3 Integrated Database [Number (%) of Patients]

	Anidulafungin			Fluconazole		
AE Preferred Term	**≤14 days (N=128)**	**>14 days (N=76)**	**Total (N=204)**	**≤14 days (N=90)**	**>14 days (N=35)**	**Total (N=125)**
Patients with at least 1 treatment-related SAE	4 (3.1)	1 (1.3)	5 (2.5)	1 (1.1)	1 (2.9)	2 (1.6)
Convulsion	2 (1.6)	1 (1.3)	3 (1.5)	0	0	0
Atrial fibrillation	1 (0.8)	0	1 (0.5)	0	0	0
Blood creatinine increased	1 (0.8)	0	1 (0.5)	0	0	0
Deep vein thrombosis	0	0	0	1 (1.1)	0	1 (0.8)
Hepatic enzyme increased	0	0	0	0	1 (2.9)	1 (0.8)

Source: Appendix A, Table 10-2. Includes data from Studies VER002-6, VER002-9, and VER002-9b.
Note: Treatment-related AEs are defined as those reported as possibly or probably related to study treatment or AEs for which the relationship was missing. Patients are only counted once at each level of summarization.

7.1.3 Dropouts and Other Significant Adverse Events

See Table 4. Patient Disposition; Phase 2-3 Integrated Database

7.1.3.1 Overall profile of dropouts

A total of 67(32.8%) versus 45(36.0%) did not complete the study. The main reasons for not completing the study were deaths and lost to follow up. See Table X. Patient Disposition: Phase 2-3 Integrated Database.

7.1.3.2 Adverse events associated with dropouts

The only treatment-related AE that led to study withdrawal for more than 1 patient in any treatment group was hepatic enzyme increased, reported by 2 (1.6%) patients in the total fluconazole group.

7.1.3.3 Other significant adverse events

Hepatic Events
An integrated analysis of hepatic safety across the clinical program has been previously reviewed. Please see medical officer's review of Vicuron's complete response to the approvable action letter for NDA 21-632.
In the preclinical studies, the majority of the hepatic adverse events in animals occurred at dosages 8 to 11-fold greater than those for the proposed dosage for esophageal candidiasis. Hepatic adverse events in preclinical studies were also found to be reversible upon cessation of drug administration. It is unlikely that any of these hepatic chemistry abnormalities were due to drug interactions because elimination of anidulafungin in preclinical studies was by chemical degradation indicating that the drug was not likely to interact with the metabolism of other drugs that might be used concomitantly with anidulafungin.
In Phase 1 studies in healthy volunteers, elevations in ALT levels tended to occur toward the end of the treatment period, were $\leq$ four times the upper limit of normal, were asymptomatic and reversible off-therapy.
Phase 1 – 2 studies provided additional evidence of the hepatic safety of intravenous anidulafungin. Results from clinical studies in patients with renal insufficiency (study VER002-3) and hepatic insufficiency (study VER002-2) found that no dosage adjustments were required to compensate for hepatic or renal dysfunction.
In a pharmacokinetic study of anidulafungin in neutropenic children (age 2 to 17y), there was no dose-limiting toxicity at the doses tested and that there were no dose- or age-dependent differences in clinical chemistry values, changes from baseline for hepatobiliary parameters, or hepatobiliary parameters of potential clinical significance.

Five major studies in the phase 2-3 program had a range of doses from 50mg to 100mg IV daily. Two studies had a dose of 50mg IV daily for 14 to 21 days, i.e. the esophageal candidiasis study

VER002-4 and the refractory mucosal candidiasis study, (VER002-11). One phase 2 study, (VER002-6) in patients with invasive candidiasis had maintenance doses of 50, 75, or 100 mg/day for 15 to 42 days. Two studies, an invasive candidiasis study (VER002-9) and an invasive aspergillosis study (VER002-7) had a maintenance dose of 100mg IV daily for $\geq$ 14 days. There were no serious hepatobiliary events in the extension, open-label in patients with candidemia/invasive candidiasis, study VER002-9b.

One case in the invasive candidiasis study,VER002-9, experienced a 5-fold increase in serum ALT and a 1.6-fold increase in serum bilirubin seven days into treatment with anidulafungin. The bilirubin level returned to normal despite continuation of anidulafungin. No case from the invasive candidiasis study was found to be related to anidulafungin therapy. One patient in the invasive aspergillosis study, VER002-7, experienced a 20-fold increase in hepatic transaminases that was attributed to anidulafungin. Following a review of this case, the clinical reviewer and FDA hepatologist concluded that anti-tuberculosis medications could have caused the hepatic chemistry abnormalities observed in this case, and therefore the case was confounded. Hepatic chemistry resolved slowly, and the patient recovered. A second case in the invasive aspergillosis study had abnormal liver transaminases at baseline, the elevations in transaminases were reversible following discontinuation of study drug; this was not a Hy's rule case. Many of the cases in these studies were confounded by severe underlying disease and concomitant medications with potential to cause hepatotoxicity.

Other than case #13-008 in study VER002-4 (esophageal candidiasis), already reviewed in the original NDA 21-632, no similar cases of fulminant liver injury were observed in other patients during the clinical development program of anidulafungin. This patient most likely died from shock liver due to right heart failure and did not represent a case of anidulafungin toxicity. Two cases with similar hepatic profiles were found in the fluconazole arm of the invasive candidiasis study; the liver injury in these cases was reported to be due to shock liver and unrelated to study drug.

In summary, a few cases of significant hepatic dysfunction and hepatitis, were reported in patients receiving anidulafungin in studies completed since the original NDA submission. However, a causal relationship to anidulafungin was not established. In the two comparative studies with fluconazole, both sets of data were confounded by co-morbid conditions and concomitant medications with potential for hepatotoxicity. No hepatic safety concerns emerged when compared to fluconazole. As with other FDA approved echinocandins, monitoring of hepatic function should be done at baseline and during anidulafungin therapy. Significant elevations in hepatic chemistry should prompt an assessment of the risks and benefits of continuing therapy.

Renal

Thirty-nine (19.1%) anidulafungin-treated patients and 30 (24.0%) fluconazole-treated patients experienced renal AEs. None of the renal AEs in either treatment group were considered treatment-related. Serious renal AEs reported by more than 1 patient in either treatment group were renal failure (4 patients [2.0%] anidulafungin, 3 patients [2.4%] fluconazole) and acute renal failure (1 patient [0.5%] anidulafungin, 6 patients [4.8%], fluconazole). None of the SAEs were considered treatment-related.

7.2

7.3 Summary

Overall, anidulafungin was well tolerated. The adverse event of concern was hepatic safety. Following a review of the hepatic safety database, anidulafungin appears to have a hepatic safety profile similar to other FDA approved echinocandin antifungal drugs. A few cases of significant hepatic dysfunction and hepatitis, were reported in patients receiving anidulafungin in studies completed since the original NDA submission. However, a causal relationship to anidulafungin was not established. In the two comparative studies with fluconazole, both sets of data were confounded by co-morbid conditions and concomitant medications with potential for hepatotoxicity. No major hepatic safety concerns emerged when compared to fluconazole. As with other FDA approved echinocandins, monitoring of hepatic function should be done at baseline and during anidulafungin therapy. Significant elevations in hepatic chemistry should prompt an assessment of the risks and benefits of continuing therapy. The frequency of infusion reactions on therapy were comparable between the study drug and fluconazole. No neurological or cardiac adverse events were definitively attributable to study drug. Significant QTc prolongation was not observed in the studies presented.

7.3.1 Other Search Strategies

7.3.2 Common Adverse Events

7.3.2.1 Eliciting adverse events data in the development program

AEs included any adverse experience, whether or not it was considered drug-related, that occurred during a patient's study participation. This included any side effect, injury, toxicity, hypersensitivity reaction, intercurrent illness, or sudden death. A pre-existing condition was one that was present at the start of the study and was reported as part of the patient's medical history. It was reported as an AE if the frequency increased or the intensity or character of the condition worsened during the study. Patients were instructed to report all AEs to the Investigator.

Information regarding AEs was documented in the CRF and included the description of the AE, start and stop dates, relationship to study drug, severity, whether or not the AE was a serious AE, the outcome of the AE, and action taken regarding study drug. An SAE was defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect. An important medical event that may not have met these criteria may have been considered a SAE, when, based upon appropriate medical judgment, it may have jeopardized the patient and may have needed medical or surgical intervention to prevent one of the outcomes listed in this definition. Source: Integrated summary of safety, NDA 21-948 submission.

7.3.2.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categories are appropriate. The integrated database contains data on anidulafungin from one comparative study and from two non-comparative studies. The fluconazole data was from one comparative study.

7.3.2.3 Incidence of common adverse events

The incidence of common adverse events are presented in the following table 8.
Nausea (24.2%), hypokalemia (18 %), diarrhea (16.4%), and vomiting (15.6%) were the most common adverse events reported in ≥ 3% of anidulafungin-treated patients. Hypokalemia (19.2%) and diarrhea (18.4%) were slightly more common, and nausea (12%) and vomiting (9.6%) were less frequent in fluconazole-treated patients. These adverse events are frequently observed in critically-ill hospitalized patients.

Common Adverse Event Tables

Table 8. Adverse Events (regardless of drug attribution) Reported in 3% or More of Patients in the Total Anidulafungin or Total Fluconazole Treatment Groups: Phase 2-3 Integrated Database [Number (%) of Patients]

	Anidulafungin			Fluconazole		
AE Preferred Term	**≤14 days (N=128)**	**>14 days (N=76)**	**Total (N=204)**	**≤14 days (N=90)**	**>14 days (N=35)**	**Total (N=125)**
Patients with at least 1 AE	125 (97.7)	76 (100.0)	201 (98.5)	87 (96.7)	35 (100.0)	122 (97.6)
Nausea	31 (24.2)	13 (17.1)	44 (21.6)	9 (10.0)	6 (17.1)	15 (12.0)
Hypokalemia	23 (18.0)	17 (22.4)	40 (19.6)	15 (16.7)	9 (25.7)	24 (19.2)
Diarrhea	21 (16.4)	16 (21.1)	37 (18.1)	13 (14.4)	10 (28.6)	23 (18.4)
Vomiting	20 (15.6)	13 (17.1)	33 (16.2)	8 (8.9)	4 (11.4)	12 (9.6)
Pyrexia	20 (15.6)	11 (14.5)	31 (15.2)	13 (14.4)	10 (28.6)	23 (18.4)
Hypotension	16 (12.5)	14 (18.4)	30 (14.7)	12 (13.3)	5 (14.3)	17 (13.6)
Blood alkaline phosphatase increased	18 (14.1)	9 (11.8)	27 (13.2)	8 (8.9)	6 (17.1)	14 (11.2)
Bacteremia	17 (13.3)	9 (11.8)	26 (12.7)	13 (14.4)	10 (28.6)	23 (18.4)
Insomnia	17 (13.3)	9 (11.8)	26 (12.7)	7 (7.8)	5 (14.3)	12 (9.6)
Urinary tract infection	14 (10.9)	9 (11.8)	23 (11.3)	12 (13.3)	10 (28.6)	22 (17.6)
Dyspnea	16 (12.5)	6 (7.9)	22 (10.8)	2 (2.2)	2 (5.7)	4 (3.2)
Constipation	11 (8.6)	10 (13.2)	21 (10.3)	6 (6.7)	8 (22.9)	14 (11.2)
Anemia	13 (10.2)	7 (9.2)	20 (9.8)	15 (16.7)	5 (14.3)	20 (16.0)
Hypomagnesemia	12 (9.4)	8 (10.5)	20 (9.8)	9 (10.0)	5 (14.3)	14 (11.2)
Edema peripheral	8 (6.3)	11 (14.5)	19 (9.3)	14 (15.6)	2 (5.7)	16 (12.8)
Pleural effusion	10 (7.8)	6 (7.9)	16 (7.8)	6 (6.7)	5 (14.3)	11 (8.8)
Headache	10 (7.8)	6 (7.9)	16 (7.8)	6 (6.7)	4 (11.4)	10 (8.0)
Hypoglycemia	12 (9.4)	4 (5.3)	16 (7.8)	6 (6.7)	4 (11.4)	10 (8.0)
Hypertension	10 (7.8)	6 (7.9)	16 (7.8)	4 (4.4)	1 (2.9)	5 (4.0)
Confusional state	7 (5.5)	8 (10.5)	15 (7.4)	7 (7.8)	3 (8.6)	10 (8.0)
Deep vein thrombosis	9 (7.0)	5 (6.6)	14 (6.9)	5 (5.6)	4 (11.4)	9 (7.2)
Hyperkalemia	7 (5.5)	6 (7.9)	13 (6.4)	10 (11.1)	4 (11.4)	14 (11.2)
Sepsis	7 (5.5)	6 (7.9)	13 (6.4)	8 (8.9)	3 (8.6)	11 (8.8)
Hyperglycemia	5 (3.9)	8 (10.5)	13 (6.4)	5 (5.6)	3 (8.6)	8 (6.4)
Respiratory distress	5 (3.9)	8 (10.5)	13 (6.4)	1 (1.1)	1 (2.9)	2 (1.6)
Abdominal pain	7 (5.5)	5 (6.6)	12 (5.9)	10 (11.1)	6 (17.1)	16 (12.8)
Abdominal distension	8 (6.3)	4 (5.3)	12 (5.9)	6 (6.7)	2 (5.7)	8 (6.4)
Cough	7 (5.5)	5 (6.6)	12 (5.9)	5 (5.6)	2 (5.7)	7 (5.6)
Chest pain	8 (6.3)	4 (5.3)	12 (5.9)	3 (3.3)	3 (8.6)	6 (4.8)
White blood cell count increased	10 (7.8)	2 (2.6)	12 (5.9)	3 (3.3)	0	3 (2.4)
Pneumonia	6 (4.7)	5 (6.6)	11 (5.4)	8 (8.9)	11 (31.4)	19 (15.2)
Back pain	7 (5.5)	4 (5.3)	11 (5.4)	9 (10.0)	4 (11.4)	13 (10.4)
Thrombocytopenia	9 (7.0)	2 (2.6)	11 (5.4)	6 (6.7)	7 (20.0)	13 (10.4)
Alanine aminotransferase increased	7 (5.5)	4 (5.3)	11 (5.4)	5 (5.6)	2 (5.7)	7 (5.6)
Leukocytosis	7 (5.5)	4 (5.3)	11 (5.4)	5 (5.6)	1 (2.9)	6 (4.8)
Anxiety	4 (3.1)	6 (7.9)	10 (4.9)	9 (10.0)	4 (11.4)	13 (10.4)
Pain	6 (4.7)	4 (5.3)	10 (4.9)	3 (3.3)	6 (17.1)	9 (7.2)
Depression	8 (6.3)	2 (2.6)	10 (4.9)	2 (2.2)	3 (8.6)	5 (4.0)
Dehydration	7 (5.5)	3 (3.9)	10 (4.9)	1 (1.1)	1 (2.9)	2 (1.6)

Chills	4 (3.1)	5 (6.6)	9 (4.4)	9 (10.0)	2 (5.7)	11 (8.8)
Pain in extremity	5 (3.9)	4 (5.3)	9 (4.4)	3 (3.3)	2 (5.7)	5 (4.0)
Blood creatinine increased	6 (4.7)	3 (3.9)	9 (4.4)	0	1 (2.9)	1 (0.8)

Table 8. (cont.) Adverse Events (regardless of drug attribution) Reported in 3% or More of Patients in the Total Anidulafungin or Total Fluconazole Treatment Groups: Phase 2-3 Integrated Database [Number (%) of Patients]

	Anidulafungin			Fluconazole		
AE Preferred Term	**≤14 days (N=128)**	**>14 days (N=76)**	**Total (N=204)**	**≤14 days (N=90)**	**>14 days (N=35)**	**Total (N=125)**
Cardiac arrest	6 (4.7)	2 (2.6)	8 (3.9)	10 (11.1)	1 (2.9)	11 (8.8)
Rash	2 (1.6)	6 (7.9)	8 (3.9)	8 (8.9)	3 (8.6)	11 (8.8)
Renal failure	4 (3.1)	4 (5.3)	8 (3.9)	11 (12.2)	0	11 (8.8)
Decubitus ulcer	5 (3.9)	3 (3.9)	8 (3.9)	6 (6.7)	4 (11.4)	10 (8.0)
Aspartate aminotransferase increased	6 (4.7)	2 (2.6)	8 (3.9)	5 (5.6)	4 (11.4)	9 (7.2)
Renal failure acute	4 (3.1)	4 (5.3)	8 (3.9)	6 (6.7)	3 (8.6)	9 (7.2)
Staphylococcal bacteremia	6 (4.7)	2 (2.6)	8 (3.9)	3 (3.3)	4 (11.4)	7 (5.6)
Fall	7 (5.5)	1 (1.3)	8 (3.9)	4 (4.4)	1 (2.9)	5 (4.0)
Atrial fibrillation	4 (3.1)	4 (5.3)	8 (3.9)	2 (2.2)	2 (5.7)	4 (3.2)
Hypernatremia	6 (4.7)	2 (2.6)	8 (3.9)	2 (2.2)	2 (5.7)	4 (3.2)
Pharyngolaryngeal pain	3 (2.3)	5 (6.6)	8 (3.9)	2 (2.2)	1 (2.9)	3 (2.4)
Pruritus	2 (1.6)	6 (7.9)	8 (3.9)	0	3 (8.6)	3 (2.4)
Dysphagia	5 (3.9)	3 (3.9)	8 (3.9)	1 (1.1)	0	1 (0.8)
Thrombocythaemia	7 (5.5)	1 (1.3)	8 (3.9)	1 (1.1)	0	1 (0.8)
Hepatic enzyme increased	5 (3.9)	2 (2.6)	7 (3.4)	5 (5.6)	9 (25.7)	14 (11.2)
Pulmonary edema	4 (3.1)	3 (3.9)	7 (3.4)	8 (8.9)	5 (14.3)	13 (10.4)
Agitation	4 (3.1)	3 (3.9)	7 (3.4)	4 (4.4)	3 (8.6)	7 (5.6)
Dizziness	3 (2.3)	4 (5.3)	7 (3.4)	6 (6.7)	1 (2.9)	7 (5.6)
Hypocalcemia	6 (4.7)	1 (1.3)	7 (3.4)	3 (3.3)	3 (8.6)	6 (4.8)
Hyponatremia	5 (3.9)	2 (2.6)	7 (3.4)	1 (1.1)	3 (8.6)	4 (3.2)
Systemic candida	3 (2.3)	4 (5.3)	7 (3.4)	3 (3.3)	1 (2.9)	4 (3.2)
Tachycardia	4 (3.1)	3 (3.9)	7 (3.4)	1 (1.1)	2 (5.7)	3 (2.4)
Clostridium colitis	5 (3.9)	2 (2.6)	7 (3.4)	0	0	0
Hypothermia	5 (3.9)	1 (1.3)	6 (2.9)	6 (6.7)	2 (5.7)	8 (6.4)
Bradycardia	4 (3.1)	2 (2.6)	6 (2.9)	6 (6.7)	1 (2.9)	7 (5.6)
Fluid overload	4 (3.1)	2 (2.6)	6 (2.9)	3 (3.3)	2 (5.7)	5 (4.0)
Gastrointestinal haemorrhage	3 (2.3)	3 (3.9)	6 (2.9)	4 (4.4)	1 (2.9)	5 (4.0)
Hypophosphataemia	5 (3.9)	1 (1.3)	6 (2.9)	1 (1.1)	4 (11.4)	5 (4.0)
Atelectasis	2 (1.6)	4 (5.3)	6 (2.9)	1 (1.1)	3 (8.6)	4 (3.2)
Clostridial infection	6 (4.7)	0	6 (2.9)	3 (3.3)	1 (2.9)	4 (3.2)
Metabolic acidosis	4 (3.1)	1 (1.3)	5 (2.5)	3 (3.3)	4 (11.4)	7 (5.6)
Respiratory failure	2 (1.6)	3 (3.9)	5 (2.5)	7 (7.8)	0	7 (5.6)
Ascites	3 (2.3)	2 (2.6)	5 (2.5)	5 (5.6)	1 (2.9)	6 (4.8)
Mental status changes	2 (1.6)	3 (3.9)	5 (2.5)	6 (6.7)	0	6 (4.8)
Arthralgia	2 (1.6)	3 (3.9)	5 (2.5)	3 (3.3)	2 (5.7)	5 (4.0)
Asthenia	3 (2.3)	2 (2.6)	5 (2.5)	4 (4.4)	0	4 (3.2)
Cardiac failure congestive	4 (3.1)	0	4 (2.0)	2 (2.2)	3 (8.6)	5 (4.0)
Multi-organ failure	2 (1.6)	2 (2.6)	4 (2.0)	3 (3.3)	2 (5.7)	5 (4.0)
Staphylococcal infection	3 (2.3)	1 (1.3)	4 (2.0)	5 (5.6)	0	5 (4.0)

Supraventricular tachycardia	3 (2.3)	1 (1.3)	4 (2.0)	4 (4.4)	1 (2.9)	5 (4.0)
Enterococcal infection	3 (2.3)	1 (1.3)	4 (2.0)	3 (3.3)	1 (2.9)	4 (3.2)
Pneumothorax	3 (2.3)	1 (1.3)	4 (2.0)	2 (2.2)	2 (5.7)	4 (3.2)
Hyperphosphatemia	2 (1.6)	1 (1.3)	3 (1.5)	3 (3.3)	2 (5.7)	5 (4.0)
Bacterial sepsis	3 (2.3)	0	3 (1.5)	3 (3.3)	1 (2.9)	4 (3.2)
Catheter site pain	1 (0.8)	2 (2.6)	3 (1.5)	3 (3.3)	1 (2.9)	4 (3.2)

Table 8 (cont.) Adverse Events (regardless of drug attribution) Reported in 3% or More of Patients in the Total Anidulafungin or Total Fluconazole Treatment Groups: Phase 2-3 Integrated Database [Number (%) of Patients]

	Anidulafungin			Fluconazole		
AE Preferred Term	**≤14 days (N=128)**	**>14 days (N=76)**	**Total (N=204)**	**≤14 days (N=90)**	**>14 days (N=35)**	**Total (N=125)**
Hypoalbuminemia	2 (1.6)	1 (1.3)	3 (1.5)	3 (3.3)	1 (2.9)	4 (3.2)
Edema	2 (1.6)	1 (1.3)	3 (1.5)	4 (4.4)	0	4 (3.2)
Pulmonary embolism	2 (1.6)	0	2 (1.0)	5 (5.6)	1 (2.9)	6 (4.8)
Vision blurred	0	2 (2.6)	2 (1.0)	6 (6.7)	0	6 (4.8)
Blood glucose increased	2 (1.6)	0	2 (1.0)	5 (5.6)	0	5 (4.0)
Somnolence	2 (1.6)	0	2 (1.0)	5 (5.6)	0	5 (4.0)
Generalized edema	1 (0.8)	1 (1.3)	2 (1.0)	3 (3.3)	1 (2.9)	4 (3.2)
Septic shock	1 (0.8)	0	1 (0.5)	7 (7.8)	3 (8.6)	10 (8.0)
Ventricular tachycardia	1 (0.8)	0	1 (0.5)	2 (2.2)	2 (5.7)	4 (3.2)

Source: Appendix A, Table 14-1. Includes data from VER002-6, VER002-9, and VER002-9b
Note: Patients are only counted once at each level of summarization.

7.3.2.4 Identifying common and drug-related adverse events

The three most commonly reported AEs in the total anidulafungin group were nausea, hypokalemia, and diarrhea; in the total fluconazole group, the most common AEs were hypokalemia, diarrhea, pyrexia, and bacteremia.
For anidulafungin-treated patients receiving IV therapy only, nausea (20.2%), diarrhea (17.8%), and hypokalemia (16.6%) were the most commonly reported events; in the total fluconazole group, bacteremia (21.3%), pyrexia (18.0%), and pneumonia (18.0%) were the most common AEs.

Thirty-nine (19.1%) anidulafungin-treated patients and 30 (24.0%) fluconazole-treated patients experienced renal AEs. None of the renal AEs in either treatment group were considered treatment-related. Serious renal AEs reported by more than 1 patient in either treatment group were renal failure (4 patients [2.0%] anidulafungin, 3 patients [2.4%] fluconazole) and acute renal failure (1 patient [0.5%] anidulafungin, 6 patients [4.8%], fluconazole). None of the SAEs were considered treatment-related.

7.3.2.5 Additional analyses and explorations

7.3.3 Less Common Adverse Events

Convulsions
In the integrated safety data base, a total of 5 (2.5%) anidulafungin-treated patients and 2 (1.6%) fluconazole-treated patients experienced convulsions. Of these, 4 (2.0%) of the anidulafungin-treated patients and both of the fluconazole-treated patients had events considered to be serious. Three patients (1.5%) in the anidulafungin group had convulsions that were considered to be possibly treatment-related. None of the patients had a history of seizure activity.
Following a review of these cases it does not appear that any of the three can be attributed to study drug. Patient ID #011-001 from Study VER002-6 has been previously reviewed. This patient had a complex medical history including hereditary cystinosis, renal transplant and iatrogenic immunosuppression; he was unresponsive to verbal stimuli and was minimally responsive to pain (following a cardiac arrest) on entry into the study. The cause of death was metabolic acidosis and respiratory failure. The underlying cause of the patient's seizures was most likely to be multifactorial including anoxia secondary to cardiac arrest, and concomitant medications. Patient ID #09b-002-302: This 50 yr old male was admitted to the study with an APACHE score of 27. Seizure activity occurred 90 minutes following anidulafungin therapy on study day 11. The patient experienced a myoclonic seizure lasting 15 seconds. The patient continued anidulafungin without further seizures. Predisposing factors for the patient's seizures included alcohol abuse and concomitant therapy with ciprofloxacin. Patient ID# 09-012-007(see review of VER002-9, Appendix A) had a seizure that appeared to be unrelated to study drug.

Overview of Convulsions in the Clinical Program
Among the 929 subjects who received intravenous anidulafungin in the anidulafungin clinical development program, there were 11 reports of seizures occurring in 10 (1.5%) of 672 subjects receiving anidulafungin in Phase 2 and 3 studies, either during (n=6, 0.9%) or after (n=5, 0.7%) treatment. Five patients had seizures occurring after therapy at 6, 15, 20, 21 and 29 days following the last dose. The frequency of seizures on therapy (n=3, 0.7%) was similar in the 426 patients treated with fluconazole in the comparative studies.
Following a review of these cases, none of them could be definitively attributed to anidulafungin. No case of seizure was reported in healthy subjects (n=202), including a small number of healthy volunteers receiving anidulafungin 130mg IV daily.
Convulsion is listed in the micafungin (Mycamine™) label as a clinically significant event that has been reported in their overall safety database. Convulsion has been reported for caspofungin in the AERS database.

Possible Infusion-Associated Adverse Events

Table 9. Possible Infusion-Associated Adverse Events: Phase 2-3 Integrated Database [Number (%) of Patients]

AE Preferred Term	Anidulafungin ≤14 days (N=128)	Anidulafungin >14 days (N=76)	Anidulafungin Total (N=204)	Fluconazole ≤14 days (N=90)	Fluconazole >14 days (N=35)	Fluconazole Total (N=125)
Patients with at least 1 infusion-associated AE	20 (15.6)	8 (10.5)	28 (13.7)	5 (5.6)	4 (11.4)	9 (7.2)
Dyspnea	16 (12.5)	6 (7.9)	22 (10.8)	2 (2.2)	2 (5.7)	4 (3.2)
Flushing	3 (2.3)	1 (1.3)	4 (2.0)	2 (2.2)	1 (2.9)	3 (2.4)
Dyspnea exacerbated	2 (1.6)	0	2 (1.0)	0	0	0
Infusion related reaction	0	1 (1.3)	1 (0.5)	1 (1.1)	2 (5.7)	3 (2.4)
Hot flush	0	1 (1.3)	1 (0.5)	0	0	0

Source: Appendix A, Table 17-3. Includes data from studies VER002-6, VER002-9, and VER002-9b.
Note: Patients are only counted once at each level of summarization.

Dyspnea: In an integrated safety database in 329 patients with candidemia, a total of 23 (10.8 %) of anidulafungin-treated patients and 4 (3.2%) of fluconazole-treated patients had dyspnea reported as an adverse event. None of the 23 anidulafungin treated patients were considered drug related and a temporal relation to infusion for 14 patients was not reported. The remaining 9 patients (all in study VER002-9) were considered possibly temporally related to infusion, and are tabulated below. A summary of each case is in the individual review of study VER002-9.

Summary of anidulafungin–treated patients with dyspnea in the pivotal comparative study, VER002-9.

Patient ID	Underlying illness	Respiratory signs and symptoms at baseline	Day of event on therapy	Drug discontinued	Clinical reviewer attribution	Investigator attribution
09-001-001	Renal failure/ intubated at baseline	Yes	3	No	Unrelated	Unrelated
09-002-008	Diabetic/renal failure/IHD	Yes	2	No	Unlikley related	Unlikley related
09-003-004	Pulm embolus/pleural effusions	Yes	3	No	Unlikley related	Unlikley related
09-019-001	Pneumonia/pleural effusions/renal failure	Yes	5	No	Unlikley related	Unlikley related
09-032-001	Small bowel obstruction/peritonitis	Yes	3	No	Unlikley related	Unlikley related
09-041-004	Metastatic cancer/pleural effusions	Yes	5	No	Unrelated	Unrelated
09-040-001	Peritonitis/pleural effusions	Yes	5	No	Unrelated	Unrelated

09-041-005	Metastatic cancer/COPD	Yes	2	No	Unrelated	Unrelated
09-068-001	Colon cancer/sleep apnea/pl. effusions	Yes	11	No	Unrelated	Unrelated

Medical officer comment
All nine patients reported with dyspnea in this study had significant underlying respiratory illnesses, including pneumonia, pleural effusions, COPD and pulmonary embolus. The interval between the start of anidulafungin therapy and the event varied from 2 to 11 days, and did not appear to be consistently related to the time of infusion. All these patients continued to receive anidulafungin daily and no doses of anidulafungin were prematurely terminated. The medical officer concluded that these events were unrelated to study drug.

Flushing of the skin associated with infusion occurred in approximately 3 (2%) of the anidulafungin- and fluconazole- treated patients. In the anidulafungin and fluconazole groups, flushing lasted for less than 24 hours in the majority of patients, in one patient the flushing lasted for 48 hours. Flushing did not result in discontinuation of anidulafungin. Urticaria was experienced by 1.0% of patients in the anidulafungin group; Urticaria was not reported in the fluconazole group. No anaphylaxis was reported.

Brief overview of infusion reactions in Phase 1 studies
In Phase 1 studies in healthy males and females, infusion reactions such as skin flushing, dyspnea, and coughing were noted, some within minutes of commencing anidulafungin infusion. A few subjects receiving the vehicle alone experienced these types of symptoms. Symptoms resolved when the infusions were discontinued and in some cases the infusion was resumed without further events. Symptoms generally occurred at concentrations of 1.0mg/kg and at infusion rates greater than 1.1mg/min.
Two patients in study H4A-EW-XBAE (single dose escalation study in healthy volunteers) experienced severe flushing and moderate shortness of breath at a dose of 1.0mg/kg at a rate of 1.17mg/min. There were no clinically significant changes in vital signs reported in this study. A rate of 1.1mg/min was used in subsequent studies to mitigate infusion related events.
In VER002-5, a multiple-dose PK study in 10 healthy volunteers, one of 10 subjects receiving 230mg loading/130mg daily maintenance dose had an infusion reaction with dyspnea, facial flushing, and nausea. The infusion rate was 1.1mg/min. Infusion reactions were not reported for patients receiving the 200/100mg dosing regimen. However, infusion reactions have been reported in other studies at doses of 100mg/70mg and 140/100mg at a rate of 1.11mg/min.
In summary, infusion reactions were generally mild and were infrequent when the infusion rate was less than 1.1mg/min.

Anaphylaxis
There were no cases of anaphylaxis in this integrated analysis of safety or in the entire clinical program.

Medical officer's comment
Though there were no reports of anaphylaxis in the anidulafungin database, an anaphylactic reaction may possibly occur with more widespread use.
Anaphylaxis has been reported for the other approved echinocandins, caspofungin and micafungin. The AERS database was searched for reports of anaphylaxis or anaphylactic shock for caspofungin and micafungin; 6 and 3 reports were found for caspofungin and micafungin, respectively. The reports for micafungin were from Japan. In the database, a total of 609 and 65 adverse event reports of any type were found for caspofungin and micafungin, respectively.

7.3.4 Laboratory Findings

Low potentially clinically significant (PCS) values were most frequently observed for hemoglobin and hematocrit. Approximately two-thirds of patients in each treatment group had PCS low (<0.8 × LLN) hemoglobin results at baseline. Less than 2% of patients in the total anidulafungin and total fluconazole groups had low PCS values for neutrophils during the study. WBC tended to increase for the majority of patients in the study which is an expected clinical response in infected patients.
Overall, there was no apparent effect of anidulafungin on hematology laboratory parameters when considered by the percentage of patients experiencing absolute PCS values, PCS changes from baseline, or PCS values that were also PCS changes from baseline. See Table 10.

Table 10. Potentially clinically significant values for key hematology parameters that were also potentially clinically significant (PCSC)changes from baseline: phase 2-3 integrated database

Number (%) with PCS and PCSC results		Anidulafungin ≤14 days		Anidulafungin >14 days		Total Anidulafungin		Fluconazole ≤14 days		Fluconazole >14 days		Total Fluconazole	
Hemoglobin		N[a]	n (%)	N[a]	n (%)	N[a]	n (%)	N[a]	n (%)	N[a]	n (%)	N[a]	n (%)
High (>1.3 x ULN) and fold increase >1.4	On-therapy	86	0	70	0	156	0	47	0	30	0	77	0
	EIV	111	0	74	0	185	0	75	0	32	0	107	0
	2w FU	79	0	57	0	136	0	51	0	24	0	75	0
	6w FU	61	0	31	0	92	0	40	0	18	0	58	0
Low (<0.8 x LLN) and fold decrease >0.25	On-therapy	86	2 (2.3)	70	6 (8.6)	156	8 (5.1)	47	1 (2.1)	30	0	77	1 (1.3)
	EIV	111	4 (3.6)	74	1 (1.4)	185	5 (2.7)	75	0	32	2 (6.3)	107	2 (1.9)
	2w FU	79	3 (3.8)	57	2 (3.5)	136	5 (3.7)	51	0	24	0	75	0
	6w FU	61	3 (4.9)	31	2 (6.5)	92	5 (5.4)	40	1 (2.5)	18	1 (5.6)	58	2 (3.4)
WBC													
High (>2 x ULN) and fold increase >2	On-therapy	86	0	70	2 (2.9)	156	2 (1.3)	47	0	30	1 (3.3)	77	1 (1.3)
	EIV	112	4 (3.6)	74	2 (2.7)	186	6 (3.2)	75	3 (4.0)	32	0	107	3 (2.8)
	2w FU	79	0	57	0	136	0	51	2 (3.9)	24	0	75	2 (2.7)
	6w FU	61	1 (1.6)	31	0	92	1 (1.1)	40	0	18	0	58	0
Low (<0.5 x LLN) and fold decrease >0.75	On-therapy	86	0	70	1 (1.4)	156	1 (0.6)	47	0	30	0	77	0
	EIV	112	1 (0.9)	74	0	186	1 (0.5)	75	0	32	0	107	0
	2w FU	79	1 (1.3)	57	0	136	1 (0.7)	51	0	24	0	75	0
	6w FU	61	0	31	0	92	0	40	0	18	0	58	0
Neutrophils													
High (>2.2 x ULN) and fold increase >2 or value >62% when baseline value = 0%	On-therapy	83	0	64	0	147	0	46	0	29	0	75	0
	EIV	97	0	67	0	164	0	69	0	30	0	99	0
	2w FU	74	0	54	0	128	0	49	0	20	0	69	0
	6w FU	58	0	26	0	84	0	33	0	17	0	50	0
Low (<0.5 x LLN) and fold decrease >0.75	On-therapy	83	1 (1.2)	64	0	147	1 (0.7)	46	0	29	0	75	0
	EIV	97	0	67	1 (1.5)	164	1 (0.6)	69	0	30	0	99	0

2w FU	74	0	54	1 (1.9)	128	1 (0.8)	49	0	20	0	69	0
6w FU	58	0	26	0	84	0	33	0	17	0	50	0

Source: Note:
Appendix A, Table 20-1. Includes data from studies VER002-6, VER002-9, and VER002-9b. On-therapy = Day 6 for study VER002-6 and the visit(s) with the most extreme PCS and/or PCSC value (or the earliest visit if there are no significant PCS or PCSC values) occurring between study day 6 and study day 10 inclusive for studies VER002-9 and VER002-9b; EIV = End of IV Therapy; 2w FU = 2-Week Follow-up; 6w FU = 6-Week Follow-up (only for studies VER002-9 and VER002-9b).
a The number of patients with available laboratory results at baseline and the specific time is used in computing percentages.

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Table 10 (cont.) Potentially Clinically Significant Values for Key Hematology Parameters That Were Also Potentially Clinically Significant Changes (PCSC) From Baseline: Phase 2-3 Integrated Database

Number (%) results Platelets	with PCS and PCSC	Anidulafungin ≤14 days N_a n (%)		Anidulafungin >14 days N_a n (%)		Total Anidulafungin N_a n (%)		Fluconazole ≤14 days N_a n (%)		Fluconazole >14 days N_a n (%)		Total Fluconazole N_a n (%)	
High (>2 x ULN) and fold increase >2	On-therapy	86	1 (1.2)	70	0	156	1 (0.6)	46	1 (2.2)	30	0	76	1 (1.3)
	EIV	112	0	74	1 (1.4)	186	1 (0.5)	75	0	32	0	107	0
	2w FU	79	2 (2.5)	57	1 (1.8)	136	3 (2.2)	50	1 (2.0)	23	0	73	1 (1.4)
	6w FU	61	2 (3.3)	31	2 (6.5)	92	4 (4.3)	39	0	18	0	57	0
Low (<0.6 x LLN) and fold decrease >0.4	On-therapy	86	2 (2.3)	70	1 (1.4)	156	3 (1.9)	46	1 (2.2)	30	3 (10.0)	76	4 (5.3)
	EIV	112	4 (3.6)	74	2 (2.7)	186	6 (3.2)	75	1 (1.3)	32	1 (3.1)	107	2 (1.9)
	2w FU	79	4 (5.1)	57	2 (3.5)	136	6 (4.4)	50	1 (2.0)	23	1 (4.3)	73	2 (2.7)
	6w FU	61	1 (1.6)	31	2 (6.5)	92	3 (3.3)	39	1 (2.6)	18	0	57	1 (1.8)

Source: Appendix A, Table 20-1. Includes data from studies VER002-6, VER002-9, and VER002-9b.

Note: On-therapy = Day 6 for study VER002-6 and the visit(s) with the most extreme PCS and/or PCSC value (or the earliest visit if there are no significant PCS or PCSC values) occurring between study day 6 and study day 10 inclusive for studies VER002-9 and VER002-9b; EIV = End of IV Therapy; 2w FU = 2-Week Follow-up; 6w FU = 6-Week Follow-up (only for studies VER002-9 and VER002-9b).

[a] The number of patients with available laboratory results at baseline and the specific time is used in computing percentages.

Chemistry Laboratory Findings

High PCS values were most frequently observed for alkaline phosphatase, total bilirubin, albumin, creatinine, and BUN. The frequency of PCS values was similar in the total anidulafungin and total fluconazole groups. Hypokalemia was present in 6/204(2.4%) anidulafungin-treated patients, and 3/125 (2.9%) fluconazole-treated patients. Hepatobiliary tests: ALT was increased in 5(2.5%) and 4 (3.2%) in the anidulafungin group and fluconazole group, respectively. Hepatic enzyme elevation required discontinuation anidulafungin in one patient. Hepatic enzymes increases have been previously discussed in the hepatic safety reviews. See integrated analysis of hepatic safety as well as the individual study review for study VER002-9 and VER002-9B, the hepatic safety analysis for the complete response as well as the hepatic safety review for NDA 21-632.

Overall, there was no apparent effect of anidulafungin on blood chemistry laboratory parameters when considered by the percentage of patients experiencing absolute PCS values, PCS changes from baseline, or PCS values that were also PCS changes from baseline.

Table 11. Potentially clinically significant changes for key chemistry parameters that were also potentially clinically significant changes from baseline: phase 2-3 integrated database

Potassium													
Low (<0.85 x LLN) and fold decrease >0.15	On-therapy	85	3 (3.5)	71	2 (2.8)	156	5 (3.2)	46	1 (2.2)	31	1 (3.2)	77	2 (2.6)
	EIV	111	1 (0.9)	74	1 (1.4)	185	2 (1.1)	76	1 (1.3)	32	1 (3.1)	108	2 (1.9)
	2w FU	79	1 (1.3)	58	0	137	1 (0.7)	50	2 (4.0)	24	0	74	2 (2.7)
	6w FU	55	1 (1.8)	32	0	87	1 (1.1)	38	0	18	0	56	0
Alk phos.													
High (>1.5 x ULN) and fold increase >2	On-therapy	71	8 (11.3)	63	8 (12.7)	134	16 (11.9)	43	5 (11.6)	27	4 (14.8)	70	9 (12.9)
	EIV	85	13 (15.3)	59	10 (16.9)	144	23 (16.0)	58	7 (12.1)	27	3 (11.1)	85	10 (11.8)
	2w FU	62	7 (11.3)	46	10 (21.7)	108	17 (15.7)	39	6 (15.4)	24	3 (12.5)	63	9 (14.3)
	6w FU	50	5 (10.0)	28	3 (10.7)	78	8 (10.3)	34	5 (14.7)	14	0	48	5 (10.4)
ALT													
High (>3 x ULN) and fold increase >3	On-therapy	73	1 (1.4)	64	0	137	1 (0.7)	42	0	27	0	69	0
	EIV	85	1 (1.2)	59	0	144	1 (0.7)	58	2 (3.4)	26	1 (3.8)	84	3 (3.6)
	2w FU	63	0	47	1 (2.1)	110	1 (0.9)	37	0	23	0	60	0
	6w FU	50	0	27	1 (3.7)	77	1 (1.3)	34	0	15	0	49	0
AST													
High (>3 x ULN) and fold increase >3	On-therapy	71	1 (1.4)	63	0	134	1 (0.7)	42	0	27	0	69	0
	EIV	86	1 (1.2)	58	1 (1.7)	144	2 (1.4)	59	4 (6.8)	27	1 (3.7)	86	5 (5.8)
	2w FU	62	0	46	0	108	0	38	0	23	0	61	0
	6w FU	49	1 (2.0)	29	0	78	1 (1.3)	33	0	15	0	48	0
Total bilirubin													
High (>2 x ULN) and fold increase >3	On-therapy	72	2 (2.8)	62	0	134	2 (1.5)	43	0	27	2 (7.4)	70	2 (2.9)
	EIV	83	3 (3.6)	59	0	142	3 (2.1)	61	4 (6.6)	27	0	88	4 (4.5)
	2w FU	62	2 (3.2)	45	0	107	2 (1.9)	38	1 (2.6)	22	0	60	1 (1.7)
	6w FU	49	0	26	0	75	0	32	2 (6.3)	15	0	47	2 (4.3)

Source: Appendix A, Table 20-1. Includes data from studies VER002-6, VER002-9, and VER002-9b.
Note: On-therapy = Day 6 for study VER002-6 and the visit(s) with the most extreme PCS and/or PCSC value (or the earliest visit if there are nosignificant PCS or PCSC values) occurring between study day 6 and study day 10 inclusive for studies VER002-9 and VER002-9b; EIV = End of IV Therapy; 2w FU = 2-Week Follow-up; 6w FU = 6-Week Follow-up (only for studies VER002-9 and VER002-9b).
a The numb patients with available laboratory lfts at baseline

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Table 11 (cont.) Potentially clinically significant changes for key chemistry parameters that were also potentially clinically significant changes from baseline: phase 2-3 integrated database

Number (%) with PCS and PCSC results		Anidulafungin ≤14 days		Anidulafungin >14 days		Total Anidulafungin		Fluconazole ≤14 days		Fluconazol >14 days	
		Na	n (%)	Na	n (%)	Na	n (%)	Na	n (%)	Na	n (%
Creatinine											
High (>2.5 x ULN)	On-therapy	86	1 (1.2)	71	0	157	1 (0.6)	46	1 (2.2)	31	1 (3.
and fold increase >2	EIV	109	1 (0.9)	72	2 (2.8)	181	3 (1.7)	76	1 (1.3)	32	0
	2w FU	78	1 (1.3)	58	0	136	1 (0.7)	50	1 (2.0)	24	0
	6w FU	56	0	32	0	88	0	38	1 (2.6)	18	0
BUN											
High (>3 x ULN)	On-therapy	85	0	66	0	151	0	45	1 (2.2)	30	1 (3.
and fold increase >3	EIV	107	0	68	1 (1.5)	175	1 (0.6)	75	1 (1.3)	31	1 (3.
	2w FU	73	2 (2.7)	52	1 (1.9)	125	3 (2.4)	50	1 (2.0)	24	0
	6w FU	54	1 (1.9)	28	0	82	1 (1.2)	38	0	17	0

Source: Appendix A, Table 20-1. Includes data from studies VER002-6, VER002-9, and VER002-9b.

Note: On-therapy = Day 6 for study VER002-6 and the visit(s) with the most extreme PCS and/or PCSC value (or the earliest visit if there are no significant PCS or PCSC values) occurring between study day 6 and study day 10 inclusive for studies VER002-9 and VER002-9b; EIV = End of IV Therapy; 2w FU = 2-Week Follow-up; 6w FU = 6-Week Follow-up (only for studies VER002-9 and VER002-9b).

a The number of patients with available laboratory results at baseline and the specific time is used in computing percentages.

7.3.4.1 Overview of laboratory testing in the development program

In studies VER002-9 and VER002-9b, hematology and chemistry tests were performed at screening, on study Day 3, on study Day 7, every 7 days while the patient was on study medication, on the last day of study medication, and at follow up if applicable. In study VER002-6, hematology and chemistry tests were performed at screening; on study Days 1, 3, and 6 and at least once weekly during the dosing period, at end of treatment, and at the follow-up (FU) visit.
In the analysis of laboratory findings, the selected hematology tests were hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential (neutrophils, lymphocytes, basophils,monocytes, bands, and eosinophils), and platelet counts. The selected blood chemistry tests were bicarbonate, sodium, potassium, chloride, alkaline phosphatase, alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), total bilirubin, glucose, albumin, creatinine, and blood urea nitrogen (BUN)/urea.
The applicant summarized data for the integrated safety database by examining potentially clinically significant (PCS) values and potentially clinically significant changes (PCSC) from baseline, according to the criteria shown in Table 5.2. Listings of PCS laboratory results, PCS changes from baseline in laboratory results, and PCS and PCSC laboratory results as defined in individual studies were generated for the integrated safety database.

7.3.4.2 Selection of studies and analyses for drug-control comparisons of laboratory values

All studies in the NDA21-948 were selected for analysis.

7.3.4.3 Standard analyses and explorations of laboratory data

7.3.4.3.1 Analyses focused on measures of central tendency

7.3.4.3.2 Analyses focused on outliers or shifts from normal to abnormal

See hepatic safety review of individual studies for hepatobiliary parameters.

7.3.4.3.3 Marked outliers and dropouts for laboratory abnormalities

See hepatic safety review

7.3.4.4 Additional analyses and explorations

Not applicable

7.3.4.5 Special assessments

Not applicable

7.3.5 Vital Signs

A complete physical examination was performed at screening or within 72 hours of the first dose of study medication. Height and weight were recorded only at screening. Any new abnormal, clinically significant physical examination findings after the screening visit were recorded as AEs. See common adverse events in the safety analysis section. Vital signs (including heart rate, blood pressure and respiratory rate) were performed at screening. Temperature was measured at screening, daily through EOT, and at the 2 week and 6 week FU visits.
There were no obvious differences in vital signs between the two treatment groups.
Temperature changes of ≥2□C from baseline were flagged. The adverse event of hypotension was balanced in the two treatment groups, and was observed in approximately 14% in both treatment groups. Case narratives were reviewed for 15 patients who experienced hypotension or hypertension while on anidulafungin therapy. Adverse effects on blood pressure attributed to study drug was not observed.

7.3.5.1 Selection of studies and analyses for overall drug-control comparisons

See section 7.3.5

7.3.5.2 Standard analyses and explorations of vital signs data

7.3.5.2.1 Analyses focused on measures of central tendencies
See section 7.3.5

7.3.5.2.2 Analyses focused on outliers or shifts from normal to abnormal
See section 7.3.5

7.3.5.2.3 Marked outliers and dropouts for vital sign abnormalities
See section 7.3.5

7.3.5.3 Additional analyses and explorations

Not applicable

7.3.6 Electrocardiograms (ECGs)

Electrocardiographic Data

Of the patients in the Phase 2-3 integrated safety database, 146 anidulafungin-treated patients and 77 fluconazole-treated patients had normal T and U waves at baseline and had a post-baseline ECG conducted. Of these, 4 (2.7%) in the anidulafungin group and 3 (3.9%) in the fluconazole group had a T-wave abnormality. No consistent or significant effects of the drug on T-wave morphology were reported.

The mean change from baseline in QTcB interval was -2.4 msec (range, -99 to 89 msec) among patients in the total anidulafungin group and 4.9 msec (range, -72 to 179) among patients in the total fluconazole group.

Four patients (2.3%) in the total anidulafungin group and 6 (6.5%) in the total fluconazole group had QTcB increases >60 msec. Five (5.6%) male anidulafungin-treated patients and 4 (7.3%) fluconazole-treated males had a post-baseline QTcB interval >500 msec; no anidulafungin-treated females and 2 (4.4%) fluconazole-treated females had a post baseline QTcB interval >500 msec.

There were no relevant findings suggesting that anidulafungin had a clinically significant effect on QT intervals using Bazett and Fredericia correction.

There were no relevant findings suggesting that anidulafungin had a clinically significant effect on QT intervals based on the Barrett and Frederichia correction.

The mean change from baseline in QTcB interval was -2.4 msec (range, -99 to 89 msec) among patients in the total anidulafungin group and 4.9 msec (range, -72 to 179) among patients in the total fluconazole group. A total of 18 (10.5%) anidulafungin-treated patients had an increase in QTcB >30 to 60 msec, compared with 7 (7.6%) fluconazole-treated patients. Four patients (2.3%) in the total anidulafungin group and 6 (6.5%) in the total fluconazole group had QTcB increases >60 msec. Five (5.6%) male anidulafungin-treated patients and 4 (7.3%) fluconazole-treated males had a post-baseline QTcB interval >500 msec; no anidulafungin-treated females and 2 (4.4%) fluconazole-treated females had a postbaseline QTcB interval >500 msec.

No ventricular rhythm disturbance was observed in any of the ECG recordings in studies VER002-9 and VER002-9b (see individual study reports).

Rhythm Disturbances

An expert cardiologist reviewed ECG reports produced for the VER002-9 and VER002-9b studies and concluded that no ventricular rhythm disturbance was observed in any of the ECG recordings analyzed.

7.3.6.1 Overview of ECG testing in the development program, including brief review of preclinical results

In studies VER002-9 and VER002-9b, a 12-lead ECG was performed at screening and on Day 3 within 3 hours of completed infusion. In study VER002-6, a 12-lead ECG was performed at screening and on Day 6 within 2 hours after the completion of anidulafungin. Abnormal, clinically significant ECG results at screening were recorded as part of the patient's medical history. Any new onset of abnormal, clinically significant ECG results after screening was recorded as AEs. All original ECG tracings were read and interpreted in a blinded fashion by an independent expert cardiologist.

7.3.6.2 Selection of studies and analyses for overall drug-control comparisons

7.3.6.3 Standard analyses and explorations of ECG data

7.3.6.3.1 Analyses focused on measures of central tendency

7.3.6.3.2 Analyses focused on outliers or shifts from normal to abnormal

An independent expert cardiologist reviewed the EKG data for study VER002-9. Comparative EKG data was available for 110 patients treated with anidulafungin, and 92 patients treated with fluconazole. A non-significant prolongation of the QTc (Bazett) interval of >60msec was observed in 1/110 patients in the anidulafungin arm, and in 6/92 patients in the fluconazole arm. In study VER002-9b, data was available for 31 of 33 patients. No patient had a QTc (Bazett) interval of >60msec.

7.3.6.3.3 Marked outliers and dropouts for ECG abnormalities

7.3.6.4 Additional analyses and explorations

7.3.7 Immunogenicity

See clinical pharmacology and biopharmaceutics review.

7.3.8 Human Carcinogenicity

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of anidulafungin. Anidulafungin did not show evidence of genotoxic potential in the chromosome

aberration assay with Chinese hamster ovary cells or the forward mutation assay with mouse lymphoma cells. Administration of anidulafungin to mice did not provide evidence of genotoxic potential using the micronucleus assay. See animal pharmacology review by Dr. O. McMaster.

7.3.9 Special Safety Studies

No treatment related adverse events emerged that were unique to anidulafungin, and not present in other members of the echinocandin class of antifungal drugs, such as caspofungin and micafungin.
Potential risks for anidulafungin include infusion-related reactions and hepatobiliary toxicities. Infusion related AEs were observed in some non-clinical studies in rats and monkeys. Similarly, in nonclinical studies utilizing rats and monkeys, the liver was a target organ as evidenced by hepatic injury with related elevations in ALT and AST levels. Dose-limiting toxicity was observed at exposures greater than the human equivalent dose.
Infusion reactions observed in preclinical studies and early clinical studies in NDA 21-632
There were few infusion-associated AEs among patients included in the integrated Phase 2-3 studies in the original submission. Ten of 473 patients (2.1%) receiving IV anidulafungin and 5 of 301 patients (1.6%) receiving oral fluconazole and matching IV placebo had an infusion-associated adverse event.

7.3.10 Withdrawal Phenomena and/or Abuse Potential

Echinocandin anti-fungal agents have little potential for addiction and abuse.

7.3.11 Human Reproduction and Pregnancy Data

Anidulafungin has not been studied in pregnancy. There were no documented pregnancies during the clinical development period. Anidulafungin is designated category C in pregnancy at this time.

7.3.12 Assessment of Effect on Growth

One PK study in 25 pediatric patients has been conducted. An effect on growth in children cannot be determined from the limited data available.

7.3.13 Overdose Experience

During clinical trials (study VER002-9b), a single 400-mg dose of anidulafungin was inadvertently administered as a loading dose. No clinical adverse events were reported.

In a phase 1 PK study of 10 healthy subjects administered a loading dose of 260 mg followed by 130mg daily, anidulafungin was generally well tolerated;3 of the 10 subjects experienced transient, asymptomatic transaminase elevations (≤3×ULN). One patient experienced an infusion reaction and recovered following drug discontinuation.

7.3.14 Post marketing Experience

There is no post marketing experience with anidulafungin at this time.

7.4 Adequacy of Patient Exposure and Safety Assessments

In the clinical program, safety data could be assessed for 929 patients across twenty studies. In with patients with candidemia who received 100mg IV anidulafungin daily, efficacy data was available for 204 anidulafungin patients. This was a relatively small number of patients. The dose and the duration of therapy were appropriate for the disease being studied. The clinical trials included an appropriate schedule of testing in exposed patients. Appropriate clinical and laboratory testing was done to elucidate adverse events. Overall, the studies in the clinical development program provided a comprehensive amount of safety data for review.

7.4.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See integrated summary of safety.

7.4.1.1 Study type and design/patient enumeration

Table 12. CLINICAL STUDIES	
VER002-9	A Phase 3, Double-Blind, Randomized, Multi-Center, Study of the Safety and Efficacy of Anidulafungin vs. Fluconazole in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications
VER002-9B	A Phase 3, Open Label, Non-Comparative, Multi-Center, Study of the Safety and Efficacy of Anidulafungin in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications
VER002-6*	A Phase 2, Open-Label, Randomized, Dose-Ranging Study of the Safety and Efficacy of Intravenous Anidulafungin (VER002) in the Treatment of Patients with Invasive Candidiasis

	Anidulafungin			**Fluconazole**		
	≤14 days	**>14 days**	**Total**	**≤14 days**	**>14 days**	**Total**
Total enrolled/randomized	**128**	**76**	**206**	**90**	**35**	**129**
Study VER002-6	21	19	41	0	0	0
Study VER002-9	86	45	132	90	35	129
Study VER002-9b	21	12	33	0	0	0
Total treated (ITT)	**128**	**76**	**204**	**90**	**35**	**125**

7.4.1.2 Demographics

Table 13. Demographics and Baseline Characteristics: Phase 2-3 Integrated Database

		Anidulafungin			Fluconazole	
	≤14 days (N=128)	>14 days (N=76)	Total (N=204)	≤14 days (N=90)	>14 days (N=35)	Total (N=125)
Age (years)						
N	128	76	204	90	35	125
Mean	56.4	56.9	56.6	60.4	56.9	59.4
SD	16.71	17.70	17.04	15.38	17.97	16.15
Median	57.0	59.0	58.5	60.5	55.0	59.0
Minimum - Maximum	16 - 89	17 - 87	16 - 89	24 - 91	25 - 89	24 - 91
Age distribution, N (%)						
<65	87 (68.0)	48 (63.2)	135 (66.2)	54 (60.0)	22 (62.9)	76 (60.8)
≥65	41(32.0)	28 (36.8)	69 (33.8)	36 (40.0)	13 (37.1)	49 (39.2)
Gender, N (%)						
Male	70 (54.7)	36 (47.4)	106 (52.0)	45 (50.0)	19 (54.3)	64 (51.2)
Female	58 (45.3)	40 (52.6)	98 (48.0)	45 (50.0)	16 (45.7)	61 (48.8)
Ethnicity, N (%)						
Caucasian/White	82 (64.1)	54 (71.1)	136 (66.7)	66 (73.3)	26 (74.3)	92 (73.6)
African-American/Black	32 (25.0)	15 (19.7)	47 (23.0)	19 (21.1)	7 (20.0)	26 (20.8)
Asian	0	1 (1.3)	1 (0.5)	0	0	0
Hispanic/Latino	11 (8.6)	5 (6.6)	16 (7.8)	3 (3.3)	2 (5.7)	5 (4.0)
Other	3 (2.3)	1 (1.3)	4 (2.0)	2 (2.2)	0	2 (1.6)

		Anidulafungin			Fluconazole	
	≤14 days (N=128)	>14 days (N=76)	Total (N=204)	≤14 days (N=90)	>14 days (N=35)	Total (N=125)
	Baseline Hepatobiliary Status, N (%)					
Elevated	47 (36.7)	26 (34.2)	73 (35.8)	29 (32.2)	15 (42.9)	44 (35.2)
Not Elevated	76 (59.4)	45 (59.2)	121 (59.3)	57 (63.3)	19 (54.3)	76 (60.8)
Unknown[a]	5 (3.9)	5 (6.6)	10 (4.9)	4 (4.4)	1 (2.9)	5 (4.0)
Baseline Apache II Score						
N	126	72	198	90	35	125
Mean	15.3	13.7	14.7	14.3	14.7	14.4
SD	7.74	7.64	7.72	6.47	7.41	6.72
Median	14.5	13.5	14.0	14.0	12.0	13.0

Minimum - Maximum	2 - 37	2 - 42	2 - 42	3 - 30	6 - 36	3 – 36
Baseline Apache II Score, N (%)						
≤20	94(73.4)	62 (81.6)	156 (76.5)	74 (82.2)	29 (82.9)	103 (82.4)
>20	32(25.0)	10 (13.2)	42 (20.6)	16 (17.8)	6 (17.1)	22 (17.6)
Unknown[a]	2 (1.6)	4 (5.3)	6 (2.9)	0	0	0
Baseline Neutrophil Count, N (%)	124 (96.9)					
≤500 cells/mm3 3 (		2 (2.6)	5 (2.5)	4 (4.4)		4 (3.2)
2.3) >500 cells/mm3		74 (97.4)	198 (97.1)	86 (95.6)	0 34 (97.1)	120 (96.0)
Unknown[a]	1 (0.8)	0	1 (0.5)	0	1 (2.9)	1 (0.8)

Source: Appendix A, Table 2-1. Includes data from VER002-6, VER002-9, and VER002-9b.
[a] Patients with missing values at baseline were categorized as unknown.

7.4.1.3 Extent of exposure (dose/duration)

The integrated data base combines results from three studies VER002-9, VER002-9b, and VER002-6 in invasive candidiasis. Of the 204 anidulafungin-treated patients in the integrated safety database, 119 had treatment durations ≥14 days. Doses of study drug and duration of exposures were appropriate for the condition studied, i.e. candidemia.

Table 14. Extent of Exposure: Phase 2-3 Integrated Database

	Anidulafungin			Fluconazole		
	≤14 days (N=128)	>14 days (N=76)	Total (N=204)	≤14 days (N=90)	>14 days (N=35)	Total (N=125)
Number of IV Doses						
N	128	76	204	90	35	125
Mean	10.0	18.8	13.3	9.1	19.6	12.0
SD	3.97	5.07	6.16	4.02	5.02	6.40
Median	11.0	17.0	14.0	10.0	18.0	11.0
Minimum - Maximum	1 - 15	12 -38	1 - 38	1 - 14	14 -36	1 - 36
Duration of IV treatment (days)						
N	128	76	204	90	35	125
Mean	10.0	19.2	13.5	9.1	19.9	12.2
SD	3.99	5.05	6.25	3.99	5.16	6.51
Median	11.0	17.0	14.0	10.0	18.0	11.0
Minimum - Maximum	1 - 14	15 -38	1 - 38	1 - 14	15 -37	1 - 37
Duration of oral treatment (days)[a]						
N	37	4	41	30	6	36
Mean	9.5	11.0	9.7	8.7	9.2	8.8
SD	6.99	10.83	7.27	8.41	3.60	7.78
Median	7.0	7.0	7.0	4.5	8.5	5.0
Minimum - Maximum	1 - 32	3 - 27	1 - 32	1 - 33	5 - 15	1 - 33

Source: Appendix A, Table 3-1. Includes data from VER002-6, VER002-9, and VER002-9b. [a] Only patients in VER002-9 and VER002-9b could continue treatment with oral fluconazole.

7.4.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.4.2.1 Other studies

Study VER002-9B
This was an open-label continuation of the invasive candidiasis study, VER002-9. The same entry criteria applied. There were 33 patients enrolled in the study. As part of the complete response these patients were evaluated for hepatic safety.
No significant hepatic injury was noted in this study. No patient, at any time during the study, had ALT > 5x ULN or had AST > 10 x ULN. No patient developed ALT >3 x ULN + Total Bilirubin >1.5 x ULN during the study. Two patients had cholecystitis and one had a biloma, none of these events were related to study drug.
Two patients in the study had a serious adverse event and both recovered. Both cases were critically ill and had confounding factors that made attribution to anidulafungin therapy inconclusive. One patient developed increased creatinine on day 2 of anidulafungin therapy. This was thought to be related to anidulafungin by the investigator. However, on review of this case, the clinical reviewer found that this case had abnormal renal function prior to anidulafungin therapy and the increased creatinine was more likely to be secondary to muscle injury due to a lower limb degloving injury and fracture and subsequent surgeries.
The second patient, with liver disease and acute bowel obstruction, was admitted with an Apache score of 27. During hospitalization he experienced hypotension and renal failure with subsequent transfer to the intensive care unit for intubation and hemodialysis. He was commenced on anidulafungin therapy for *C. albicans* candidemia. He had a seizure following anidulafungin infusion on study day 11. On the same day, the patient developed respiratory acidosis, pulmonary edema and sepsis related to candidemia due to *C. parapsilosis*. All of these concomitant events could have contributed to seizure activity in this patient.

7.4.2.2 Post marketing experience

There is no post marketing experience with anidulafungin at this time.

7.4.2.3 Literature

7.4.3 Adequacy of Overall Clinical Experience

7.4.4 Adequacy of Special Animal and/or In Vitro Testing

See Animal Pharmacology review by Dr. O. Mc Master.

7.4.5 Adequacy of Routine Clinical Testing

7.4.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See biopharmaceutics review by Dr. D. Chilukuri

7.4.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Anidulafungin was generally well tolerated by a patient's when compared to fluconazole. In general, other echinocandins (caspofungin, micafungin) are well tolerated as a class of antibiotics.
Adverse events for other echinocandins, caspofungin and micafungin are summarized in the following tables. Adverse events are similar to those observed for anidulafungin. The following tables are adapted from the caspofungin, Cancidas™ and micafungin, Mycamine™ FDA approved labels.

15. Drug-Related* Clinical Adverse Experiences among Patients with Persistent Fever and Neutropenia
Incidence ε2% for at least one treatment group by Body System.

	CANCIDAS** N=564 (percent)	AmBisome*** N=547 (percent)
Body as a Whole		
Abdominal Pain	1.4	2.4
Chills	13.8	24.7
Fever	17.0	19.4
Flushing	1.8	4.2
Perspiration/Diaphoresis	2.8	2.2
Cardiovascular System		
Hypertension	1.1	2.0
Tachycardia	1.4	2.4
Digestive System Diarrhea	2.7	2.4
Nausea	3.5	11.3
Vomiting	3.5	8.6
Metabolism and Nutrition		
Hypokalemia	3.7	4.2
Musculoskeletal System Back Pain	0.7	2.7
Nervous System & Psychiatric		
Headache	4.3	5.7
Respiratory System Dyspnea	2.0	4.2
Tachypnea	0.4	2.0
Skin & Skin Appendage Rash	6.2	5.3

Drug-related adverse events which occurred in ≥ 0.5% of all subjects who received Micafungin (MYCAMINE) in these trials are shown in the following table.

Common Drug-Related* Adverse Events in Subjects† Who Received MYCAMINE in Clinical Trials

Adverse Events [1] (MedDRA System Organ Class and Preferred Term)	**MYCAMINE n (%)**
Number of Patients	2402
Blood and Lymphatic System Disorders	
Leukopenia	38 (1.6)
Neutropenia	29 (1.2)
Thrombocytopenia	20 (0.8)
Anemia	19 (0.8)
Gastrointestinal Disorders	

Nausea	67 (2.8)
Vomiting	58 (2.4)
Diarrhea	38 (1.6)
Abdominal pain	23 (1.0)
Abdominal pain upper	11 (0.5)
General Disorders and Administration Site Conditions	
Pyrexia	37 (1.5)
Rigors	23 (1.0)
Injection site pain	21 (0.9)
Hepatobiliary Disorders	
Hyperbilirubinemia	25 (1.0)
Laboratory Tests	
Aspartate aminotransferase increased	64 (2.7)
Alanine aminotransferase increased	62 (2.6)
Blood alkaline phosphatase increased	48 (2.0)
Liver function tests abnormal	36 (1.5)
Blood creatinine increased	14 (0.6)
Blood urea increased	12 (0.5)
Blood lactate dehydrogenase increased	11 (0.5)
Metabolism and Nutrition Disorders	
Hypokalemia	28 (1.2)
Hypocalcemia	27 (1.1)
Hypomagnesemia	27 (1.1)
Nervous System Disorders	
Headache	57 (2.4)
Dizziness	16 (0.7)
Somnolence	12 (0.5)
Skin and Subcutaneous Tissue Disorders	
Rash	38 (1.6)
Pruritus	18 (0.7)
Vascular Disorders	
Phlebitis	39 (1.6)
Hypertension	14 (0.6)
Flushing	12 (0.5)

Post marketing events for micafungin

The following is a summary from Dr. M. Singer's review of post marketing events for micafungin at the time of FDA approval. The following adverse events have been identified during the post-approval use of an echinocandin, micafungin sodium for injection in Japan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency. A causal relationship to micafungin sodium for injection could not be excluded for these adverse events, which included:

- *Hepatobiliary disorders:* hyperbilirubinemia, hepatic function abnormal, hepatic disorder, hepatocellular damage
- *Renal and urinary disorders*: acute renal failure and renal impairment
- *Blood and lymphatic system disorders*: white blood cell count decreased, hemolytic anemia
- *Vascular disorders*: shock

7.4.8 Assessment of Quality and Completeness of Data

In the clinical program, safety data could be assessed for 929 patients across twenty studies. In with patients with candidemia who received 100mg IV anidulafungin daily, efficacy data was available for 204 anidulafungin patients. This was a relatively small number of patients. The dose and the duration of therapy were appropriate for the disease being studied. The clinical trials included an appropriate schedule of testing in exposed patients. Appropriate clinical and laboratory testing was done to elucidate adverse events. Overall, the studies in the clinical development program provided a comprehensive amount of safety data for anidulafungin.

7.4.9 Additional Submissions, Including Safety Update

Not applicable

7.5 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There is limited data in patients with neutropenia, and therefore the efficacy results may not be applicable to these patients. There is one well conducted PK study in immunocompromised children. The efficacy and safety in children remains to be elucidated.
Hepatic safety and infusion reactions have emerged as potential risks in patients. Careful monitoring of hepatic chemistry is recommended in the anidulafungin label. Similar hepatic effects and infusion reactions were observed during clinical trials of caspofungin and micafungin.

7.6 General Methodology

Comment: Cheryl's review

7.6.1 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data was combined across all the clinical studies in this NDA 21-948.
Efficacy data was not pooled because the three studies were different in design, for example, there was one blinded comparative study, VER002-9 versus open label non comparative studies, VER002-6, and VER002-9B.
Safety data across the entire clinical program is summarized in this NDA and was previously reviewed in a clinical review of the complete response to the approvable letter for NDA21-632.

7.6.1.1 Pooled data vs. individual study data

See above section

7.6.1.2 Combining data

See above section

7.6.2 Explorations for Predictive Factors

See clinical pharmacology review by Dr. D. Chilukuri

7.6.2.1 Explorations for dose dependency for adverse findings

7.6.2.2 Explorations for time dependency for adverse findings

7.6.2.3 Explorations for drug-demographic interactions

7.6.2.4 Explorations for drug-disease interactions

7.6.2.5 Explorations for drug-drug interactions

7.6.3 Causality Determination

Hepatic safety and infusion reactions have emerged as potential risks in patients. Careful monitoring of hepatic chemistry is recommended in the anidulafungin label. Similar hepatic effects and infusion reactions were observed during clinical trials of two echinocandin antifungal drugs, caspofungin and micafungin.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The loading dose is 200mg IV followed by 100mg IV daily. No dosing adjustment is recommended based on age, gender or race, renal function or liver function.

8.2 Drug-Drug Interactions

Anidulafungin is not metabolized by hepatocytes, nor was it found to be a clinically relevant inhibitor or inducer of cytochrome P450 enzymes. The majority of drug is eliminated by slow chemical degradation with a small amount of intact drug (<10% of the dose) and resultant peptidic degradants excreted through the feces via the bile. Renal clearance, at less than 1% of the dose eliminated in the urine, is negligible (see Item 6 of Original NDA 21-632). No drug interactions when tested against tacrolimus, cyclosporine, voriconazole, and rifampin. No dosage adjustment is required.

8.3 Special Populations

No dosing adjustment is recommended based on age, gender or race, renal function or liver function. Anidulafungin has not been studied in pregnancy.
See clinical pharmacology review by Dr. D Chilukuri

8.4 Pediatrics

The safety and efficacy has not been adequately established in children. A PK study has been conducted in immunocompromised children and will be included in the anidulafungin label.

8.5 Advisory Committee Meeting

An advisory committee was not required.

8.6 Literature Review

8.7 Bibliography

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8.8 Post marketing Risk Management Plan

8.9 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

From a clinical perspective, anidulafungin appears safe and effective for the treatment of candidemia in non-neutropenic patients. Small numbers of patients with deep tissue *Candida* infections were studied, therefore based on the data provided, anidulafungin can be only

recommended for intra-abdominal abscess and peritonitis. Further study is required in neutropenic adults, and in children.

9.2 Recommendation on Regulatory Action

From a clinical perspective, anidulafungin can be approved for the indication of candidemia, as well as the following *Candida* infections, intra-abdominal abscesses, and peritonitis.

9.3 Recommendation on Post marketing Actions

9.3.1 Risk Management Activity

9.3.2 Required Phase 4 Commitments

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

On November 25th 2004 , labeling changes recommended by the FDA with regard to the esophageal candidiasis indication were sent to the applicant. In the evaluation of the current label, and the label for caspofungin and voriconazole was also reviewed with regard to the indication of candidemia and other forms of invasive candidiasis. Clinical studies of voriconazole and caspofungin also enrolled small numbers of patients with invasive candidiasis other than candidemia; these studies are summarized below.

Caspofungin
Treatment Indications
Treatment of Candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. CANCIDAS has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida.*

Studies of Invasive candidiasis other than candidemia

In a Phase III randomized, double-blind study, patients with a proven diagnosis of invasive candidiasis received daily doses of CANCIDAS (50 mg/day following a 70-mg loading dose on Day 1) or amphotericin B deoxycholate (0.6 to 0.7 mg/kg/day for non-neutropenic patients and 0.7 to 1.0 mg/kg/day for neutropenic patients). Patients were stratified by both neutropenic status and APACHE II score. Patients with *Candida* endocarditis, meningitis, or osteomyelitis were excluded from this study. In this study, the efficacy of CANCIDAS in patients with intra abdominal abscesses, peritonitis and pleural space *Candida* infections was evaluated in 19 non-neutropenic patients. Two of these patients had concurrent candidemia. *Candida* was part of a polymicrobial infection that required adjunctive surgical drainage in 11 of these 19 patients. A favorable response was seen in 9 of 9 patients with peritonitis, 3 of 4 with abscesses (liver, parasplenic, and urinary bladder abscesses), 2 of 2 with pleural space infections, 1 of 2 with mixed peritoneal and pleural infection, 1 of 1 with mixed abdominal abscess and peritonitis, and 0 of 1 with *Candida* pneumonia. In a separate compassionate use study, 4 patients with hepatosplenic candidiasis received prolonged therapy with caspofungin following other long-term antifungal therapy; three of these patients had a favorable response.

Voriconazole
Voriconazole is indicated for Candidemia in nonneutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds.

Studies of Invasive candidiasis other than candidemia
In Studies 608 and 309/604 (non-comparative study in patients with invasive fungal infections who were refractory to, or intolerant of, other antifungal agents), voriconazole was evaluated in 35 patients with deep tissue *Candida* infections. A favorable response was seen in 4 of 7 patients with intraabdominal infections, 5 of 6 patients with kidney and bladder wall infections, 3 of 3 patients with deep tissue abscess or wound infection, 1 of 2 patients with pneumonia/pleural space infections, 2 of 4 patients with skin lesions, 1 of 1 patients with mixed intraabdominal and pulmonary infection, 1 of 2 patients with suppurative phlebitis, 1 of 3 patients with hepatosplenic infection, 1 of 5 patients with osteomyelitis, 0 of 1 with liver infection, and 0 of 1 with cervical lymph node infection.

9.5 Comments to Applicant

10 APPENDICES

10.1 Review of Individual Study Reports

INVASIVE CANDIDIASIS STUDY VER002-9
This is a phase 3, double-blind, randomized, multi-center, study of the safety and efficacy of anidulafungin vs. fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis and prevention of complications.

Overview of Study VER002-9
This phase 3, double-blind (third-party unblinded) randomized, multi-center, comparative study enrolled and treated 256 patients, 131 received 100 mg IV anidulafungin, and 125 received 400 mg IV fluconazole for 14 to 42 days, in the ITT population. Candidemia was present in more than 90% of patients in both study arms. Approximately half of all patients had invasive candidiasis related to an IV catheter per investigator attribution. Most patients had a single baseline pathogen; *Candida albicans* and *Candida glabrata* were the baseline pathogens most frequently isolated.

Protocol Objectives

Primary objective:

- to determine if anidulafungin is at least as effective as fluconazole with respect to the global response (combined clinical and microbiological response at the end of IV therapy) for the treatment of patients with a diagnosis of candidemia and/or other forms of invasive candidiasis

Secondary objectives:

- to compare anidulafungin with fluconazole in this patient population for safety profile, the prevention of late infections and the clinical and microbiological efficacy at various time points

10.2 Study Design

As described previously, this study is a phase 3, double-blind, randomized, multi-center, study of the safety and efficacy of anidulafungin vs. fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis. All patients were to receive the study medication for minimum treatment duration of 14 days from the time of the last negative culture

and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Total treatment duration was not to exceed 42 days.
Patients in either group were permitted to switch to oral fluconazole (400 mg/daily) after at least 10 days of IV treatment if the following criteria were met,

- the patient was afebrile for at least 24 hours;
- the patient was able to tolerate oral medications;
- the last blood culture was negative for *Candida* species;
- reduction of signs and symptoms of the *Candida* infection such that the investigator felt it was appropriate to switch to oral fluconazole (oral fluconazole was not to be given as prophylaxis).

The patients were followed for safety through the 6-week follow-up (FU) visit.

Randomization and stratification

Patients were stratified by APACHE II score and absolute neutrophil count. Patients were randomly assigned in a 1:1 ratio.

Dosage

The dose of anidulafungin (200mg loading dose/100mg daily) selected for this study was determined by phase 1 dose-ranging studies in healthy subjects, and by a phase 2, dose-ranging study (VER002-6) of anidulafungin in patients with invasive candidiasis, Table 2. The dose of fluconazole 400mg IV daily used is the highest approved dose for invasive fungal infections.

Table 2.GLOBAL SUCCESS IN VER002-6

		Anidulafungin Dose		
Population	50 mg/day	75 mg/day	100 mg/day	All Patients
Time point	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Micro-ITT				
End of Therapy	25/37 (68)	30/40 (75)	27/39 (69)	82/116 (71)
2-week Follow-up	14/37 (38)	23/40 (58)	20/39 (51)	57/116 (49)
Efficacy Evaluable				
End of therapy	21/25 (84)	27/30 (90)	25/28 (89)	73/83 (88)
2-week Follow-up	13/18 (72)	22/26 (85)	20/24 (83)	55/68 (81)

Data from VER002-6 Clinical Study Report Appendix 14 and Appendix 18

Medical officer's comment

The dose of anidulafungin (200mg IV loading dose followed by 100mg IV daily) in this study is twice the dose (100mg IV loading dose followed by 50mg daily) used in the original esophageal candidiasis study, VER002-4. The original clinical reviewer for NDA21-632 commented that the dose in the esophageal candidiasis study may have been too low based on subsequent data from dose ranging studies.

Study Sites

Study sites were located in six countries: 33 in the United States, 8 in Canada and 4 in Europe. Forty-seven of 70 investigators enrolled patients. The majority of patients were enrolled in the United States. The number of treated patients by country was USA (185), Canada (59), Belgium (2), Germany (3) and Italy (6) and Netherlands (1). The largest number of patients (25) was enrolled at a single site in Canada.

Inclusion Criteria

Patients were eligible to participate in the study if they met the following inclusion criteria.

1. Diagnosis of candidemia or other forms of invasive candidiasis from a blood culture or a culture of a specimen from a normally sterile site, preferably taken within 96 hours before study entry. The diagnosis was to be based on the following,
   - Candidemia defined as at least one blood culture positive for yeast (in the absence of other demonstrated foci of infection).
   - Other forms of invasive candidiasis defined as a positive culture for yeast from a specimen from a normally sterile site with or without a positive blood culture; positive yeast culture from a newly-placed drain in a normally sterile site; or any positive blood culture for yeast plus ophthalmic examination consistent with *Candida* endophthalmitis. Positive yeast cultures from urine or a positive yeast culture from sputum (including those obtained by bronchoalveolar lavage or an endotracheal aspirate) did not qualify as a positive culture.

AND

At least one of the following:

- A fever defined as an oral/tympanic temperature ≥ 100.4°F (38.0°C), rectal temperature ≥101.4°F (38.6°C) or an axillary temperature ≥ 99.4°F (37.4°C)
- Hypothermia defined as a temperature less than 96.8°F (36.0°C)
- A systolic blood pressure of less than 100 mm Hg or a decrease in systolic blood pressure of at least 30 mm Hg from baseline
- Signs or symptoms of candidemia/invasive candidiasis
- Radiologic findings consistent with a diagnosis of invasive candidiasis

2. Male or female ≥ 16 years of age. Some sites may have enrolled patients ≥ 18 years of age only.
3. Willing and able to give signed informed consent, or have a legally authorized representative who was willing and able to give consent.
4. Reliable and willing to make themselves available for the duration of the study and to abide by the study restrictions.
5. Expected hospitalization for at least three days.

Exclusion Criteria

Patients were excluded from this study if any of the following criteria were present:

1. Female patients who were pregnant, lactating, or planning a pregnancy during the course of the study, or who were of child bearing potential and not using an acceptable method of birth control (i.e. surgically sterile, intrauterine device, oral contraceptive plus barrier contraceptive, hormone delivery system *plus* barrier contraceptive or condom in combination with

contraceptive cream, jelly or foam). Patients were to continue contraceptive methods during the study and for at least 30 days after receiving their last treatment.
2. Patients who received greater than 48 hours of systemic antifungal therapy for the *Candida* infection for which they were enrolled.
3. Patients who failed antifungal therapy with any systemic antifungal for this episode of candidiasis/candidemia. Recurrence within 2 weeks was considered failure of previous therapy.
4. Patients who received prophylactic administration of fluconazole, itraconazole, or voriconazole for more than one week within 30 days prior to enrollment.
5. Patients who had received and who were to continue to receive terfenadine or cisapride.
6. Patients who had, at any time, previously received anidulafungin.
7. Known *Candida krusei* infection.
8. Patients with any of the following abnormal laboratory values: Bilirubin > 5 times the upper limit of normal (ULN), AST or ALT > 10 times the ULN.
9. Patients who required continued treatment with another systemic antifungal agent [oral nonabsorbable azoles (e.g., clotrimazole troches) were permitted].
10. Patients with poor venous access that would preclude IV drug delivery or multiple blood draws.
11. Patients with a known hypersensitivity to echinocandin therapy or azole therapy.
12. Patients who participated in a study of an investigational drug or device (without any FDA approved indications) within four weeks of study entry. The investigational use of antiretroviral agents and the investigational use of licensed agents were permitted if the patient was on a stable regimen for four weeks prior to study start.
13. Life expectancy ≤ 72 hours.
14. Patients on hemodialysis unable to tolerate the volume of fluid in the placebo infusion on non-dialysis days.
15. Patients with suspected *Candida* osteomyelitis, endocarditis, or meningitis.
16. Patients with prosthetic devices at a suspected site of infection were excluded unless the device was removed at study entry or soon after randomization. [Hemodialysis shunts (AV fistulae) could remain in situ)].
17. Patients with a prosthetic heart valve or vascular graft suspected to be the site of the *Candida* infection and positive blood cultures.

Medical officer's comments
The inclusion criteria were adequate to include patients with invasive candidiasis and to exclude patient with colonization with Candida species. Patients with known Candida krusei infection were excluded because of its resistance to fluconazole. It is appropriate to exclude patients with culture positive urine and sputum including BAL cultures as these cultures are often due to yeast colonization, and not true infection with Candida. "A positive yeast culture from a newly-placed drain in a normally sterile site" is an inclusion criterion; positive cultures from newly placed drains may not always indicate a true Candida infection, however the numbers of cultures from newly placed drains in this study are small and do not affect the overall results.

Duration of treatment

Treatment was for a minimum of 14 days to maximum of 42 days. Treatment could switch to oral fluconazole following ≥ 10 days of IV therapy. If patients had a fluconazole-nonsusceptible baseline *Candida* strain other than *C. krusei,* the investigator determined if the patient should continue on the study medication.

Appears This Way
On Original

Schedule of Monitoring

Table 3 : Schedule of monitoring for study patients		STUDY SCHEDULE*									
	Screen[1]	**Daily through EOT**	**D3**	**D4**	**D7**	**Day 10**	**D8-D41**	**End of IV Therapy**	**End of Oral Therapy (if applicable)**	**Follow-up Visit Week 2 (± 2 days)**	**Long term Follow-up Week 7 (± 1 wk)**
Informed Consent	X										
Medical and Medication History, APACHE II	X										
Physical Examination[2]	X										
Temperature	X	X								X	X
Assessment of clinical signs & symptoms of											
	X					X		X	X	X	X
Candida infection											
Serum Pregnancy Test[4]	X										
Fundoscopic Exam	X[3]							X[3]	X[3]	X[3]	X
Standard 12 lead ECG[5]	X		X								
Blood Cultures[6]	X		X		X	X[7]	X[7]	X	X	X	X
Specimen Culture[7]	X	X									
CBC with Diff[8]	X		X		X		X[8]	X[8]	X[8]	X[10]	X[10]
Chemistry Panel[9]	X		X		X		X[9]	X[9]	X[9]	X[10]	X[10]
Saliva Samples[11]	X			X							
Sampling for Assays for Glucan and *Candida* DNA						X	X				
	X		X								
DNA[12]											
Study Medication		X	X								
Adverse Events		X	X							X	X

1. Screening procedures/assessments were completed before the first dose of study medication.
2. Could occur within 72 hours before the first dose of study medication.
3. Completed only if the baseline fundoscopic examination was positive for endophthalmitis.
4. A serum pregnancy test was performed before the first dose of study medication on women of childbearing potential.
5. ECGs were done before the first dose of study medication and on Day 3, 0-3 hours after the completion of the infusion.

6. *Table 3 contd.*	Screening blood cultures were obtained on all patients. If the screening blood culture was >24 hours before study entry, blood cultures were repeated at baseline. If the screening blood culture was <24 hours before study entry, the baseline blood cultures did not need to be repeated. Blood cultures were be repeated on Day 3, 7, and every three days until negative while on study medication and as clinically indicated
7.	Cultures of other normally sterile sites as clinically indicated.
8.	Hematology: CBC with differential count (RBC, WBC, absolute neutrophil count, platelet count, hemoglobin, hematocrit)
9.	Serum Chemistry: Creatinine, BUN (urea), AST, ALT, alk phos, total bilirubin, albumin, CO2 , NA, K, CL, glucose.
10.	Hematology and Chemistry tests were repeated at the follow-up visits if clinically significantly abnormal on the last day of study medication.
11.	At selected sites, patients had saliva samples obtained at baseline and anytime following the Day 4 dose.
12.	Blood specimens were collected at baseline, Day 3, Day 7, and weekly until the end of study medication and on the last day of study medication.

Screening Blood Cultures

Two aerobic blood cultures from 2 different sites were performed at screening on all patients. Peripheral venipuncture was the preferred method for obtaining blood cultures. If the patient had an indwelling central venous catheter, one blood culture was from a peripheral site if at all possible; the other culture could be drawn from one lumen of the catheter.
Baseline Cultures (other than blood): These were obtained as clinically indicated. The type/site of the culture, the culture results, and date of the culture used for entry into the study were recorded in the case report form.
On-Study Cultures: Blood cultures were obtained on Day 3, Day 7, and every 3 days thereafter until negative while on study medication; at the end of IV therapy; at the end of oral therapy; and at the 2-week and 6-week FU visits from the end of therapy. Additional cultures could be obtained at the Investigator's discretion as clinically indicated. For patients whose baseline isolates (or histological evidence of infection) was obtained from samples other than blood, culture or histology from the same site was repeated as clinically indicated.

Medical officer's comment
The procedures used for obtaining blood cultures in this study are consistent with current guidelines. Current guidelines for suspected iv catheter-related infection state that two blood cultures should be drawn for culture with a least one set drawn percutaneously,(Mermel 2001). A negative blood culture drawn through an IV catheter is helpful for excluding catheter-related blood stream infection; in a study of hospitalized patients, catheter and percutaneous blood cultures had a positive predictive value of 63% and 73%, but had a greater negative predictive value of 99% and 98%, respectively, for IV catheter related infection, (de Jardin 1999).

Central Venous Catheter Management
The relationship between the catheter and the invasive candidiasis was based on the investigator's assessment. Insertion and removal dates as well as catheter cultures from insertion site and catheter tip were documented. Central venous catheter removal was guided by currently

published recommendations, (Walsh 2002 and Mermel 2001). Current data indicate that catheter removal should generally be considered early in the management of candidemia.

Medical officer's comment
It is not clear what criteria the investigator used to establish the candidemia was catheter-related. The numbers of patients with catheters and the rates of catheter removal were balanced between study arms.

Withdrawal from Study

Patients were free to withdraw from the study at any time for any reason.
Only those patients who died, were lost to follow-up, or refused any further contact with respect to the study was prematurely withdrawn from the study. Patients withdrawn from the study were not replaced, regardless of the reason for withdrawal.

Discontinuation from Study Medication

Patients could have been discontinued from study medication for any of the following reasons: any adverse event (AE); patient noncompliance or unwillingness to comply with the procedures required by the protocol; worsening clinical status (lack of efficacy); absence / presence of certain pathogens; or request by the patient (withdrawal of consent), investigator, or Vicuron.

Study Populations

ITT: All patients who received at least one dose of study medication were included in the intent to treat (ITT) population.
MITT: The primary efficacy population was the Microbiological-ITT population. This population included all patients who received at least one dose of study medication and who had a positive culture from a normally sterile site at baseline for *Candida* species, preferably within 96 hours before entry into the study.
Efficacy Evaluable: The Efficacy Evaluable population was a subset of the Micro-ITT population. Patients in the efficacy evaluable populations had both clinical and microbiological data available for analysis at entry and test of cure visits. There were five distinct groups in the efficacy evaluable population: Efficacy evaluable at Day 10 of IV therapy, at the end of IV therapy, at the end of all therapy (oral and/or IV), at 2-week follow-up, and at 6-week follow-up.

Safety population

All safety analyses were conducted in the ITT population.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was the global response (based on the clinical and microbiological responses) at the end of IV therapy in the Micro-ITT population.

Patients were assigned a **global response** in the Micro-ITT population as follows:
Success: required both a clinical and microbiological success as described below

Clinical Success

- Cure: Resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or oral fluconazole required to complete the course of therapy. OR
- Improvement: Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or additional oral fluconazole required.

AND

Microbiological success

- Eradication (documented or presumed): Culture was negative for all *Candida* species present at baseline (documented), or culture data were not available for a patient with a successful clinical response (presumed).

Failure:

Clinical failure

- No significant improvement in signs and symptoms, or death due to the *Candida* infection.

Microbiological failure

- Documented or presumed persistence or recurrence of baseline *Candida* infection;superinfection with a new *Candida* species while on study medication; emergence of a new *Candida* species at an original site of infection or at distant, sterile site after study medication completion.
- The sponsor considered the following patients "indeterminate" and evaluated them as failures,
    - patients who received fewer than 3 doses of study medication
    - death not due to the *Candida* infection;
    - withdrawal from study medication for reasons other than failure

Medical officer's comment

In the efficacy evaluable population, the same criteria of success and failure were applied, except that patients with an "indeterminate" response were excluded from the evaluation.

Microbiological Response at the Baseline Pathogen Level

Success:

- Eradication (documented or presumed): Culture was negative for the *Candida* species present at baseline (documented), or culture data were not available for a patient with a successful clinical response (presumed).

Failure:

- Persistence (documented or presumed): The baseline *Candida* species was present in repeat cultures (documented), or culture data were not available for a patient with a clinical response of failure (presumed).
- Recurrence (documented or presumed): The baseline *Candida* species isolated following eradication (documented), or culture data were not available for a patient with a clinical response of failure after a previous response of success (presumed).
- Indeterminate: culture data were not available for a patient with a clinical response of indeterminate.

Secondary Endpoints

Global response at all secondary time points in the Micro-ITT population
Global response at the end of IV therapy in the modified Micro-ITT population
Global response at all time points in the efficacy evaluable population
Clinical response at all time points in the Micro-ITT and efficacy evaluable populations
Patient level microbiological response at all time points in the Micro-ITT and efficacy evaluable populations
Pathogen level microbiological response in the Micro-ITT and efficacy- evaluable populations at the end of IV therapy and 2 week FU time points only.
Death directly attributable to invasive candidiasis/candidemia and all cause mortality

Data Integrity

A total of seven patients in the fluconazole arm were unblinded. None of the patients in the anidulafungin arm were unblinded. Five were unblinded by investigator request and two were accidentally unblinded. Two patients were not protocol evaluable.

Table 4. UNBLINDED PATIENTS

Patient ID	Treatment	Efficacy Evaluable Status
Reason for the Unblinding		
Randomization fax accidentally sent to study coordinator		
25-001	FLU	Yes, study coordinator not involved in efficacy assessment*
73-001	FLU	Yes, study coordinator not involved in efficacy assessment*
Per Investigator request for patients with clinical failure		
02-012	FLU	Yes, not a protocol violation
39-001	FLU	Yes, not a protocol violation
71-001	FLU	Yes, not a protocol violation
Per Investigator request for patients with serious adverse events		
10-002	FLU	No, received only 1 dose of study drug
31-002	FLU	No, received only 1 dose of study drug

* Both study coordinators were removed from care of unblinded patients
Data from Section 16.2.3, Listing 1.5

Efficacy Results

Patient Disposition

Table 5.

Population	Anidulafungin	Fluconazole	Reasons for exclusion
ITT [a]	**131 (100%)**	**125 (100%)**	
Excluded	4	7	Did not have a positive baseline culture for *Candida*
Micro-ITT	**127 (96.9%)**	**118 (94.4%)**	
Excluded [b]	13	12	< 7 days of IV therapy and did not have a clinical response of failure
	7	10	Clinical response of indeterminate at end IV therapy
	3	2	≥ 3 days of prior antifungal therapy
	1	1	Violation of inclusion/ exclusion criteria w/o waiver
	0	2	Patient unblinded and not a clinical failure
Total Excluded	28	34	
Efficacy Evaluable @ end of IV therapy (Primary time point)	103 (78.6%)	91 (72.8%)	
Efficacy Evaluable at 6 Week Follow-up	79 (60.3)	69 (55.2)	See Table 6

a Denominator for all % calculations is N of ITT population in each treatment arm.
b. For all patients who had multiple reasons for exclusion, only the primary reason is listed

The primary efficacy population, the Micro-ITT population, included all patients who received at least 1 dose of study medication and who had a positive culture from a normally sterile site at baseline for *Candida* species. The Micro-ITT population was comprised of 245 patients; 127 (127/131, 96.9%) in the anidulafungin arm and 118 (118/125, 94.4%) in the fluconazole arm. The Efficacy Evaluable population at the end of IV therapy was a subset of the Micro-ITT population. The percentage of patients evaluable for efficacy was (103)78.6% for the anidulafungin arm compared with 91(72.8%) for the fluconazole arm. Twenty-eight patients in the anidulafungin arm and 34 in the fluconazole arm had protocol violations that led to exclusion from the efficacy evaluable population and the end of IV therapy, Table 5.

Table 6.PATIENT DISPOSITION AND REASONS FOR WITHDRAWAL DURING STUDY PERIOD		
Category	Anidulafungin	Fluconazole
Event	N (%)	N (%)
Intent-to-Treat	131	125
Total completed the study through 6 week follow-up	94 (71.8)	80 (64.0)
Total discontinued from study prior to 6 week follow-up	37 (28.2)	45 (36.0)
Reasons for discontinuation from study prior to 6 week follow-up		
Death	29 (22.1)[a]	38 (30.4)[b]
Patient lost to follow-up	8 (6.1)	7 (5.6)

NOTE: Denominator for all % calculations is N of ITT population in each treatment arm.

a: Patient 27-003 died after the 6-week follow-up period and is not included in this table.
b: Patient 40-014 was counted as completing the study through the 6-week follow-up period on the CRF termination page with a completion date of 11 Aug 2004, although the patient died on the same day and was counted in the number of deaths in the time to death (Section 11.4.8) and safety (Section 12.4) sections.

Table 7. PATIENT DISPOSITION AND REASONS FOR WITHDRAWAL FROM STUDY MEDICATION

Category Event **Intent-to-Treat**	Anidulafungin N (%) 131	Fluconazole N (%) 125
Total completed full course of study medication[a]	97 (74.0)	77 (61.6)
Total withdrawn from study medication[b]	34 (26.0)	48 (38.4)
Reasons for withdrawal from study medication		
Adverse Event	12 (9.2)	21 (16.8)
Patient Withdrew Consent	5 (3.8)	4 (3.2)
Patient Noncompliant	1 (0.8)	0
Worsening Clinical Status/Lack of Efficacy	11 (8.4)	16 (12.8)
Investigator Discretion	5 (3.8)	5 (4.0)
Vicuron's Request	0	1 (0.8)[c]
Patient Lost To Follow-Up	0	1 (0.8)

a: Total completed full course of study medication- refers to completion of IV and oral (if applicable) study medication. Note: *Not all patients went onto oral therapy following IV therapy.*
b: For each patient who withdrew from study medication, only 1 reason (the primary) for withdrawal is tabulated.
c: Patient 07-008 had study medication discontinued by Sponsor request due to a diagnosis of cryptococcal meningitis.
Source: Table modified from Section 14.1, Table 1.1.

Medical officer's comment

More patients in the fluconazole arm prematurely discontinued study medication for an adverse event: 21(16.8%) vs. 12 (9.2%) or for lack of efficacy 16 (12.8%) vs. 11(8.4%) compared with the anidulafungin arm, respectively. Withdrawals from study are discussed in more detail in the safety evaluation sections.

Protocol violations in the ITT population

Overall, the most common violation was an indeterminate clinical response at 6-week follow-up visit and indeterminate clinical response at 2-week follow-up visit for patients in both study arms. Slightly more patients in the fluconazole arm compared to anidulafungin arm, 28 (21.4 %) vs. 38 (30.4 %) respectively, had an indeterminate clinical response at the 2 week follow up time point, and at the 6 week follow-up i.e. 36 (27.5%) vs. 43 (34.4%), respectively.

TABLE 8. SUMMARY OF PROTOCOL VIOLATIONS AND DEVIATIONS (INTENT-TO-TREAT POPULATION)

Category	Anidulafungin (N=131)		Fluconazole (N=125)	
Event	n	(%) [a]	n	(%) [a]
Protocol Violations [b]				
Violation of inclusion/exclusion criteria and no waiver granted	1	(0.8)	2	(1.6)
< 7 days of IV therapy and did not have a clinical response of failure	14	(10.7)	16	(12.8)
> 24 h of concomitant systemically absorbed antifungals & not a failure	15	(11.5)	14	(11.2)
Absence of a positive baseline culture for *Candida* spp	4	(3.1)	7	(5.6)
Clinical response of indeterminate at Day 10	21	(16.0)	21	(16.8)
Clinical response of indeterminate at End of IV Therapy	18	(13.7)	26	(20.8)
Clinical response of indeterminate at End of Oral Therapy		0	5	(4.0)
Clinical response of indeterminate at 2 Week Follow-up Visit	28	(21.4)	38	(30.4)
Clinical response of indeterminate at 6 Week Follow-up Visit	36	(27.5)	43	(34.4)
Day 10 clinical assessment not done within Days 9 to 11	1	(0.8)		0
Patient unblinded and not a clinical failure		0	2	(1.6)
Patient received at least 3 days of prior antifungal medication and was not a clinical failure	4 (3.1)		3 (2.4)	
Protocol Deviations [b]				
Diagnosis Of Candidemia Or Other Forms Of Invasive Candidiasis	4	(3.1)	1	(0.8)
nt who received greater than 72 hours of prior systemic antifungal ...rapy	1	(0.8)	2	(1.6)
Bilirubin >5 times the upper limit of normal	1	(0.8)	4	(3.2)
Prosthetic devices at a suspected site of infection		0	2	(1.6)
Prosthetic heart valves or vascular grafts and positive blood cultures.	1	(0.8)	2	(1.6)

a: Denominator for % calculations is N of ITT
b: This table includes all protocol violations and deviations, whether or not they affect evaluability.
For patients with more than one violation and/or deviation, all violations and/or deviations were tabulated
Source: Data from Section 14.1, Table 1.3.1.

Baseline characteristics of the Micro-ITT population.

Demographics

Table 9. CHARACTERISTICS (MICRO-ITT POPULATION)

	Anidulafungin	Fluconazole
Gender, n (%)	N = 127	N = 118
Male	65 (51.2)	60 (50.8)
Female	62 (48.8)	58 (49.2)
Age, years	N = 127	N = 118
Mean (SD)	57 (17.1)	59.2 (16.5)
Median	59	57.5
Min - Max	16 - 89	24 - 91
Ethnic Origin, n (%)	N = 127	N = 118
White	92 (72.4)	87 (73.7)
Black/African American	23 (18.1)	25 (21.2)
Other	12 (9.4)	6 (5.1)
Weight, kg	N = 127	N = 117
Mean (SD)	76.4 (25.5)	76.3 (22.5)
Median	70.4	72.7
Min - Max	35 196.5	40.8 - 159
Apache II Score	N=127	N=118
< 20, n (%)	101 (79.5)	98 (83.1)
> 20, n (%)	26 (20.5)	20 (16.9)
Mean (SD)	15 (7.7)	14.4 (6.8)
Median	14	13
Min - Max	2 - 42	3 - 36
Absolute Neutrophil Count, cells/mm^3	N=127	N=118
> 500, n (%)	124 (97.6)	114 (96.6)
< 500, n (%)	3 (2.4)	4 (3.4)
Mean (SD) [a]	8110.6 (5589.6)	8197.4 (6440.5)
Median [a]	7342.8	6600
Min Max [a]	0 - 26800	0 - 33840

a: For one patient, only ANC category (>500, 500) was known, and therefore this patient was excluded from this summarization of ANC count.
Source: Data from Section 14.1, Table 1.4.1.

All demographic characteristics were well balanced between the two treatment arms.

Most patients were white >70%, ≤25% black patients and ≤12% of patients of other ethnic origins. Approximately 20% of anidulafungin-treated patients and 17% fluconazole-treated patients had Apache II scores > 20, indicative of a sick population often found in intensive care units.

Few neutropenic patients were enrolled in this study. Less than 4% of patients in both arms were neutropenic (ANC ≤500). Approximately 20% of anidulafungin-treated patients and 17% fluconazole-treated patients had Apache II scores > 20, indicative of a critically ill population.

Medical Officer's comments

The results of the study may not be applicable to neutropenic patients because of the small numbers of patients with neutropenia in the study.

Underlying disease and risk factors for invasive candidiasis

The study population was well balanced with regard to co morbid conditions and risk factors for invasive candidiasis. There was a 9% difference between the two arms for immunosuppressive therapy; 18 (14%) anidulafungin-treated patients versus 27 (23 %) fluconazole-treated patients received immunosuppression, (p=0.099 by Fisher's exact test). There were more diabetic patients in the anidulafungin arm, 34% versus 25%. Approximately ≤ 10 % of patients had hematopoeitic disorders. Approximately 5 % of patients had transplants, mostly solid organ transplants. Two patients in each arm had bone marrow transplants. In patients who were diagnosed with catheter related invasive candidiasis, catheter removal was more frequent in the anidulafungin arm, 95.2% versus 85.9%. There was no statistically significant difference between these baseline characteristics. See Dr. Dixon's statistical review for further detail.

Table 10. BASELINE CHARACTERISTICS: COMORBIDITIES AND RISK FACTORS (MICRO-ITT POPULATION)

Characteristic Detail	Anidulafungin N = 127 n (%)	Fluconazole N = 118 n (%)
Comorbid Diseases Assoc. with IC, n (%)		
Endocrine/Metabolic Disorders	68 (53.5)	57 (48.3)
Bacterial Sepsis	58 (45.7)	49 (41.5)
Recent Surgical History	50 (39.4)	55 (46.6)
Neoplastic Disease	28 (22.0)	27 (22.9)
Genitourinary	17 (13.4)	17 (14.4)
Hematopoietic Lymphatic	13 (10.2)	12 (10.2)
Rheumatologic	7 (5.5)	6 (5.1)
Transplantation	7 (5.5)	4 (3.4)[a]
Other	78 (61.4)	80 (67.8)
Invasive Candidiasis Risk Factors, n (%)		
Central venous catheter	99 (78.0)	92 (78.0)
Broad-spectrum antibiotics	88 (69.3)	82 (69.5)
Recent surgery	53 (41.7)	51 (43.2)
Recent hyperalimentation	31 (24.4)	31 (26.3)
Underlying malignant condition	28 (22.0)	25 (21.2)
Immunosuppressive therapy	18 (14.2)	27 (22.9)
Receipt of a transplant	6 (4.7)	4 (3.4)[a]

Other	16 (12.6)	14 (11.9)
Catheter and IC, n (%)		
Invasive Candidiasis related to IV Catheter [b]	N = 127	N = 118
Yes	63 (49.6)	64 (54.2)
If yes, catheter removed[b]	N = 63	N = 64
Yes	60 (95.2)	55 (85.9)

Abbreviation: IC = invasive candidiasis.
a: Five fluconazole-treated patients had transplant in their medical history. For 1 of these patients, the transplant was recorded under "other" rather than "transplant."
b: Per Investigator assessment
Note: The number (%) of patients with neoplastic diseases, recent surgery, and transplants (comorbid conditions) does not exactly match the number (%) of patients with malignancies, recent surgery, and receipt of a transplant (risk factors) because of Investigator discretion in determining what situations were considered risk factors.
Source : Data from Section 14.1, Table 1.4.1.

Prior Antifungal Therapy

In the ITT population, the two arms were well balanced with regard to use of prior antifungal drugs. A large number of patients (>70%) in both arms had fluconazole therapy in the 48hr period prior to the start of the study, Table 11. Patients who received more than 48 hours of systemic antifungal therapy were excluded from the study, as well as those who received prophylactic antifungals for more than 7 days within the 30 days prior to the study. Antifungal agents other than fluconazole were administered to small numbers of patients prior to the study. Six patients received Amphotericin B formulations prior to study in both groups. All patients were evaluable.

Table 11. ANTIFUNGAL MEDICATIONS TAKEN PRIOR TO STUDY THERAPY (ITT POPULATION)

Antifungals, systemic	Prior
Drug	n (%)
Anidulafungin (N=131)	
Any systemic antifungal	93 (71.0)
Fluconazole	82 (62.6)
Caspofungin	8 (6.1)
Amphotericin B, liposome	3 (2.3)
Amphotericin B	3 (2.3)
Voriconazole	1 (0.8)
Fluconazole (N=125)	
Any systemic antifungal	94 (75.2)
Fluconazole	86 (68.8)
Caspofungin	5 (4.0)
Amphotericin B, liposome	1 (0.8)
Amphotericin B	5 (4.0)
Voriconazole	0
Itraconazole	1 (0.8)

Flu cytosine 0
Source: Adapted from Data from Section 14.1, Tables 1.8.1 and 1.8.2.

Sites of infection

The majority > 90% of patients had candidemia. The remainder of patients had *Candida* infection in sterile sites such as peritoneal fluid/ abscess, pancreas, skin, kidney, eye and other sites.

Baseline Fungal Cultures
In the Micro-ITT population, 53 (41.7%) patients and 36 (30.5%) of patients in the anidulafungin group and the fluconazole group, respectively, had a single positive culture at baseline. Sixty-seven (52.8%) in the anidulafungin arm and 71 (60.2%) in the fluconazole arm had multiple positive blood cultures at baseline. The majority of patients, 93.7% and 89.8% had a single baseline pathogen in the anidulafungin and fluconazole arms, respectively. The percentages were similar in the two arms for the efficacy evaluable population at the end of IV therapy, and during follow-up.

Medical officer's comment
Screening blood cultures had to be taken within 24 hours of study entry. If screening blood cultures were taken within > 24 hours of study entry, blood cultures were repeated.

Baseline Microbiology

The distribution of baseline pathogens is similar between the two treatment arms.
The relative proportion of isolates is consistent with the Candida species found in hospitalized patients. In the Micro-ITT population, *C. albicans* accounted for 61.6% of the total number of Candida isolates, i.e. 63.8 % of isolates in the anidulafungin arm and 59.3% in the fluconazole arm. These percentages did not change significantly in the efficacy evaluable population at end of IV therapy. There was a higher number of *Candida glabrata* (fluconazole known to have higher MIC against this species) in the fluconazole Micro-ITT population and efficacy evaluable population at the end of IV therapy. *Candida parapsilosis* (anidulafungin known to have higher MIC against this species) was lower in the anidulafungin arm compared to the fluconazole arm. The number of isolates is small for these two species in each arm. It must be emphasized that a correlation between antifungal MIC and clinical outcome has not been established.

TABLE 12. PER-PATIENT DISTRIBUTION OF BASELINE PATHOGENS

Population	Anidulafungin	Fluconazole	Total
Species	N (%)	N (%)	N (%)
Micro-ITT	N=127	N=118	N=245
Candida albicans	81 (63.8)	70 (59.3)	151 (61.6)
Candida glabrata	20 (15.7)	30 (25.4)	50 (20.4)
Candida parapsilosis	13 (10.2)	16 (13.6)	29 (11.8)
Candida tropicalis	15 (11.8)	11 (9.3)	26 (10.6)
Candida lusitaniae	1 (0.8)	2 (1.7)	3 (1.2)
Candida guilliermondii	2 (1.6)	0	2 (0.8)
Candida krusei	2 (1.6)	0	2 (0.8)
Candida famata	0	1 (0.8)	1 (0.4)
Candida spp.	1 (0.8)	0	1 (0.4)
Efficacy Evaluable at End of IV Therapy	N=103	N=91	N=194
Candida albicans	66 (64.1)	56 (61.5)	122 (62.9)
Candida glabrata	16 (15.5)	22 (24.2)	38 (19.6)
Candida parapsilosis	11 (10.7)	15 (16.5)	26 (13.4)
Candida tropicalis	13 (12.6)	6 (6.6)	19 (9.8)
Candida lusitaniae	1 (1.0)	1 (1.1)	2 (1.0)
Candida guilliermondii	2 (1.9)	0	2 (1.0)
Candida famata	0	1 (1.1)	1 (0.5)
Candida spp.	1 (1.0)	0	1 (0.5)

N = number of patients in the respective population.
The sum of the percent column for each population may be >100% due to some patients presenting with more than one pathogen at baseline.
Source: Data from Section 14.1, Table 1.6.2.

Duration of therapy

Median exposure to IV study drug was 14 days for anidulafungin, and 11 days for fluconazole (in ITT population).

TABLE 39. EXTENT OF EXPOSURE (DAYS) TO IV STUDY DRUG (ITT POPULATION)

Number of Days of IV Study Drug Category or Statistic	Anidulafungin (N=131) n (%)	Fluconazole (N=125) n (%)
<3	5 (3.8)	8 (6.4)
3 to 10	35 (26.7)	46 (36.8)
11 to 14	46 (35.1)	36 (28.8)
15 to 21	36 (27.5)	24 (19.2)
22 to 28	6 (4.6)	9 (7.2)
29 to 35	3 (2.3)	1 (0.8)
36 to 42	0	1 (0.8)
>42	0	0
Mean	13.31	12.17
SD	6.19	6.51
Median	14.00	11.00
Minimum, Maximum	1,33	1,37

Exposure to IV study drug is calculated as Stop date Start date + 1 day.
Source: Data from Section 14.3, Table 3.1.1.

Primary Efficacy Analysis

Global responses (combined clinical responses and microbiological responses) were evaluated in the Micro-ITT and Efficacy Evaluable populations.

A. MICRO-ITT
There were 127patients in the anidulafungin arm, and 118 patients in the fluconazole arm in the Micro-ITT population.

Global Response at End of IV Therapy (primary time point)
In the anidulafungin arm, 96 patients (75.6%) had a global success versus 71 patients (60.2%) in the fluconazole arm. The between group difference in global success rate (anidulafungin minus fluconazole) was 15.42% (95% CI 3.85, 26.99). Anidulafungin was found to be superior to fluconazole in the primary analysis of efficacy. Global response at the end of IV therapy in the Micro-ITT population is presented in Table 13.

TABLE 13. GLOBAL RESPONSE AT END OF IV THERAPY (MICRO-ITT POPULATION)

Response Outcome	Anidulafungin (N = 127) n (%)	Fluconazole (N = 118) n (%)	Between-Group Difference[a]	(95% CI)
Success	96 (75.6)	71 (60.2)	15.42%	(3.85 , 26.99)
Failure	31 (24.4)	47 (39.8)		

a: Anidulafungin minus fluconazole.
Source: Data from Section 14.2, Table 2.1.1.

Medical officer's comment
There is a statistically significant difference between the global success rate for fluconazole and anidulafungin at the end of IV therapy. This was not explained by differential activity against various Candida species, see Table 20. Anidulafungin is a fungicidal agent against most Candida species and fluconazole, similar to other azoles, is a fungistatic antifungal drug- this may account for inferior efficacy.

Failures and Indeterminate responses
Indeterminate responses are considered to be failures. There were 31 and 47 failures in the anidulafungin and fluconazole arm, respectively, Table 14; eighteen and 23 patients respectively had indeterminate responses. The reasons why a patient could be assigned a global response of "indeterminate" at the end of IV therapy were:

- received less than 3 doses of study medication
- death not due to the *Candida* infection
- withdrawal from study medication for reasons other than failure defined as worsening clinical status/lack of efficacy.

All patients with an indeterminate global response at the end of IV therapy were discontinued from study medication. The two most common reasons for discontinuation in both treatment

arms was an adverse event, or death (not due to invasive candidiasis infection), Table 14, Table 15.

TABLE 14. GLOBAL RESPONSE AT END OF IV THERAPY (MICRO-ITT POPULATION)

Response Outcome	Anidulafungin (N = 127) N (%)	Fluconazole (N = 118) N (%)	Between-Group Difference	(95% CI)
Success	96 (75.6)	71 (60.2)	15.42%	(3.85 , 26.99)
Failure	31 (24.4)	47 (39.8)		
Observed Failure	13 (10.2)	24 (20.3)		
Indeterminate	18 (14.2)	23 (19.5)		

A: Anidulafungin minus fluconazole.
Source: Data from Section 14.2, Table 2.1.1.

TABLE 15. REASONS THAT PATIENTS HAD INDETERMINATE GLOBAL RESPONSES AT END OF IV THERAPY (MICRO-ITT POPULATION)

Reason [a]	Anidulafungin (N = 18)	Fluconazole (N = 23)
Withdrew from the study or study medication	18	23
Reason for withdrawal		
Adverse Event	11	16
Patient withdrew consent	4	4
Investigator Discretion	3	3
Death, not due to candidemia or invasive candidiasis	10	16
Received less than 3 doses of study medication	5	8

Data from Appendix 16.2.1, 16.2.7, Listing 1.1, Listing 1.2 , Listing 5.7
[a]*Note: Each patient is represented more than once in reasons for withdrawal.*

Global Response at Secondary Time Points in the Micro-ITT Population

At all secondary time points, anidulafungin was either superior to fluconazole or at least as effective as fluconazole for the proportion of patients with global success, Table 16 and Table 17.

Table 16. GLOBAL RESPONSE AT END OF IV THERAPY AND SECONDARY TIME POINTS IN THE MICRO-ITT POPULATION

Time point	**Anidulafungin**	**Fluconazole**	
Global Success (Micro-ITT)	N (%)	N (%)	Between-Group Difference (95%CI)
End of IV Therapy	96/127 (75.6)	71/118 (60.2)	15.42% (3.85 , 26.99)
End of Oral Therapy	31/33 (93.9)	28/33 (84.8)	9.09% (-5.60 , 23.79)
End of All Therapy	94/127 (74.0)	67/118 (56.8)	17.24% (5.49 , 28.99)
2-Week Follow-Up	82/127 (64.6)	58/118 (49.2)	15.41% (3.14 , 27.68)
6-Week Follow-Up	71/127 (55.9)	52/118 (44.1)	11.84% (-0.60 , 24.28)

TABLE 17. GLOBAL RESPONSE AT SECONDARY TIME POINTS (MICRO-ITT POPULATION)

Secondary Time point Response Outcome	Anidulafungin N (%)	Fluconazole N (%)	Between-Group Difference[a]	(95% CI)
End of Oral Therapy	N=33	N=33		
Success	31 (93.9)	28 (84.8)	9.09%	(-5.60 , 23.79)
Failure	2 (6.1)	5 (15.2)		
Observed Failure	2 (6.1)	1 (3.0)		
Indeterminate	0	4 (12.1)		
End of All Therapy	N=127	N=118		
Success	94 (74.0)	67 (56.8)	17.24%	(5.49 , 28.99)
Failure	33 (26.0)	51 (43.2)		
Observed Failure	15 (11.8)	24 (20.3)		
Indeterminate	18 (14.2)	27 (22.9)		
2-Week Follow-Up	N=127	N=118		
Success	82 (64.6)	58 (49.2)	15.41%	(3.14 , 27.68)
Failure	45 (35.4)	60 (50.8)		
Observed Failure	18 (14.2)	27 (22.9)		
Indeterminate	27 (21.3)	33(28.0)		
6-Week Follow-Up	N=127	N=118		
Success	71 (55.9)	52 (44.1)	11.84%	(-0.60 , 24.28)
Failure	56 (44.1)	66 (55.9)		
Observed Failure	21 (16.5)	28 (23.7)		
Indeterminate	35 (27.6)	38 (32.2)		

a: Anidulafungin minus fluconazole.
Source: Data from Section 14.2, Table 2.2.1 of submission

B. EFFICACY EVALUABLE POPULATION

There were 103 patients in the anidulafungin arm and 91 patients in the fluconazole arm in the efficacy evaluable population.

Global Response at End of IV Therapy
In the anidulafungin arm, 90 patients (87.4%) had a global success versus 68 patients (74.7%) in the fluconazole arm. The between group difference in global success rate (anidulafungin minus fluconazole) was 12.65% (95% CI 1.66, 23.65). Anidulafungin was found to be superior to fluconazole in this analysis of efficacy. Global response at the end of IV therapy in the efficacy evaluable population is presented in Table 18.

Medical officer's comment
In the efficacy evaluable populations, trends were consistent with those seen in the Micro-ITT population. At all time points, anidulafungin was either superior to fluconazole or at least as effective as fluconazole for the proportion of patients with global success.

Table 18. Global Response at all Time Points (Efficacy Evaluable Population)

TABLE 21. GLOBAL RESPONSE AT ALL TIMEPOINTS (EFFICACY EVALUABLE POPULATIONS)

Time point Response	Anidulafungin n (%)	Fluconazole n (%)	Between-Group Difference (%)[a]	(95% CI)
End of IV Therapy	N = 103	N = 91		
Success	90 (87.4)	68 (74.7)	12.65%	(1.66 , 23.65)
Failure	13 (12.6)	23 (25.3)		
End of Oral Therapy	N = 30	N = 27		
Success	28 (93.3)	26 (96.3)	-2.96%	(-14.38 , 8.46)
Failure	2 (6.7)	1 (3.7)		
End of All Therapy	N = 103	N = 87		
Success	88 (85.4)	64 (73.6)	11.87%	(0.37 , 23.37)
Failure	15 (14.6)	23 (26.4)		
2-Week Follow-Up	N = 88	N = 76		
Success	71 (80.7)	51 (67.1)	13.58%	(0.17 , 26.98)
Failure	17 (19.3)	25 (32.9)		
6-Week Follow-Up	N = 79	N = 69		
Success	59 (74.7)	43 (62.3)	12.36%	(-2.56 , 27.29)
Failure	20 (25.3)	26 (37.7)		

a: Anidulafungin minus fluconazole.
Data from Section 14.2, Table 2.3.1 and Table 2.4.

Antifungal medications taken during and after study therapy, (ITT population)
There were 35 (26.7%) patients in the anidulafungin treatment group and 42 (33.6%) in the fluconazole treatment group who received antifungal therapy after the study drug was completed. Two patients in the anidulafungin arm and two patients in the fluconazole arm received amphotericin B formulations during the study period. The majority of the patients had global, clinical, or microbiological failure at the end of study therapy. Some patients received antifungal therapy for prophylaxis or empiric therapy, Table 19.

Table 19: ANTIFUNGAL MEDICATIONS TAKEN DURING AND AFTER STUDY THERAPY (ITT POPULATION)

Antifungals, systemic	During	After
Drug	N (%)	N (%)
Anidulafungin (N=131)		
Any systemic antifungal	9 (6.9)	35 (26.7)
Fluconazole	3 (2.3)	23 (17.6)
Caspofungin	3 (2.3)	11 (8.4)
Amphotericin B, liposome	2 (1.5)	5 (3.8)
Amphotericin B	0	2 (1.5)
Voriconazole	1 (0.8)	1 (0.8)
Fluconazole (N=125)		
Any systemic antifungal	7 (5.6)	42 (33.6)
Fluconazole	1 (0.8)	23 (18.4)
Caspofungin	4 (3.2)	19 (15.2)
Amphotericin B, liposome	1 (0.8)	7 (5.6)
Amphotericin B	1 (0.8)	6 (4.8)
Voriconazole	0	2 (1.6)
Itraconazole	0	0
Flucytosine	0	1 (0.8)

Adapted from

Medical officer's comment
The numbers of patients who received antifungal therapy during or after the study period was balanced in both treatment groups.

Table 20. GLOBAL SUCCESS AT END OF IV THERAPY BY PATHOGEN (MICRO-ITT POPULATION)

	Anidulafungin	**Fluconazole**
Baseline Species	n/N (%)	n/N (%)
All species	92/119 (77.3)	65/106 (61.3)
Candida albicans	60/74 (81.1)	38/61 (62.3)
Non-*albicans* species	32/45 (71.1)	27/45 (60.0)
Candida glabrata	9/16 (56.3)	11/22 (50.0)
Candida tropicalis	13/14 (92.9)	4/8 (50.0)
Candida parapsilosis	7/11 (63.6)	10/12 (83.3)
Candida guilliermondii	2/2 (100.0)	--
Candida krusei	0/1 (0.0)	--
Candida lusitaniae	1/1 (100.0)	1/2 (50.0)
Candida famata	--	1/1 (100.0)

Note: N=Number of patients with a single baseline pathogen.
Source: Data from Section 14.2, Table 2.12.

In the Micro-ITT patients with a single baseline *Candida* species, there was a significant difference in global success between the anidulafungin and fluconazole arms by pathogen isolated. Anidulafungin- treated patients had more global success than fluconazole- treated patients for all species of *Candida* except *C. parapsilosis*.
The majority of patients had infection with *C. albicans*; the outcome for these patients was 60/74 (81.1%), and 38/61 (62.3%) in the anidulafungin and fluconazole arms, respectively. The number of non-albicans *Candida* isolates is small in this study. Patients with *C. parapsilosis* infection had a global success of 63.6% compared to 83.3% in the fluconazole arm. The difference in global success was also noticeable for *C. tropicalis*; 13/14 (92.9%) and 4/8 (50.0%) in the anidulafungin and fluconazole arms, respectively. All but one of the *C. tropicalis* isolates were documented as sensitive to fluconazole.

Minimum Inhibitory Concentrations
For baseline isolates from the Micro-ITT population, the median MIC50 and MIC90 of anidulafungin were, respectively, 0.008 and 0.5 mg/L. For fluconazole, the corresponding values were 0.25 and 8 mg/L. These MIC ranges are consistent with published literature. Please refer to Dr. Steele-Moore's microbiology review for more detailed commentary.

Medical Officer's comment
Higher MIC -2 results were observed for anidulafungin against C. parapsilosis, and fluconazole against C. glabrata, than for most other species tested- this is consistent with published literature. There were more global successes in the fluconazole-treated patients with C. parapsilosis infection and more global success in the anidulafungin- treated patients for C. glabrata. C. parapsilosis is known to have higher MIC compared to C. albicans and most other species of Candida when tested against echinocandins. It must be emphasized, however, that a correlation between MIC and clinical outcome has not been established.

Global Response by Source of *Candida* Infection

Candidemia

Given that approximately 90% of patients in each treatment group had candidemia only, results for these patients closely paralleled results for the overall population with global success observed for 88 (75.9%) patients in the anidulafungin arm and 63 (61.2%) patients in the fluconazole arm. The difference (anidulafungin minus fluconazole) between treatment groups in global success rate was 14.70% (95% CI: 2.48, 26.91). Anidulafungin was superior to fluconazole in this analysis.

Table 21.GLOBAL RESPONSES AT END OF IV THERAPY FOR PATIENTS WITH CANDIDEMIA [1], MICROBIOLOGICAL INTENT-TO-TREAT POPULATION

Subgroup: Candidemia = Yes

	Treatment Group			
	Anidulafungin (N=116)	Fluconazole (N=103)	Between-Group Difference (%)	95% Confidence
Response	N (%)	N (%)	Anidulafungin - Fluconazole	Interval
Global				
Success [2]	88 (75.9)	63 (61.2)	14.70	(2.48 , 26.91)
Failure	12 (10.3)	23 (22.3)		
Indeterminate	16 (13.8)	17 (16.5)		

Source: Table 2.1.5 in submission

[1] Patients with candidemia only at baseline.
[2] A global success represents a clinical success and a patient microbiological success. A 95% confidence interval is based on the difference in success rates.

Other Forms of Invasive Candidiasis

Results were similar for the few patients with other forms of invasive candidiasis. Among the small number of patients with documented infections at a normally sterile site other than blood (with or without concomitant positive blood cultures), 8 (72.7%) patients receiving anidulafungin and 8 (53.3%) patients receiving fluconazole had global success at the end of IV therapy.

Global Response in Subgroups of the Efficacy Evaluable Population

A number of subgroups were analyzed for outcome based on the presence or absence of IV catheters, and disease severity related to APACHE score and immunosuppressive therapy.

Global Response at End of IV Therapy by Catheter Removal Status

The numbers of IV catheter removals was well balanced between the two treatment arms. Therefore the global response was analyzed in patients who had catheters removed or left in place, and those who did not have an IV catheter. The global success rates were higher in the anidulafungin arm compared to the fluconazole arm.

Table 22.
Subgroup: Catheter Removal Status = Had catheter and it was removed

	Treatment Group			
	Anidulafungin (N=87)		Fluconazole (N=68)	Between-Group Difference (%)
Response	n	(%)	n (%)	Anidulafungin - Fluconazole
Global Success *	74 (85.1)		50 (73.5)	11.53
Failure	13 (14.9)		18 (26.5)	

Subgroup: Catheter Removal Status = Had catheter and it was NOT removed

	Treatment Group			
	Anidulafungin (N=3)		Fluconazole (N=4)	Between-Group Difference (%)
Response	n	(%)	n (%)	Anidulafungin - Fluconazole
Global Success *	3 (100.0)		3 (75.0)	25.00
Failure	0		1 (25.0)	

Subgroup: Catheter Removal Status = Did NOT have catheter

	Treatment Group			
	Anidulafungin (N=13)		Fluconazole (N=19)	Between-Group Difference (%)
Response	n	(%)	n (%)	Anidulafungin - Fluconazole
Global Success *	13 (100.0)		15 (78.9)	21.05
Failure	0	(0.0)	4 (21.1)	

Source: VER002-9 Study report, Section 14.2.1, tables 2.3.9

* clinical and microbiological success

Outcomes in Special Populations

Results were similar for the low numbers of patients with other forms of invasive candidiasis. Among patients with documented infections at a normally sterile site other than blood (with or without concomitant positive blood cultures), 8 (72.7%) patients receiving anidulafungin and 8 (53.3%) patients receiving fluconazole had global success at the end of IV therapy, Table 23.

TABLE 23. GLOBAL SUCCESS AT END OF IV THERAPY FOR OTHER FORMS OF INVASIVE CANDIDIASIS (MICRO-ITT POPULATION)

Baseline Site of Infection, n (%)	Anidulafungin N (%)	Fluconazole N (%)
Other Forms of Invasive Candidiasis	8/11 (72.7)	8/15 (53.3)
Peritoneal fluid and/or IA abscess	4/6 (66.7)	5/6 (83.3)
Pleural fluid	1/1 (100)	-
Pelvic abscess	-	1/2 (50.0)
Pancreas	-	0/3 (0.0)
Blood and peritoneal (and/or IA abscess)	2/2 (100)	0/2 (0.0)
Blood and pleural fluid	0/1 (0.0)	-
Blood and left thigh lesion biopsy	1/1 (100)	-
Blood and bile	-	1/1 (100)
Blood and renal	-	1/1 (100)

Abbreviation: IA = intra-abdominal.
Source: Adapted from Data from Appendix 16.2.6, Listing 4.3, Appendix 16.2.8, Listing 6.8

Sub Group Analysis based on Apache II Score

The APACHE (Acute Physiology, Age, and Chronic Health Evaluation) score is a severity of disease classification system. The APACHE system is designed to assess the severity of illness of patients in intensive care units (ICUs). APACHE II uses a point score based upon initial values of routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. An increasing score correlates with increased severity of disease. Anidulafungin had more global successes in the patients with APACHE II < 20. Results are similar to that in the global success rate at the end of IV therapy, the primary time point. The rates of global success were similar between the two arms in patients with APACHE II > 20, Table 24a, and Table 24b.

Table 24a
Global Responses At End of IV Therapy For Patients with APACHE II Score Subgroup
Microbiological Intent-To-Treat Population

Subgroup: Apache II Score = <= 20

	Treatment Group		
Response	Anidulafungin (N=101) n (%)	Fluconazole (N=98) n (%)	Between-Group Difference (%) Anidulafungin - Fluconazole
Global			
Success [1]	82 (81.2)	60 (61.2)	19.96
Failure	9 (8.9)	18 (18.4)	
Indeterminate	10 (9.9)	20 (20.4)	

Source : Data from section 14.2.1, Table 2.1.7

Table 24b
Global Responses At End of IV Therapy For Patients with APACHE II Score Subgroup
Microbiological Intent-To-Treat Population

Subgroup: Apache II Score = > 20

	Treatment Group		
Response	Anidulafungin (N=26) n (%)	Fluconazole (N=20) n (%)	Between-Group Difference (%) Anidulafungin - Fluconazole
Global			
Success [1]	14 (53.8)	11 (55.0)	-1.15
Failure	4 (15.4)	6 (30.0)	
Indeterminate	8 (30.8)	3 (15.0)	

Source: Data from section 14.2.1, Table 2.1.7

Outcomes in Patients on Immunosuppressive Therapy

Global success in patients with immunosuppressive therapy was similar in both arms, with slightly more global success in patients in the slightly more global success in the anidulafungin arm, Table 25.

Table 25. Global Response Patients who received Immunosuppressive Therapy
Micro ITT Population

Treatment Group	Global Response End-of IV Therapy	n (%)
ANIDULAFUNGIN	Success	12 (66.7%)
	Failure	3 (16.7%)
	Indeterminate	3 (16.7%)
FLUCONAZOLE	Success	16 (59.3%)
	Failure	4 (14.8%)
	Indeterminate	7 (25.9%)

Source: Data from section 14.2.1, Table 2.23

10.3 Conclusions Regarding Efficacy Data in Study VER002-9

Anidulafungin was superior to fluconazole for the treatment of invasive candidiasis/candidemia in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population. In all secondary efficacy analyses, anidulafungin was superior to, or at least as effective as, fluconazole, consistent with the primary efficacy analysis. Anidulafungin-treated patients had higher rates of global, clinical, and microbiological success at all time points on therapy and at the end of therapy. Candidemia was present in more than 90% of patients in both study arms. Approximately half of all patients had invasive candidiasis related to an IV catheter. Most patients had a single baseline pathogen; *C. albicans* and *C. glabrata* were the baseline pathogens most frequently isolated.

- Anidulafungin (96/127, 75.6%) was superior to fluconazole (71/118, 60.2%) for the treatment of invasive candidiasis/candidemia in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population.
- At the end of IV therapy, 6.3% of patients treated with anidulafungin had a documented persistent *Candida* infection compared with 14.4% of patients treated with fluconazole.
- In all secondary efficacy analyses anidulafungin was superior to (end of IV therapy, end of all therapy and 2-week FU time points), or at least as effective as (end of oral therapy

and 6-week FU time points), fluconazole which is consistent with the primary efficacy analysis.

- The results of the study may not be applicable to neutropenic patients due to the low numbers of patients with neutropenia in the study. Neutropenic patients accounted for 3 (2.4%), and 4 (3.4%) in the anidulafungin and fluconazole arms, respectively.

10.4 Safety Results

Safety Summary
In this study, no hepatic safety concerns emerged when compared to fluconazole. The safety data provided from patients with invasive candidiasis suggest that anidulafungin at a dose of 100 mg IV daily has a safety profile similar to and, in some instances, more favorable than that of fluconazole 400 mg IV daily.

- Adverse events rates were similar in the two treatment arms. AEs were reported by 130 (99.2%) patients in the anidulafungin arm and 122 (97.6%) patients in the fluconazole arm. The proportion of patients with related AEs was similar in the two treatment arms (approximately 25%). Fewer anidulafungin-treated patients (15, 11.5%) than fluconazole-treated patients (27, 21.6%) experienced an AE that led to discontinuation of study drug.
- Serious adverse events (SAEs) were reported by 49.6% of patients in the anidulafungin arm and 56.8% of patients in the fluconazole arm; however, SAEs were considered related to treatment for only 2 patients in each study arm. The three most common SAE in the anidulafungin arm were cardiac arrest, multiorgan failure and respiratory arrest, none of which were attributable to anidulafungin.
- There were 4 (3.1%) patients in the anidulafungin group and 7 (5.6%) patients in the fluconazole group who reported clinical AEs categorized under the hepatobiliary category. Only 4 of these events were severe in intensity and all 4 occurred in fluconazole-treated patients. One hepatic AE in anidulafungin-treated patient was considered possibly related to study drug.
  - Fewer anidulafungin-treated patients (15, 11.5%) than fluconazole-treated patients (27, 21.6%) experienced an AE that led to discontinuation of study drug.
  - No cases of hepatic failure, anaphylaxis, or QT prolongation occurred. The safety data show that anidulafungin at a dose of 100 mg daily has a safety profile similar to fluconazole 400 mg IV daily.

Deaths: Fewer anidulafungin-treated patients (30, 22.9%) than fluconazole-treated patients (39, 31.2%) died during and shortly after the study.

Exposure to Study Drug

A total of 89.3% and 84.8% of patients in the ITT population received anidulafungin and fluconazole, respectively for 1 to 3 weeks. Approximately, 62% and 48% of patients received anidulafungin and fluconazole respectively for 11 to 21 days. The mean length of exposure to anidulafungin and fluconazole was 13 days and 12.17, respectively.
Most patients (> 70%) completed IV therapy and were not switched to oral therapy with fluconazole. Similar percentages of patients in each study arm switched to oral therapy, 26.0% in the anidulafungin arm and 28.8 % in the fluconazole arm. The mean exposure to fluconazole was 15.7days for the anidulafungin treatment group and 14.7 for the fluconazole treatment group.

Extent of exposure Study VER002-9

TABLE 26. EXTENT OF EXPOSURE (DAYS) TO IV STUDY DRUG (ITT POPULATION)

Number of Days of IV Study Drug Category or Statistic	Anidulafungin (N=131) N (%)	Fluconazole (N=125) N (%)
<3	5 (3.8)	8 (6.4)
3 to 10	35 (26.7)	46 (36.8)
11 to 14	46 (35.1)	36 (28.8)
15 to 21	36 (27.5)	24 (19.2)
22 to 28	6 (4.6)	9 (7.2)
29 to 35	3 (2.3)	1 (0.8)
36 to 42	0	1 (0.8)
>42	0	0
Mean	13.31	12.17
SD	6.19	6.51
Median	14.00	11.00
Minimum, Maximum	1,33	1,37

Exposure to IV study drug is calculated as Stop date Start date + 1 day.
Source: Data from Section 14.3, Table 3.1.1.

10.5Adverse Events

The percentages of patients with ≥ 1 mild, moderate, or severe AE were similar for both treatment arms. Approximately 50% of patients in both arms had a severe adverse event. Approximately 25% of patients in both arms had an AE considered possibly or probably related to the study medication.

TABLE 27. OVERALL SUMMARY OF ADVERSE EVENTS (ITT POPULATION) VER002-9

	Anidulafungin (N=131)	Fluconazole (N=125)
Patients with:	N (%)	N (%)
≥ 1 AE	130 (99.2)	122 (97.6)
≥ 1 AE of mild severity	113 (86.3)	104 (83.2)
≥ 1 AE of moderate severity	106 (80.9)	98 (78.4)
≥ 1 AE of severe severity	65 (49.6)	68 (54.4)
≥ 1 AE related to study drug	32 (24.4)	33 (26.4)
≥ 1 AE leading to study drug discontinuation	15 (11.5)	27 (21.6)
≥ 1 related AE leading to study drug discontinuation	1 (0.8)	4 (3.2)
≥ 1 SAE	65 (49.6)	71 (56.8)
≥ 1 related SAE	2 (1.5)	2 (1.6)
Death	30 (22.9)[a]	39 (31.2)[b]

a: Includes 1 anidulafungin patient who died after the final (6-week follow-up) study visit.
b: Includes 2 patients in the ITT population who were not in the Micro-ITT population.
Note: A patient who experienced multiple events was counted once for Patients with at least one AE .
Source: Section 14.3, Table 3.5.

Withdrawals from Study

A total 9.2% of the anidulafungin patients and 16.8 % of the fluconazole patients withdrew for any adverse event. Approximately 6 % of patients in both arms were lost to follow up, Table 6 and Table 7.

Medical officer's comment

More patients withdrew from study in the fluconazole arm than in the anidulafungin arm, 45 (36%) versus 37(28%), respectively. Five patients who withdrew from study, (one patient in the anidulafungin arm and four of the patients in the fluconazole arm) did not receive study drug. The arms are not significantly different with regard to withdrawals from study.

Deaths

There were 68 deaths during the study, 29 of 131 (22%) anidulafungin-treated patients, and 39 of 125 (31%) fluconazole-treated patients. One anidulafungin treated patient died after the 6 week follow–up and was not included in withdrawals from study. Withdrawal from study due to death occurred in 29 (22.1%) in the anidulafungin arm and 38 (30.4%) in the fluconazole arm. In both the anidulafungin and fluconazole groups, cardiac arrest (2.9% anidulafungin, 5.6% fluconazole) was the most common adverse event resulting in death. Two of patients who died in the fluconazole arm never received a dose of study drug. There was no distinguishable pattern in the causes of death among anidulafungin-treated patients or between the anidulafungin and fluconazole treatment populations. Table 28 summarizes the cause of death for all individuals in both study arms.

Medical officer's comment

The case report forms for each of the 68 patients who died were reviewed. The clinical reviewer and the investigator concluded that the deaths in the study are unlikely to be related to anidulafungin or fluconazole.

TABLE 28. PATIENT DEATHS

Treatment Arm Patient ID	Sex	Age (years)	Primary Cause	Days on Study Medication	Elapsed time* (days)
Anidulafungin					
01-001	M	60	Renal failure	6	1
03-002	M	79	Respiratory failure	1	0
04-007	F	51	Worsening of cervical cancer	36	15
07-001	F	73	Metastatic pancreatic cancer	11	7
10-001	F	59	Cardiac/pulmonary arrest	26	11
10-004	M	76	Cardiac arrest	35	21
10-009	M	66	Cardiac arrest	17	3
12-010	F	57	Withdrawal of care secondary to pseudomembranous colitis and sepsis	13	4
12-014	M	60	Renal failure	18	9
12-018	F	49	Multisystem organ failure	10	1
17-004	F	77	Sepsis	10	3
18-001	F	71	Sepsis	15	4
18-005	F	67	Worsening pancreatic cancer	28	14
19-001	F	59	Cardiac failure	10	1
20-004	M	83	Anoxic brain injury secondary to respiratory failure/arrest	33	18
20-008	F	33	Multisystem organ failure	21	10
31-005	M	78	Cardiopulmonary arrest	14	0
32-003	M	56	Worsening of multisystem organ failure	22	1
33-004	M	78	Sepsis due to candidemia	2	1
38-003	F	61	Cardiogenic/septic shock	2	1
40-001	M	77	Bacteremia	41	16
40-004	M	77	Cardiac and respiratory arrest	24	8
40-017	F	24	Respiratory failure	36	17
41-004	F	46	Cardiac arrest	36	22
41-011	M	76	Respiratory arrest	12	1
42-002	M	21	Chronic lung disease resulting from cystic fibrosis	68	42
47-001	M	65	Multiorgan failure	26	1
52-004	F	65	Respiratory failure	67	39
82-001	F	40	Intracerebral hemorrhage	24	7
27-003**	F	51	Respiratory Distress	10	48
Fluconazole					
01-002	M	84	Aspiration	34	14

04-002	M	56	Worsening of terminal lung/brain cancer- respiratory failure secondary to brain metastases	7	0
04-005	M	24	GI hemorrhage	31	17
04-010	M	62	Respiratory failure leading to death may have been caused by bacteremia or candidemia	6	1
10-002	F	54	Cardiac arrest	2	1
10-005	F	83	Cardiac arrest	31	17
10-008	F	64	Septic shock	21	8
11-002	F	56	Multiple myeloma, renal failure, bilateral pulmonary emboli, respiratory arrest	3	1
12-001	F	27	Worsening multiorgan failure	37	19
12-008	M	75	Withdrawal of care secondary to multisystem organ failure	16	1
12-009	F	74	Complications of blunt trauma	55	39
12-011	M	41	Multisystem organ failure	11	3
17-002	M	79	Multisystem organ failure	5	1
18-003	F	68	Worsening cholangiocarcinoma	72	30
20-002	M	74	Cardiac arrest	13	5
24-001	F	50	Possible cardiac arrest or pulmonary embolism	17	1
24-004	M	49	Anoxic brain injury, secondary to asystole with subsequent respiratory arrest	12	1
24-009	M	52	Worsening renal failure, worsening hyperkalemia and bacterial sepsis	8	1
24-012	F	34	Septic shock and polymicrobial bacteremia	17	1
24-013	F	57	Septic shock with multiple organ failure	4	1
25-001	M	54	Polymicrobial sepsis, AIDS, hepatitis C	38	21
30-001	F	73	Lung cancer	23	1
31-002	F	52	Bradycardia	3	2
32-002	F	62	Cardiac arrest	3	1
33-002	M	71	Worsening renal failure due to progression of metastatic prostate cancer	7	0
37-002	M	50	Multiple myeloma	37	13
38-007	M	70	Renal failure	50	36
39-002	M	51	Cardiac arrest and do not resuscitate	35	29
40-006	F	80	Sepsis	11	5
40-012	F	76	Acute renal failure	31	9
40-014	M	69	Respiratory failure	49	41
41-021	M	77	Bradycardia	12	1
46-002	F	45	Multiorgan failure and pulmonary arrest	14	3
47-002	M	65	Respiratory failure	14	0
52-001	M	86	Acute renal failure	43	27

Patient deaths

continued-

Fluconazole					
56-002	M	64	Respiratory failure	7	2
67-001	F	60	Worsening sepsis	9	1
73-001	M	81	Cardiac arrest	14	1
75-001	M	72	Septic shock	71	38

* Number of days elapsed between end of study therapy and death.
Source: Data from Appendix 16.2.4, Listing 2.1; Appendix 16.2.5, Listing 5.1; Appendix 16.2.7, Listings 5.6 and 5.7.
Deaths considered related to study drug by investigator = 0

All-Cause Mortality

The all cause mortality was lower in the anidulafungin treated patients, Table 29. The autopsy rate was very low in both treatment arms; 4 (13.8%) and 3(7.7%) in the anidulafungin and fluconazole treatment groups, respectively. At the time of death, 65% and 59% of patients had negative cultures for *Candida.*

Table 29. All Cause Mortality, Intent-To-Treat-Population

	Treatment Group Anidulafungin (N=131) N (%)	Fluconazole (N=125) N (%)
What was patient status at last contact? [1]		
Alive	102 (77.9)	86 (68.8)
Dead	29 (22.1)	39 (31.2)
Was the death directly attributable to invasive candidiasis / candidemia?		
No	27 (93.1)	34 (87.2)
Yes	2 (6.9)	5 (12.8)
What was the culture status at time of death? [2]		
No Growth	19 (65.5)	23 (59.0)
Growth	2 (6.9)	7 (17.9)
Unknown	8 (27.6)	9 (23.1)
Was an autopsy performed? [2]		
No	25 (86.2)	36 (92.3)
Yes	4 (13.8)	3 (7.7)
At autopsy, was there histopathology or culture evidence of Candida? [2]		
No	4 (13.8)	3 (7.7)
Yes	0	0

Source: section 14.2.1, Table 2.17.1
[1] Percentages are based on the N in each treatment arm.
[2] Percentages are based on the patients who died in each treatment arm.

1. All Adverse events in the ITT population

Adverse events that occurred more frequently in the anidulafungin arm included hypokalemia, nausea, vomiting, insomnia, hypertension, dyspnea, increased white blood cell count, and thrombocythemia. Adverse events that occurred more frequently in the fluconazole arm included anemia, pneumonia, abdominal pain, hyperkalemia, increased hepatic enzyme levels, back pain, anxiety, cardiac arrest, renal insufficiency, pulmonary edema, thrombocytopenia, rash, increased AST, and septic shock.

TABLE 30. ADVERSE EVENTS EXPERIENCED BY ≥ 5% PATIENTS IN EITHER STUDY ARM, Study VER002-9 (ITT POPULATION)

	Anidulafungin (N = 131)	Fluconazole (N = 125)
Adverse Event	N (%)	N (%)
Hypokalaemia	33 (25.2)	24 (19.2)
Nausea	32 (24.4)	15 (12.0)
Diarrhoea	24 (18.3)	23 (18.4)
Bacteraemia	23 (17.6)	23 (18.4)
Pyrexia	23 (17.6)	23 (18.4)
Vomiting	23 (17.6)	12 (9.6)
Insomnia	20 (15.3)	12 (9.6)
Urinary tract infection	19 (14.5)	22 (17.6)
Hypotension	19 (14.5)	18 (14.4)
Alkaline phosphatase increased	15 (11.5)	14 (11.2)
Hypomagnesaemia	15 (11.5)	14 (11.2)
Hypertension	15 (11.5)	5 (4.0)
Dyspnoea	15 (11.5)	4 (3.2)
Edema peripheral	14 (10.7)	16 (12.8)
Pleural effusion	13 (9.9)	11 (8.8)
Deep vein thrombosis	13 (9.9)	9 (7.2)
Anaemia	**12 (9.2)**	**20 (16.0)**
Constipation	11 (8.4)	14 (11.2)
Headache	11 (8.4)	10 (8.0)
White blood cell count increased	11 (8.4)	3 (2.4)
Confusional state	10 (7.6)	10 (8.0)
Sepsis	9 (6.9)	11 (8.8)
Hypoglycemia	9 (6.9)	10 (8.0)
Cough	9 (6.9)	7 (5.6)
Pneumonia	**8 (6.1)**	**19 (15.2)**
Abdominal pain	**8 (6.1)**	**16 (12.8)**
Hyperkalaemia	**8 (6.1)**	**14 (11.2)**
Hyperglycemia	8 (6.1)	8 (6.4)
Depression	8 (6.1)	5 (4.0)
Dehydration	8 (6.1)	2 (1.6)
Respiratory distress	8 (6.1)	2 (1.6)
Thrombocythaemia	8 (6.1)	1 (0.8)
Hepatic enzyme increased	**7 (5.3)**	**14 (11.2)**
Back pain	7 (5.3)	13 (10.4)
Decubitus ulcer	7 (5.3)	10 (8.0)

Chest pain	7 (5.3)	6 (4.8)
Leukocytosis	7 (5.3)	6 (4.8)
Blood creatinine increased	7 (5.3)	1 (0.8)
Anxiety	6 (4.6)	13 (10.4)
Rigors	**6 (4.6)**	**11 (8.8)**
Agitation	6 (4.6)	7 (5.6)
ALT increased	6 (4.6)	7 (5.6)
Staphylococcal bacteremia	6 (4.6)	7 (5.6)
Cardiac arrest	5 (3.8)	11 (8.8)
Renal insufficiency	**5 (3.8)**	**11 (8.8)**
Renal failure acute	5 (3.8)	9 (7.2)
Hypothermia	5 (3.8)	8 (6.4)
Pulmonary edema	**4 (3.1)**	**13 (10.4)**
Thrombocytopenia	**4 (3.1)**	**13 (10.4)**
Rash	4 (3.1)	11 (8.8)
Abdominal distension	4 (3.1)	8 (6.4)
Bradycardia	3 (2.3)	7 (5.6)
Dizziness	3 (2.3)	7 (5.6)
AST increased	**2 (1.5)**	**9 (7.2)**
Septic shock	**1 (0.8)**	**10 (8.0)**
Metabolic acidosis	**1 (0.8)**	**7 (5.6)**

Source: Data from Section 14.3, Table 3.7.

Medical officer's comment

The anidulafungin treatment group had more GI symptoms such as nausea and vomiting compared to the fluconazole treatment group. Diarrhea was similar between the groups. Hepatic enzymes were elevated more often in the fluconazole arm. Metabolic acidosis, pulmonary edema, renal failure, renal insufficiency and pneumonia were more common in the fluconazole arm. Sepsis and bacteremia was balanced between the two arms but septic shock was more common in the fluconazole arm. Based on this table, the overall impression is that the fluconazole patients may have been a slightly sicker group of patients.

2. Adverse Events Related to Study Drugs

Most patients did not experience adverse events related to study medication. The two most common related AEs for anidulafungin were hypokalemia (3.1%) and diarrhea (3.1%). For fluconazole, the two most common related AEs were hepatic enzyme increased (7.2%) and blood alkaline phosphatase increased (4.0%). Table 31

Hepatic enzymes including alkaline phosphatase were elevated in more patients receiving fluconazole IV therapy alone. Patients received a median of 11 to 14 days of IV therapy with either fluconazole or anidulafungin, Table 32.

TABLE 31. RELATED ADVERSE EVENTS EXPERIENCED BY > 2 PATIENTS IN EITHER STUDY ARM (ITT POPULATION) VER002-9

Adverse Event	Anidulafungin (N = 131) n (%)	Fluconazole (N = 125) n (%)
Patients with at least one related AE	32 (24.4)	33 (26.4)
Total number of related AEs[a]	59 (4.7)	64 (4.8)
Hypokalaemia	4 (3.1)	3 (2.4)
Diarrhoea	4 (3.1)	2 (1.6)
ALT increased	3 (2.3)	4 (3.2)
Hepatic enzyme increased	2 (1.5)	9 (7.2)
Blood alk. phos. increased	2 (1.5)	5 (4.0)
Flushing	2 (1.5)	2 (1.6)
Blood bilirubin increased	2 (1.5)	1 (0.8)
Hypomagnesaemia	2 (1.5)	1 (0.8)
Electrocardiogram QT prolonged	2 (1.5)	0
Pruritus	2 (1.5)	0
AST increased	1 (0.8)	3 (2.4)
Deep vein thrombosis	1 (0.8)	3 (2.4)
Anaemia	0	2 (1.6)
Dizziness	0	2 (1.6)
Rigors	0	2 (1.6)

Note: If a patient had multiple occurrences of the same event, the event with the least complimentary relationship is presented and the patient was counted once for the event. Numerator and denominator are AEs/total AEs. Source: Data from Section 14.3, Table 3.10.

TABLE 32. RELATED ADVERSE EVENTS IN ≥ 2 PATIENTS IN EITHER STUDY ARM: ITT PATIENTS RECEIVING ONLY IV STUDY MEDICATION

Adverse Event	Anidulafungin (N = 97) n (%)	Fluconazole (N = 89) n (%)
Diarrhoea	4 (4.1)	0
Hepatic enzyme increased	2 (2.1)	7 (7.9)
Blood bilirubin increased	2 (2.1)	1 (1.1)
Hypokalaemia	2 (2.1)	0
Alanine aminotransferase increased	1 (1.0)	4 (4.5)
Blood alkaline phosphatase increased	1 (1.0)	3 (3.4)
Deep vein thrombosis	1 (1.0)	2 (2.2)
Flushing	1 (1.0)	2 (2.2)
Aspartate aminotransferase increased	0	3 (3.4)

Source: Data from Section 14.3, Table 3.20.

3. **Serious adverse events (SAEs)**

In the anidulafungin arm, 65(49.6%) had 89 SAEs compared with the fluconazole arm, in which 71(56.8%) had 111 SAEs. The three most common SAEs for patients treated with anidulafungin were cardiac arrest, multi-organ failure, and respiratory arrest. The three most common SAEs for patients treated with fluconazole were cardiac arrest, sepsis, and septic shock. SAEs with frequencies differing by at least 3% in the treatment arms were cardiac arrest, sepsis and septic shock, and acute renal failure; these SAEs were more frequent in the fluconazole arm.

TABLE 33. SERIOUS ADVERSE EVENTS IN ≥ 2 PATIENTS IN EITHER STUDY ARM: ITT PATIENTS VER002-9

Serious Adverse Event	Anidulafungin (N = 131) n (%)	Fluconazole (N = 125) n (%)
Cardiac arrest	5 (3.8)	11 (8.8)
Multi-organ failure	4 (3.1)	5 (4.0)
Respiratory arrest	4 (3.1)	2 (1.6)
Sepsis	3 (2.3)	8 (6.4)
Respiratory failure	3 (2.3)	6 (4.8)
Bacteraemia	3 (2.3)	4 (3.2)
Abdominal pain	3 (2.3)	1 (0.8)
Respiratory distress	3 (2.3)	0
Pulmonary embolism	2 (1.5)	3 (2.4)
Renal insufficiency	2 (1.5)	3 (2.4)
Cardio-respiratory arrest	2 (1.5)	1 (0.8)
Hypotension	2 (1.5)	1 (0.8)
Mental status changes	2 (1.5)	1 (0.8)
Atrial fibrillation	2 (1.5)	0
Dehydration	2 (1.5)	0

Intestinal obstruction	2 (1.5)	0
Septic shock	1 (0.8)	8 (6.4)
Deep vein thrombosis	1 (0.8)	3 (2.4)
Bacterial sepsis	1 (0.8)	2 (1.6)
Convulsion	1 (0.8)	2 (1.6)
Pneumonia	1 (0.8)	2 (1.6)
Renal failure acute	0	6 (4.8)
Hyperkalaemia	0	3 (2.4)
Anaemia	0	2 (1.6)
Bradycardia	0	2 (1.6)
Hepatic enzyme increased	0	2 (1.6)

Source: Data from Section 14.3, Table 3.14.

Related Serious Adverse Events

Four patients (two patients per arm) in the study were assessed to have serious adverse events related to study drug. All patients recovered from the events. A brief synopsis of each case history is presented. Most of the events occurred following one week of therapy. There was no anaphylaxis described in the study.

Table 34. RELATED SERIOUS ADVERSE EVENTS

Patient ID	Study Arm	Sex	Age	SAE	Start Day*
04-003	Anid	66	M	Atrial fibrillation	2
12-007	Anid	49	F	Convulsion/seizure	6 (+1)
07-010	Flu	61	F	Deep vein thrombosis	15 (+1)
33-007	Flu	81	F	Hepatic enzyme increased	19

*Relationship to start day of study medication
Source: Data from Appendix 16.2.7, Listing 5.5.
A brief description of each patient except (33-007) is provided below. Full SAE narratives for these patients are available in Section 14.3.2.2

Overview of Case Histories

Anidulafungin (1 case)

Patient ID # 04-003
Adverse Event: Atrial Fibrillation
Relationship to Study Drug: Possibly Related, (investigator assessment)
Study Drug: Anidulafungin
This is a 66 year old black male with a history of myocardial infarction, coronary artery bypass graft surgery x 4, hypertension, dyslipidemia, COPD, diabetes mellitus and renal insufficiency. He was admitted with congestive heart failure and hypotension and required mechanical ventilation. He developed MRSE bacteremia and subsequently developed candidemia. A serious adverse event of atrial fibrillation was reported on study day 2. Two hours after the second

infusion of anidulafungin the patient developed atrial fibrillation. The event resolved the same day. The patient continued to receive anidulafungin without the event reoccurring.

Medical officer's comment
This patient's underlying cardiac and pulmonary diseases are risk factors for atrial fibrillation; it is difficult to attribute any causality to study drug in this case.

Patient ID # 12-007
Adverse Event: Convulsion
Relationship to Study Drug: Possibly Related, (investigator assessment)
Study Drug: Anidulafungin
A 49 year old black female with a history of respiratory failure, ventilator associated pneumonia, pulmonary hypertension, acute renal failure on dialysis, and septic shock. She was admitted for hypoxia, respiratory distress and was placed on mechanical

ventilation. During her hospitalization, the patient developed ventilator- associated pneumonia, septic shock, multi-system dysfunction, pleural effusion, anemia, metabolic acidosis, connective tissue disorder, a sacral decubitus ulcer and candiduria and candidemia.
On study day 6 the patient developed questionable seizure activity, described as irregular, rhythmic jaw movements/mouth twitching, which occurred intermittently throughout the day. She remained responsive during these episodes. A brain CT scan and EEG were non-diagnostic, a neurology consultant questioned whether this event was a seizure. The patient was on imipenem/cilastatin for pseudomonas pneumonia during this time period. According to the investigator, the questionable seizure activity was "unlikely but possibly" related to study medication or possibly due to imipenem/cilastatin.
Concurrent to this event, the patient had a respiratory acidosis and eventually required intubation. One month later, the patient experienced a grand mal seizure that was considered unlikely related to study drug.

Medical officer's comment
In this case, it appears that the actual diagnosis of seizure was in question. The patient has multiple risk factors for the development of seizure activity such as concurrent hypoxia, and metabolic acidosis. I agree with the investigators assessment that imipenem/ cilastatin could have contributed to seizure activity in this case.

Fluconazole cases (2 cases)

Patient ID # 33-007
Adverse Event: Elevated Liver Enzymes
Relationship to Study Drug: Possibly Related, (investigator assessment)
Study Drug: Fluconazole
This 81-year-old Black female had a significant medical history of hypertension, congestive heart failure, gastrointestinal cancer, breast cancer/mastectomy, dementia, bilateral renal stent placement and suspected retroperitoneal fibrosis. She was hospitalized on [redacted] for impaired mental status. She was found to be in acute renal failure (creatinine 7.6 mg/dL,

BUN 119 mg/dL) and urosepsis. She was treated with ampicillin, gentamicin, cefazolin, and aggressive rehydration. A renal ultrasound performed on [redacted] revealed moderate right and mild left hydronephrosis. Blood and urine cultures on [redacted] and [redacted] were positive for Candida *albicans*. She received blinded study drug from 08June2004 to 25June2004. Her baseline alkaline phosphatase, ALT and AST values were within normal limits. However on the last day of study drug these enzyme values were found to be elevated: alkaline phosphatase (alk Phos) 489 U/L (baseline 73 U/L); ALT 227 U/L (baseline 12 U/L); and AST 425 U/L (baseline 17 U/L). Oral fluconazole 400 mg daily began on 26June2004. Since the last day of study drug the enzyme values have been progressively decreasing. Fluconazole was completed on 02July2004. On 06July2004 the ALT was 72 U/L, alk phos 210 and the AST 43 U/L. The investigator considered the event of enzyme elevations to be fully resolved. Concomitant medications during study drug administration were doxycycline, cefazolin, potassium chloride, sulfamethoxazole, metoprolol and diltiazem for hypertension, digoxin, Roxanol (morphine sulfate), and furosemide. According to the investigator, the event of increased hepatic enzymes was possibly related to the blinded study drug.

Medical officer's comment
The patient does not fulfill the criteria for Hy's rule. The fluconazole label carries a warning regarding hepatic toxicity. The patient was receiving ampicillin and cefazolin; both drugs can cause transient increases in SGOT, SGPT, and alkaline phosphatase levels. As with other cephalosporins, reports of hepatitis have been reported.

Patient ID # 07-010
Adverse Event: Deep Vein Thrombosis
Relationship to Study Drug: Possibly Related (investigator assessment)
Study Drug: Fluconazole
This is a 61 year old white female with a history of Crohn's disease and numerous other medical complications. She was hospitalized for complications of Crohn's disease, and *C. difficile* colitis. She developed candidemia and received 14 days of fluconazole therapy during her 22-day hospitalization. On Day +1, the patient was readmitted for pain and swelling in the lower left leg. An ultrasound revealed a thrombus extending to her iliac vein. She responded to medical therapy, completely recovered and was discharged from the hospital. According to the investigator the event was related to the study medication and to the recent prolonged hospital stay.

4. Discontinuations from Study Medication

Fifteen (15 [11.5%]) patients in the anidulafungin arm and 27 (21.6%) patients in the fluconazole arm had AEs leading to discontinuation of study medication. In general, the most common adverse events leading to study drug discontinuation were multi-organ failure and systemic *Candida* infection for the anidulafungin arm. The most common adverse events leading to discontinuation were cardiac arrest and septic shock for the fluconazole arm. The investigator considered the event related to anidulafungin for one patient, and related to fluconazole for four

patients. One patient, ID #03-004 discontinued anidulafungin due to moderately increased liver enzymes.

TABLE 10 RELATED ADVERSE EVENTS LEADING TO DISCONTINUATION OF STUDY DRUG

Treatment Patient ID	Sex	Age (years)	Event	Start Day*	Severity	Outcome
Anidulafungin						
03-004	M	63	Elevated liver enzymes	5 (+1)	Moderate	Recovered
Fluconazole						
04-016	F	77	Worsening of candidemia	3	Moderate	Recovered
23-004	F	45	Increased liver function tests	1	Moderate	Recovered
			Clogged hearing	2	Mild	Recovered
			Weakness	2	Mild	Recovered
			Chest tightness	2	Mild	Recovered
			Light Headed	2	Mild	Recovered
38-001	F	31	Rash	1	Severe	Ongoing
75-001	M	72	Elevated liver enzymes	33	Moderate	Ongoing

* Relative to start day of study medication with an additional "(+X)" to indicate days after stopping study medication.
Source: Data from Appendix 16.2.4, Listing 2.1, Appendix 16.2.7, Listing 5.4.

Anidulafungin (1 case)

Study patient, ID #03-004
This 63-year-old White male had a significant medical history of seizure disorder, poorly differentiated lymphoma (1986) that required resection of a lymphomatous abdominal mass and repeat radiation therapy. He also had a history of a lung abscess (1999), deep vein thrombosis (DVT) and pulmonary embolism [(PE) (2003)], hypothyroidism, and respiratory insufficiency that required tracheostomy in [ ] with reversal in [ ]
The patient was hospitalized on [ ] with pleural effusions and candidemia due to *C. albicans*. He was enrolled in VER002-9 for treatment of candidemia and received anidulafungin from [ ] when study medication was discontinued due to elevations in hepatic enzymes. The patient received cefepime, [ ]
(day (day 10) The patient was also receiving phenytoin, primidone for seizure prophylaxis, and warfarin because of the prior DVT and PE. He continued on caspofungin from [ ]ebruary to [ ], and fluconazole [ ], and then caspofungin from [ ]
He developed a DVT, and was subsequently discharged on [ ] The baseline AST =31 (9-45), and the highest AST =144 U/L on the 5th day of therapy. The investigator stopped the drug on day 4 of anidulafungin therapy. The liver enzymes began to trend down within 24 hours after stopping drug and had completely resolved off anidulafungin at day 16. Cefepime therapy was stopped on [ ], day 10.

Hepatic Chemistry, Patient ID #03-004

	[day 1)	(day3)	(day 5)	(day 6)	(day 16).	(day 42).]
AST *U/L*	31	48	144	61	25	26
ALT *U/L*	37	57	125	91	20	26
ALKP *U/L*	139	132	275	288	200	133
Total bilirubin *mg/dl*	0.3	0.1	0.4	0.3	0.2	0.2
Albumin g/dl	2.2	2.2	1.9	2.2	2.0	2.9

Medical officer's comment
There was a gradual increase and decrease in hepatic transaminases. Concurrent therapy with cefepime could have contributed to the elevation in hepatic transaminases. Similar to other cephalosporins, cefepime can cause hepatic dysfunction and cholestasis. It is reassuring that the elevation in liver enzymes was gradual and reversible.

Fluconazole (2 cases)

Two of the study patients, ID #23-004, and ID #75-001 discontinued fluconazole due to elevated liver enzymes. Patient ID #23-004 recovered, and patient ID # 75-001 later died due septic shock 38 days after the end of the study period.

Patient ID # 75-001
A 72-year-old White male was hospitalized [ ] for an aortic valve replacement. On the same day, he developed a cerebral infarction and was diagnosed with *Staphylococcus aureus* endocarditis. Post-surgical hospitalization was complicated by bacterial sepsis, septic shock, cortical adrenal insufficiency, acute tubular necrosis and renal failure that required hemodialysis. Other complications occurring during hospitalization included, splenic bleeding and splenectomy, a duodenal perforation requiring a partial duodenal resection, and episodes of atrial fibrillation. Blood cultures from an arterial line and cultures of peritoneal fluid were positive for *C. albicans* and *Enterococcus faecium*. He was then enrolled in VER002-9 for treatment of candidemia. He received intravenous fluconazole as study medication beginning [ ]. On [ ] the patient experienced a rectal bleed that resolved in one day. On [ ], he developed systemic inflammatory response syndrome that resolved following surgical evacuation of an abdominal hematoma and insertion of a drain.
Study medication was permanently discontinued on [ ] (day 33) for elevated hepatic enzymes. Screening values for ALT and AST (23 U/L and 42 U/L, respectively) rose to 45 U/L and 69 U/L, respectively, by Day 22 [ ] and increased further by [ ] (80 U/L and 79 U/L, respectively). The investigator considered the elevations to be ongoing at the end of the study (ALT: 54 U/L; AST: 51 U/L on [ ]. Concomitant medications included flucloxacillin, dobutamine, norepinephrine, midazolam, nadroparin, hydrocortisone, morphine, metoclopramide, human insulin, amiodarone, potassium chloride, pantoprazole, fentanyl, propofol, ciprofloxacin, heparin, ipratropium bromide and teicoplanin. According to the investigator, the elevation in hepatic enzymes was possibly related to the study

medication. The patient died 38 days after the end of the study due to septic shock, assessed to be unrelated to previous study drug therapy.

Patient ID # 75-001

	Screen, [ ]	, day 22 [ ]	[ ] 33	[ ] day 47
AST U/L	42	69	79	51
ALT U/L	23	45	80	54
ALKP U/L	Not available			

Patient ID # 23-004

A 45 year old Black female with a significant history of hypertension, obesity, cocaine abuse, congestive heart failure, hypercholesterolemia, Type 2 diabetes mellitus [ ] COPD, and respiratory failure [ ], developed MRSA pneumonia in [ ] and was hospitalized. She underwent thoracotomy open lung biopsy and lung lavage. In [ ] she was diagnosed with lung cancer and interstitial lung disease. In addition, she developed bacterial sepsis that was treated with vancomycin in combination with other antibiotics (metronidazole, cefepime, cefazolin and gatifloxacin).

She developed candidemia due to *C. albicans* on [ ] She received one dose of intravenous fluconazole and was then enrolled and randomized to fluconazole. She received IV fluconazole on [ ], when study medication was discontinued due to moderate elevations in liver enzymes and a series of other mild, non-serious adverse events (i.e. clogged hearing, weakness, chest tightness, and light-headedness).

ALT and AST were elevated at baseline on [ ] (55 and 78 U/L, respectively) and rose steadily beginning [ ] to maximum values of 153 U/L over subsequent days. The investigator indicated that the elevations resolved by [ ] Values obtained for ALT and AST on [ ] were 40 and 36 U/L, respectively. According to the investigator, the elevation in hepatic enzymes and all of the other events that led to discontinuation of study medication were possibly related to treatment.

Medical Officers Comment

The gradual increase and decrease in hepatic transaminases are similar between fluconazole and anidulafungin in these three patients.

Table 36: All adverse events classified as hepatobiliary disorders in Study VER002-9

Patient ID	Event	Intensity	Related to Study Drug?	Action Taken	Outcome
ANID					
24-003	Cholecystitis	Moderate	No	Cholecystotomy	Recovered
37-003	Cholestasis	Moderate	Possibly	None	Ongoing
42-002	Hepatomegaly	Moderate	No	None	Ongoing
52-004	Cholecystitis	Mild	No	Surgery	Recovered
52-004	Jaundice	Moderate	No	None	Recovered
FLU					
12-011	Cholecystitis	Moderate	No	Non-pharm Rx added	Ongoing
24-008	Portal vein thrombosis	Moderate	No	New Drug Rx	Ongoing
24-012	Hyperbilirubinemia	Moderate	Unlikely	None	Ongoing
24-012	Hyperbilirubinemia	Severe	Unlikely	None	Ongoing
25-003	Cholestasis	Severe/SAE	No	Non-pharm Tx added	Recovered
32-002	Hepatic infarction	Severe	No	None	Recovered
39-002	Hepatic pain	Moderate	No	None	Ongoing
41-010	Gangrenous cholecystitis	Severe/SAE	Unlikely	New or prolonged hospitalization	Recovered

Data Source: VER002-9 CSR, Table 47.

10.6 Hepatobiliary Adverse Events

(See also Hepatic Safety Review)

1. All Hepatic Adverse Events Reported

There were more hepatobiliary events in the fluconazole arm compared to the anidulafungin arm. A total of five anidulafungin treated patients and eight fluconazole treated patients had a hepatobiliary adverse event, Table. 36. Only one hepatic adverse event was considered possibly related to study drug. One patient in the anidulafungin arm (ID #37-003), developed cholestasis on Study Day 9. This case is described in further detail.

Patient ID # 37-003

Adverse Event: Cholestasis
Relationship to Study Drug: Possibly Related
Study Drug: Anidulafungin

Patient 37-003 was a 53-year old white female with acute myelogenous leukemia, immunostimulant therapy, and disseminated candidiasis. The patient had undergone two rounds of inductive chemotherapy and one round of consolidation chemotherapy in the months preceding admission to the study. She received her first dose of anidulafungin on 18-Aug-2004. On Day 9 of therapy the patient was diagnosed with cholestasis that was considered as possibly related to study drug by the investigator. The patient completed the study. The cholestasis was ongoing at the time of the 6-week follow-up visit, 41 days after the last dose of study drug. Significant concomitant medications the patient received along with the study drug were: valsartan, estradiol, ciprofloxacin, acyclovir, omeprazole, filgrastim, phytomenadione, morphine, ceftriaxone sodium, diphenhydramine, piperacillin/tazobactam, lorazepam, diazepam, lidocaine, pethidine, vancomycin, paracetamol, and pamidronate sodium. Hepatobiliary

parameters were as follows:

Hepatic Chemistry

	Study Day*	ALKP (IU/L)	AST (IU/L)	ALT (IU/L)	T. Bilirubin (mg/dL)
Normal Range		**0-120**	**10-32**	**0-30**	**0.3-1.8**
Screening	-1	ND	ND	ND	1.0
Screening	1	59	15	15	ND
Day 3	3	65	11	11	0.9
On Therapy	7	227 H CS	19	14	0.7
On Therapy	9	298 H CS	24	31 H	0.7
On Therapy	14	330 H CS	48 H	45 H	0.5
On Therapy	20	324 H CS	21	22	0.6
End-of-Therapy	28	287 H CS	12	7	0.5
2 Wk Follow-up	42 (+14)	412 H CS	21	20	0.6
6 Wk Follow-up	69 (+41)	360 H CS	38 H	13	0.4

Note: Abnormal values are flagged Low (L) or High (H), as appropriate, based on the normal range, and Clinically Significant (CS) if so designated by the investigator on the CRF.
ND = Not done.
* (-x) = number of days prior to the first dose of study drug; (x) = number of days since the first dose of study drug, i.e., since Day 1; (+x) = number of days after the last dose of study drug.
Data Source: VER002-9 CSR, Section 12.3.5.3.

Medical officer's comment
The elevated alkaline phosphatase is possibly related to the study drug, however a common abnormal finding in patients with chronic disseminated candidiasis is an increase in alkaline phosphatase. The level of alkaline phosphatase in some cases may exceed 10 - fold normal values. One could speculate that the patients underlying disseminated candidiasis may have been the cause of the abnormal alkaline phosphatase or at least contributing to the elevation in hepatic enzymes that was observed. (Masood 2004, Thaler 1988, Haron 1987, Talbot 1988).

2. Special Analysis Based On Hepatic Chemistry Parameters

To address the FDA request for additional hepatic safety data the sponsor submitted a hepatologist's ([redacted]) expert report covering eight studies. The findings in the report for this study of invasive candidiasis, VER002-9 are summarized.
To analyze the data, the hepatologist requested the following data in the following order:
1) Liver chemistry data from all clinical subjects who at any time experienced elevations ≥ 2 fold in any of the standard liver chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or bilirubin. These data were presented by graphing the serial value (expressed as log ULN on the y axis) versus time in study on the x-axis. *(This method of data presentation was first proposed by the FDA).*

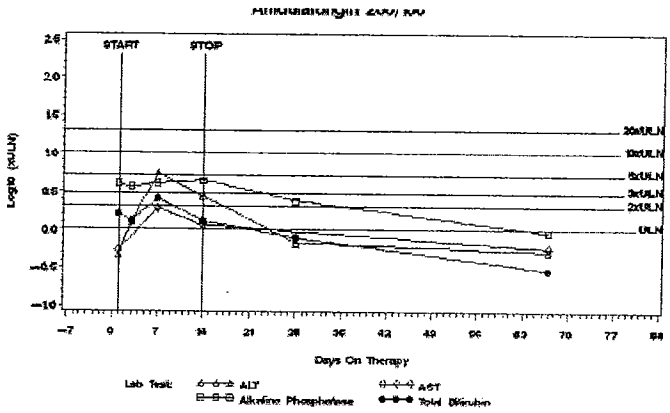
2) Dr. [ ] then examined each subject graph and selected for further study any subject that fit the following conservative Hy's Rule definition:
ALT rise to > 2 X ULN, and concomitant or up to one month delayed rise in bilirubin > 1.5 X ULN.

There were more Hy's rule cases in the fluconazole arm. The hepatologist found one case in the anidulafungin arm and six cases in the fluconazole arm in the invasive candidiasis study(VER002-9). Case summaries for these patients are taken directly from the hepatologist's expert report.

Anidulafungin (1 case)

Patient ID #41-006:
This is a 46 year-old white male with a history of lymphoma, recent renal failure/insufficiency, node dissection, and splenectomy. At screening he
presented with candidemia. He received study drug from 17-Oct-2003 to 30-Oct-2003.
Prior and concomitant medications included ciprofloxacin, cefazolin sodium, vancomycin, cyclophosphamide, vinblastine, dexamethasone, and procarbazine.
He experienced a 5-fold increase in serum ALT and a 1.6-fold increase in serum bilirubin 7 days into treatment with anidulafungin. Serum alkaline phosphatase was elevated throughout treatment, but did not show much rise during treatment However, the bilirubin returned to normal despite continued treatment with anidulafungin, which is not consistent with severe drug induced liver injury. AST and ALT trended down between day 7 and Day 14 despite continued therapy with anidulafungin. The hepatologist concluded that this case was unrelated to anidulafungin.

Patient # 41-006	[					]	
Hepatic Parameter	Day 1	Day 3	Day 7	Day 14	Day 28	Day 67	Upper Limit Normal Range
Alk Phos	478	433	484	523	290	110	120 U/L
ALT	19	51 H	221	110	27	21	40 U/L
AST	19	ND	67	40	ND	20	35 U/L
Total Bilirubin	1.6	1.3	2.6	1.3	0.8	0.3	1 mg/dL



Fluconazole (6 cases)
Five cases fulfilled the criteria for Hy's rule. Two cases were characterized as ischemic liver injury. Definitive etiologies were not given for the other two cases but they were thought to be unrelated to fluconazole. The two of these cases that were possibly related to fluconazole are summarized first.

1. Patient (ID #11-004): This is a 24 year old man who experienced 3-fold increases in both serum ALT and bilirubin ten days after termination of fluconazole therapy.
Alkaline phosphatase was only elevated 1.5 fold at this time. The investigator considered this event possibly related to fluconazole.

2. Patient ID#18-010: This is a 74 year old man who experienced a 2.5 fold increase in ALT and a 2-fold increase in serum bilirubin at the end of two weeks of
treatment with fluconazole. This event was thought by the investigator to be possibly related to fluconazole.

3. Patient ID #32-002: This is a 62 year old woman who experienced a sudden and greater than 40-fold elevation in serum ALT and a > 5 fold elevation in bilirubin However, the patient experienced a cardiac arrest and the investigator felt the liver injury was due to **ischemic hepatitis**, which seems very likely.

4.Patient ID #04-009 is a 26 year old woman who also experienced a sudden elevation of > 20 fold elevation in serum ALT and a 2-fold elevation in serum bilirubin in the setting of a cardiac arrest. This **is a Hy's Rule case,** but it seems likely that the liver injury was **ischemic** in nature. This case also has biochemical similarities to the anidulafungin case 13-008 in the VER002-4 trial. Dr. [ ] noted that this case was biochemically very similar to the index anidulafungin case ID #13-008 in the VER002-4 trial. *Note: Patient #13-008 died during the esophageal candidiasis study, VER-004.*

Please refer to page 116 of this document and the original review of NDA 21-632 for further detail on this case.

4. Patient ID #07-003: This is a 49 year old man who experienced a 4- and 2-fold increase in serum ALT and bilirubin, respectively. However, the serum alkaline phosphatase also rose, so this is not a Hy's Rule case.

5. Patient ID #20-010: This is a 62 year old man who experienced a 3-fold increase in serum bilirubin without a corresponding serum ALT recorded. However, serum AST rose > 4 fold so this case is included as a possible Hy's Rule case. This event was felt to be unrelated to fluconazole by the investigator but no other cause was assigned.

10.7 Clinical Laboratory Data

General Safety - Serum Chemistry

There were no obvious differences in changes in creatinine, BUN and potassium levels between the two treatment arms, Table 37.

TABLE 37. NUMBER (%) PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHEMISTRY VALUES THAT WERE ALSO POTENTIALLY CLINICALLY SIGNIFICANT CHANGES FROM BASELINE, VER002-9

Parameter	Day 3	On Therapy[a]	End of IV Therapy	End of Oral Therapy	2 Week Follow-up	6 Week Follow-up
Anidulafungin						
Creatinine	N=123	N=104	N=114	N=30	N=89	N=71
High, inc(n,%)	1	2	2	0	0	0
BUN [a]	N=117	N=98	N=108	N=24	N=78	N=65
High, Increase (n,%)	0	1 (1.0)	1 (0.9)	0	0	1 (1.5)
Potassium	N= 123	N= 104	N= 118	N= 30	N= 90	N= 70
High, Increase (n,%)	0	1(1.0)	0	0	0	0
Low, Increase (n,%)	5(4.1)	5(4.8)	2(1.7)	0	1(1.1)	0
Fluconazole						
Creatinine	N=114	N=85	N=108	N=23	N= 74	N=56
High, inc(n,%)	1(0.9)	2 (2.4)	1(0.9)	0	1(1.4)	1(1.8)
BUN [a]	N=113	N=83	N=106	N=24	N=74	N=55
High, Increase (n,%)	0	2 (2.4)	2 (1.9)	0	1 (1.4)	0
Potassium	N=116	N=86	N=108	N= 24	N= 74	N= 56
High, Increase (n,%)	0	0	0	1 (4.2)	2 (2.7)	0
Low, Increase (n,%)	2 (1.7)	3 (3.5)	2 (1.9)	0	2 (2.7)	0

a: If BUN was not available then urea value was used.
Note: N is the number of patients included in the analysis for the specified parameter at the specified visit. Percentages are based on the number of patients in the ITT population with a baseline value and a post-baseline value for the specified parameter at the specified vis Post baseline potentially clinically significant changes still within normal range are not included.

Source: Data from Section 14.3, Table3.27.

3. Significant Hepatic Chemistry Abnormalities

Hepatic Chemistry

A total of 20 anidulafungin patients and 27 fluconazole patients who had an ALT > X3ULN, an AST > X3 ULN, and/or an ALT > X3 ULN plus a total bilirubin >1.5 ULN.
No anidulafungin-treated patient, at any time during the study, had ALT > 20 x ULN or an AST > 10 x ULN.

TABLE 38. NUMBER (%) OF PATIENTS WITH SPECIFIED ABNORMALITIES IN HEPATIC PARAMETERS DURING THE STUDY, VER002-9

Treatment Group Parameter Criterion	Baseline	Day 3	On Therapy*	End of IV Therapy	End of Oral Therapy	2-Week Follow-up	6-Week Follow-up
ANIDULAFUNGIN ARM							
Patients with ALT >3 x ULN + Total Bilirubin >1 x ULN	N=122 1 (0.8)	N=115 2 (1.7)	N=90 2 (2.2)	N=84 0	N=25 0	N=70 0	N=58 0
Patients with ALT >3-5xULN	N=128 3 (2.3)	N=116 3 (2.6)	N=93 2 (2.2)	N=87 1 (1.1)	N=25 1 (4.0)	N=71 2 (2.8)	N=61 2 (3.3)
ALT >5-10xULN	2 (1.6)	1 (0.9)	1 (1.1)	0	0	1 (1.4)	0
ALT >10-20xULN	0	0	0	0	0	0	1 (1.6)
Patients with AST >3-5xULN	N=127 4 (3.1)	N=115 1 (0.9)	N=91 2 (2.2)	N=88 1 (1.1)	N=25 2 (8.0)	N=70 2 (2.9)	N=61 1 (1.6)
AST >5-10xULN	2 (1.6)	1 (0.9)	0	0	0	0	1 (1.6)
FLUCONAZOLE ARM							
Patients with ALT >3 x ULN + Total Bilirubin >1 x ULN	N=117 3 (2.6)	N=102 2 (2.0)	N=82 0	N=88 2 (2.3)	N=23 0	N=62 0	N=50 0
Patients with ALT >3-5xULN	N=120 8 (6.7)	N=104 5 (4.8)	N=84 3 (3.6)	N=88 4 (4.5)	N=23 0	N=64 0	N=51 0
ALT >5-10xULN	3 (2.5)	0	2 (2.4)	0	0	1 (1.6)	0
ALT >10-20xULN	0	1 (1.0)	0	0	0	0	0
ALT >20xULN	0	1 (1.0)	0	1 (1.1)	0	0	0
Patients with AST >3-5xULN	N=120 7 (5.8)	N=105 4 (3.8)	N=83 4 (4.8)	N=90 4 (4.4)	N=23 0	N=65 0	N=50 0
AST >5-10xULN	2 (1.7)	2 (1.9)	0	2 (2.2)	0	0	0
AST >10-20xULN	0	1 (1.0)	0	0	0	0	0
AST >20xULN	0	1 (1.0)	0	1 (1.1)	0	0	0

* "On Therapy" includes patients with a value after Day 3 but before End of IV Therapy.
Note: Percentages are based on the number of patients in the ITT population who have appropriate laboratory values at the specified visit. N is the number of patients in the analyses for the specified parameters at the specified visit.
Source: Data from Section 14.3, Table 3.28. Table 58

Hepatobiliary Parameters

This table summarizes shifts from baseline in AST, ALT and Alkaline phosphatase for the two treatment arms. The majority (>96%) of patients in both arms had AST and ALT levels ≤ X3 normal at baseline. There were slightly more patients with abnormal baseline LFTs in the fluconazole arm compared to the anidulafungin arm, 96.1% versus 99.1%, respectively. There were more patients in the fluconazole arm with larger transitions in AST (X 3-5 ULN, and X 5-10 ULN), and ALT levels (X 3-5 ULN, and X 5-10 ULN).

TABLE 39. SUMMARY OF TRANSITIONS IN HEPATOBILIARY PARAMETERS FROM BASELINE AT ANY STUDY VISIT (ITT POPULATION)

	Parameter Range at Any Post-Baseline Study Visit							
Parameter	**Anidulafungin Arm**				**Fluconazole Arm**			
Baseline Category	≤ 3xULN	>3-5xULN	>5-10xULN	>10xULN	□ 3xULN	>3-5xULN	>5-10xULN	>10xULN
ALT	N=112	N=7	N=3	N=1	N=103	N=10	N=1	N=3
<=3xULN	111 (99.1)	5 (71.4)	3 (100.0)	0	99 (96.1)	5 (50.0)	0	2 (66.7)
>3-5xULN	1 (0.9)	1 (14.3)	0	1 (100.0)	3 (2.9)	3 (30.0)	1 (100.0)	1 (33.3)
>5-10xULN	0	1 (14.3)	0	0	1 (1.0)	2 (20.0)	0	0
AST	N=112	N=8	N=2	N=0	N=100	N=10	N=5	N=3
<=3xULN	109 (97.3)	7 (87.5)	1 (50.0)	0	98 (98.0)	6 (60.0)	3 (60.0)	2 (66.7)
>3-5xULN	2 (1.8)	1 (12.5)	1 (50.0)	0	1 (1.0)	3 (30.0)	2 (40.0)	1 (33.3)
>5-10xULN	1 (0.9)	0	0	0	1 (1.0)	1 (10.0)	0	0
Alkaline Phosphatase	N=99	N=15	N=6	N=2	N=97	N=8	N=10	N=1
<=3xULN	98 (99.0)	11 (73.3)	4 (66.7)	1 (50.0)	97 (100.0)	5 (62.5)	8 (80.0)	0
>3-5xULN	1 (1.0)	4 (26.7)	0	0	0	2 (25.0)	2 (20.0)	0
>5-10xULN	0	0	2 (33.3)	1 (50.0)	0	1 (12.5)	0	0
>10xULN	0	0	0	0	0	0	0	1 (100.0)

Note: "N" is the number of patients with a value for baseline and at least one on-treatment value (irrespective of study visit) for the specified parameter. All percentages are based on the presented "N" values.
Data from Section 14.3, Table 3.29. Table 59

VITAL SIGNS

There were no obvious differences in vital signs between the two treatment groups.

10.8 Cardiac Safety, QT prolongation

In the clinical safety database, there were 4 patients with an AE of QT prolongation. Three of the 4 patients received anidulafungin (Patients 02-008, 04-014 and 33-008) and the fourth patient received fluconazole (Patient 30-001). Centralized ECG reading by an independent expert cardiologist did not confirm any QT abnormalities for the 3 patients treated with anidulafungin. Patient ID #02-008 was a 59 year-old female with bacterial sepsis, diabetes mellitus, stroke and peritoneal dialysis for chronic renal failure. Baseline ECG was reported as abnormal. Patient ID #04-014 was a 63-year-old female who was ventilator dependent upon enrollment into the study following a cardiac arrest. Past medical history included marked hypertension. On

Study Day 3, QT prolongation was reported as possibly related to blinded study medication. This patient was on numerous concomitant medications including levofloxacin, which can cause QT abnormalities.
Patient 33-008 was a 57-year-old female who had bacterial sepsis, renal failure, and an Apache II score of 18 at baseline. Past medical history included coronary artery disease, angioplasty with stents and CABG. Anidulafungin was administered for 14 days. On Study Day 3, mild QT prolongation was reported as unlikely to be related to study drug.

Standard 12-lead EKGs were recorded for 245 patients. EKGs were done at screening and on day 3 of the study. Five patients in the fluconazole arm had a protocol violation, i.e. no EKG pre-therapy. Twenty-six patients (13 patients in each arm) did not have an EKG on therapy. Paired EKGs were recorded for 214 patients. Paired EKGs with pre and on-therapy QT measurements were done for 202 patients. A cardiology expert analysis of these EKGs found that exposure to anidulafungin fluconazole had a slight effect on heart rate (-5 and -3msec respectively). These drugs did not elicit any effect on atrioventricular conduction (PR interval) and on intraventricular conduction (QRS interval). The effect on QTcF (Fredericia correction) was close to 0.0 msec for anidulafungin, and was 6.1msec for fluconazole for the 202 patients.
In the full data set, 2 patients in the anidulafungin arm had a QTC over 500msec (i.e. 515 and 516 msec, respectively) and they both had abnormal baseline QT intervals (491, and 484msec, respectively. There was no significant increase in QT interval after drug exposure. Related clinical adverse events of QT prolongation were not confirmed by a cardiology expert.
In summary, cardiology experts found no clinically significant electrophysiological effect on EKG morphology by anidulafungin.

Review of Specific Organ Systems

Renal adverse events

Renal SAEs were experienced by 2.9% of patients in the anidulafungin group and 7.2% of patients in the fluconazole group. None of these renal SAEs were considered treatment-related.

Anaphylaxis

Anaphylaxis
There were no cases of anaphylaxis in this integrated analysis of safety or in the entire clinical program for anidulafungin.
Medical officer's comment
Though there were no reports of anaphylaxis in the anidulafungin database, an anaphylactic reaction may possibly occur with more widespread use.
Anaphylaxis has been reported for the other approved echinocandins, caspofungin and micafungin. The AERS database was searched for reports of anaphylaxis or anaphylactic shock for caspofungin and micafungin; 6 and 3 reports were found for caspofungin and micafungin, respectively. The reports for micafungin were from Japan. In the database, a total of 609 and 65 adverse event reports of any type were found for caspofungin and micafungin, respectively.

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Neurological Adverse Events

Convulsions were reported by 2.5% of anidulafungin-treated patients and 1.6% of fluconazole-treated patients. In one case, the investigator reported that the convulsion maybe possibly related to anidulafungin. The case is described below.

Patient 12-007 (Candidemia: *C. glabrata*)

A 49 year old black female with a history of respiratory failure, ventilator associated pneumonia, pulmonary hypertension, acute renal failure on dialysis, and septic shock. On study day 6 the patient developed questionable seizure activity described as irregular, rhythmic jaw movements/mouth twitching, which occurred intermittently throughout the day. She remained responsive during these episodes. A brain CT scan and EEG were non-diagnostic, a neurology consultant questioned whether this event was a seizure. The event occurred at 18 hrs after the last dose of anidulafungin.

The patient was started on imipenem/cilastatin for pseudomonas pneumonia on [redacted] (day3). Concurrent to this event, the patient had a respiratory acidosis (arterial blood gas pH 7.13, pO_2 48, HCO_3 25) and eventually required intubation. One month later, the patient experienced a grand-mal seizure that was considered unlikely related to study drug.

Note: This case is also described in the serious adverse events section.

Medical officer's comment

The diagnosis of seizure in this case was questioned by the neurologist who saw the patient. The neurological symptoms (rhythmic jaw movements/mouth twitching while the patient remained responsive), described (on day 6) for this patient is unlikely to be related to study drug. The case is confounded by other possible etiologies for neurological dysfunction or seizures that include hypoxia, acidemia, and imipenem/cilastatin therapy. Imipenem /cilastatin can be associated with CNS side effects including encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, and psychic disturbances including hallucinations.

Infusion Reactions

No anaphylaxis was reported in this study. Approximately, 2% of patients in each treatment group experienced flushing, with all events being mild or moderate. Urticaria was experienced by 1.0% of patients in the anidulafungin group; urticaria was not reported in the fluconazole

group. Rash was reported by 1.5% of anidulafungin-treated patients versus 7.2% of fluconazole-treated patients.

In study VER002-9, there was a differential in the number of patients experiencing dyspnea compared to fluconazole, 9(6.9%) versus 4(3.2%), respectively. Following a review of the case reports for the patients who experienced dyspnea, the respiratory adverse events described were unlikely to be related to anidulafungin or fluconazole. As discussed in the integrated summary of safety, all these patients continued to receive anidulafungin daily and no doses of anidulafungin were prematurely terminated.

Summary of the nine anidulafungin-treated cases with dyspnea

Table 40a			Related to Anidulafungin	
Patient ID	Respiratory signs and symptoms at baseline	Intubated	Clinical reviewer attribution	Investigator attribution
09-001-001	Yes	intubated at baseline	Unrelated	Unrelated
09-002-008	Yes		Unlikley related	Unlikley related
09-003-004	Yes		Unlikley related	Unlikley related
09-019-001	Yes		Unlikley related	Unlikley related
09-032-001	Yes		Unlikley related	Unlikley related
09-041-004	Yes		Unrelated	Unrelated
09-040-001	Yes		Unrelated	Unrelated
09-041-005	Yes		Unrelated	Unrelated

Medical officer comment: All nine patients reported with dyspnea in this study had significant underlying respiratory illnesses, including pneumonia, pleural effusions, COPD and pulmonary embolus. The interval between the start of anidulafungin therapy and the event varied from 2 to 11 days, and did not appear to be consistently related to the time of infusion. All these patients continued to receive anidulafungin daily and no doses of anidulafungin were prematurely terminated. The medical officer concluded that these events were unrelated to study drug.

09-001-001: 60 year old white male with renal failure, intubated at baseline. On day 3 of anidulafungin, the patient developed worsening dyspnea, shallow respirations and an isolated episode of hypotension, all not related to study drug. No doses of anidulafungin were missed, interrupted or prematurely terminated. The patient died of renal failure on day 6.

09-002-008: 59 year old white male with history of insulin dependent diabetes, ischemic heart disease, renal failure and hypertension. At baseline, the patient had bilateral wheezing and decreased aeration in the base of the right lung as a result of recent staph sepsis. On day 2 of anidulafungin, the patient developed severe shortness of breath, unlikely related to study drug by the investigator, and was treated with atrovent and albuterol for several days. No doses of anidulafungin were missed, interrupted or prematurely terminated. Patient completed full course of study medication with no subsequent reports of dyspnea.

09-003-004: 63 year old white male with history of non-Hodgkin's lymphoma, deep vein thromboses, pulmonary embolisms, pleural effusions and respiratory insufficiency. On day 3 of anidulafungin, the patient had a worsening of dyspnea, moderate in severity. The investigator considered the event to be "unlikely" related to study drug. No doses of anidulafungin were missed, interrupted or prematurely terminated for this event.

09-019-001: 59 year old black female with diabetes, renal failure, peritonitis, pulmonary hypertension, pneumonia and pleural effusions at baseline. On day 5 of anidulafungin, the patient experienced mild dyspnea with cough, which resolved the following day following dialysis. No doses of anidulafungin were missed, interrupted or prematurely terminated for this event. The patient died of cardiac failure five days later.

09-032-001: 50 year old white female with Crohn's disease, s/p small bowel resection, peritonitis with decreased breath sounds bilaterally at baseline. On day 3 of anidulafungin, the patient reported mild shortness of breath, unrelated to study drug, which resolved the same day. No doses of anidulafungin were missed, interrupted or prematurely terminated for this event. The patient developed pneumonia and collapsed lung 4 days later.

09-041-004: 46 year old white female with ovarian cancer with ascites and pleural effusions at baseline. On day 5 of anidulafungin, the patient developed decreased breath sounds at the left base of the lung, and reported mild dyspnea the following day, not related to study drug. No doses of anidulafungin were missed, interrupted or prematurely terminated for this event. Two days later the patient was diagnosed with a left pleural effusion.

09-040-001: 77 year old white male with peritonitis and pleural effusions at baseline. On day 5 of anidulafungin, the patient reported worsening shortness of breath, unrelated to study drug, moderate in intensity, resolved after 3 days of treatment with salbutamol. No doses of anidulafungin were missed, interrupted or prematurely terminated for this event. The patient completed 10 days of study drug with no subsequent reports of shortness of breath.

09-041-005: 61yo white female with COPD, metastatic cancer, recent abdominal surgery. On day 2 of anidulafungin, the patient developed chest tightness and shortness of breath described by the investigator as mild in intensity, caused by exacerbation of COPD, and treated with combivent. No doses of anidulafungin were missed, interrupted or prematurely terminated for this event. Patient received study drug for 15 days with no subsequent reports of dyspnea.

09-068-001: 68 year old white male with history of colon cancer, hypertension, sleep apnea and pleural effusions. On days 11 and 12 of anidulafungin, the patient reported venous thrombosis and mild shortness of breath, unlikely related to study drug. No doses of anidulafungin were missed, interrupted or prematurely terminated for this event. Study drug was discontinued on day 12 because of clinical progression.

TABLE 40b. POSSIBLE INFUSION EVENTS DURING IV TREATMENT ONLY (ITT POPULATION)

Event	Anidulafungin N = 131 n (%)	Fluconazole N = 125 n (%)
Dyspnea*	9 (6.9)	4 (3.2)
Infusion related reaction	0	3 (2.4)
Flushing / Hot flushes	3 (2.3)	3 (2.4)

* includes dyspnea exacerbated
Data from Section 14.3, Table 3.7, and Appendix 16.2.7, Listing 5.3

TABLE 41. POSSIBLE HYPERSENSITIVITY EVENTS DURING IV TREATMENT ONLY (ITT POPULATION)

Event	Anidulafungin N = 131 n (%)	Fluconazole N = 125 N (%)
Pruritus[a]	4 (3.1)	0
Rash[a]	2 (1.5)	9 (7.2)
Dermatitis	0	1 (0.8)
Face edema/swelling	1 (0.8)	1 (0.8)

a: includes all forms
Data from Section 14.3, Table 3.7 and Appendix 16.2.7, Listing 5.3

In an integrated safety database in 329 patients with candidemia, a total of 28 (13.7%) of anidulafungin-treated patients and 9 (7.2%) of fluconazole-treated patients had infusion reactions. Dyspnea was the most common infusion-associated adverse event, it was reported in 10.8% of anidulafungin treated patients, and 3.2% of fluconazole treated patients. Two of the 22 patients in the anidulafungin group who experienced dyspnea had events classified as severe. Patient ID #06-030-002 was a 58 yo male who was intubated at baseline and had evidence of

increasing pulmonary hemorrhage on chest CT on the day prior to commencing anidulafungin therapy. The patient completed a 14 day course of anidulafungin. The patient's hospitalization was complicated with multiple pleural effusions,methicillin resistant *Staphylococcus aureus* in his sputum, atrial tachycardia, infective endocarditis, small bowel obstruction, uncontrolled bleeding from his tracheostomy, jugular axillary venous thrombosis, herpes lesions on the abdomen and fungemia. The fungemia resolved and the patient later expired due to respiratory failure due to worsening pulmonary hypertension. Patient 09-002-008 from study VER002-9 is described above, Table 40a.

Medical officer' s comment
An additional analysis was performed because of the difference observed between the two arms with regard to dyspnea during infusion (10.8% and 3.2%) in an integrated analysis of patients with appropriate exposure in NDA 21-948. The ITT database was searched for any adverse event related to respiratory symptoms such as dyspnea, shortness of breath, or wheeze. Twenty-three anidulafungin-treated patients and four fluconazole treated patients were identified. The case reports for each patient was reviewed. The majority of patients had active respiratory co-morbid conditions such as COPD, pneumonia, respiratory insufficiency due to pleural effusions. Dyspnea did not lead to discontinuation of study drug. The respiratory adverse events described were unlikely to be related to anidulafungin or fluconazole.

10.9 Conclusions Regarding Safety Data in Study VER002-9

Anidulafungin was generally well tolerated in this group of critically ill patients with invasive candidiasis, mostly candidemia. Adverse events of interest that emerged during the studies include hepatic enzyme elevations, infusion.

Adverse events were reported by 130 (99.2%) patients in the anidulafungin arm and 122 (97.6%) patients in the fluconazole arm. SAEs were considered related to treatment for only 2 patients in each study arm.

The proportion of patients with related adverse events was similar in the two treatment arms (approximately 25%). Fewer anidulafungin-treated patients (15, 11.5%) than fluconazole-treated patients (27, 21.6%) experienced an AE that led to discontinuation of study drug. Fewer anidulafungin-treated patients (30, 22.9%) than fluconazole-treated patients (39, 31.2%) died during and shortly after the study. None of the deaths were attributed to study drugs by the investigator. This review did not identify any deaths related to study drug. There were no cases of anaphylaxis. Infusion reactions were generally mild and infrequent. Seizure activity appears unrelated to study drug.

The additional hepatic safety data provided in this study demonstrates that there were more hepatic adverse events in the fluconazole group. Six patients in the fluconazole arm and one patient in the anidulafungin arm fulfilled the criteria for Hy's rule (ALT rise to > 2 X ULN, and concomitant or up to one month delayed rise in bilirubin >
1.5 X ULN). The Hy's rule patient in the anidulafungin arm was unrelated to study drug, and the patient continued on anidulafungin. The bilirubin returned to normal despite continued treatment

with anidulafungin, which is not consistent with severe drug induced liver injury. Two patients who fulfilled the criteria for Hy's rule in the fluconazole arm were possibly related to study drug. Serious adverse events related to hepatic enzyme elevations were reported for one fluconazole patient and none of the anidulafungin treated patient.
No cases of hepatic failure, anaphylaxis, or QT prolongation occurred in either arm. Few systemic infusion reactions were reported. There was no major difference in adverse events. The safety data show that anidulafungin at a dose of 100 mg IV daily (for approximately two weeks) has a safety profile similar to and, in some instances, more favorable than that of fluconazole 400 mg IV daily in this critically- ill population.

11 HEPATIC SAFETY ACROSS STUDIES

Background
The FDA expressed concerns about potential liver toxicity at the time of the original review of NDA 21-362, following recognition of case #13-008. This was a confounded case of severe hepatic injury in a patient who died after three days of anidulafungin therapy. Therefore, additional safety was requested by the FDA on anidulafungin.
The applicant was advised to collate and analyze hepatic chemistry data from the clinical development program. Two hepatic safety documents were submitted by the applicant as

part of the complete response, a hepatologist's expert report and a hepatic safety summary for the clinical program.
Preclinical studies were reviewed in NDA21-632. In the preclinical studies in animals, mild to moderate liver toxicity was observed. In four- and thirteen week studies in rats and monkeys, increased liver weights, hepatocellular hypertrophy, increased AST and ALT and single cell hepatic necrosis were reported. Most of the hepatic adverse events in animals occurred at dosages 8 to 11-fold greater than those for the proposed dosage for esophageal candidiasis. (See Dr. Mc Master's and Dr. Ibia's original review of NDA 21-632). In healthy volunteer studies receiving multiple doses of anidulafungin, ALT elevations (< x 4 ULN) were asymptomatic and reversible upon cessation of treatment. These elevations tended to occur toward the end of the treatment period. Concomitant elevations in bilirubin were not observed. (See Dr Ibia's original review of NDA 21-632)

Medical officer's comment
A review of preclinical studies and healthy volunteer studies is contained in the original review of the NDA 21-632. The animal hepatotoxicity data presented is similar to that observed with other echinocandins. The ALT elevations observed in the healthy volunteer studies are not by themselves a significant liver safety signal. Results from all these studies indicate that close monitoring of liver function tests should be performed in patients receiving anidulafungin.

Methodology for Integrated Analysis of Hepatic Safety Across Studies
The applicant followed the strategy suggested by the FDA for collating hepatic chemistry data from the clinical program, i.e. hepatic chemistry data was collated from all clinical subjects who at any time experienced elevations ≥ 2 fold in any of the standard liver chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or bilirubin. These data were represented by graphing the serial value (expressed as log ULN on the y axis) versus time in study on the x-axis.
An expert hepatologist, Dr [ ] reviewed each subject graph and selected for further study, hepatic chemistry that fit the following conservative Hy's Rule definition:
*ALT rise to > 2 X ULN, **and** concomitant or up to one month delayed rise in bilirubin >*

1.5 X ULN. If the patient's baseline ALT or bilirubin was elevated, this baseline value replaced ULN in the search criteria. Following this analysis, narratives, and where indicated, original case report forms were reviewed for each of the cases identified by the above criteria.

Medical officer's comment
This methodology captures all significant hepatic chemistry abnormalities from the studies. The criteria used, ALT rise to > 2 X ULN, and concomitant or up to one month delayed rise in bilirubin > 1.5 X ULN is conservative. Concomitant elevations in serum bilirubin are recognized to indicate significant liver dysfunction. Low level elevations in ALT levels alone would not indicate significant hepatic injury.

Results

In the entire clinical development program, 1060 patients were exposed to anidulafungin. This included subjects who received oral doses, single-dose IV therapy, and sub-therapeutic doses. These types of exposures were not considered to reflect the safety of the proposed dosage regimen, and were excluded.

Table 42. Exposure to Anidulafungin During The Clinical Program

Route of Administration **Dose Range**	**Clinical Phase**	**No. of Subjects**
Oral		
Single dose: 25 – 1000 mg	1	35
Multiple dose: 100 – 600 mg	1 - 2	99[a]
Single-Dose Intravenous		
0.1 – 100 mg	1 - 2	113
Multiple-Dose Intravenous	1 - 3	
100 mg/day		337
< 100 mg/day		479
	Total	**1060**

Note;
a Includes three subjects in Study XBAW who received both single- and multiple-dose regimens.
Source: Submission 2005-05-27, Integrated Review of Safety, section 4.1

Route of Administration **Dose Range**	**Clinical Phase**	**No. of Subjects**
Oral		
Single dose: 25 – 1000 mg	1	35
Multiple dose: 100 – 600 mg	1 - 2	99[a]
Single-Dose Intravenous		
0.1 – 100 mg	1 - 2	113

Multiple-Dose Intravenous	1 - 3	
100 mg/day		337
< 100 mg/day		479
	Total	**1060**

Note;
a Includes three subjects in Study XBAW who received both single- and multiple-dose regimens.
Source: Submission 2005-05-27, Integrated Review of Safety, section 4.1

The remaining patients included a total of 690 anidulafungin-treated patients and 426 fluconazole-treated patients who were evaluated for hepatic safety assessment across studies. Among the 690 patients, 292 were new patients who were not reported in the original NDA 21-632.

These patients received multiple therapeutic doses ranging from 50mg and 100mg IV daily. Of the 690 anidulafungin-treated and 426 fluconazole-treated patients who had repeated IV doses, 294 (42.6%) and 152 (35.7%) patients respectively had elevations ≥ 2 x ULN in AST, ALT, ALKP, or total bilirubin. Patients who had baseline hepatic chemistry abnormalities were included.

Following a review of each subject graph, case narratives for 10/294 (3.4%) anidulafungin-treated patients and 8/152 (5.3%) fluconazole-treated patients were further reviewed, Table 43. A case by case assessment was done on whether each of these patients fulfilled the predefined criteria for Hy's rule.

Table 43: Number of Patients with Hepatic Figures and Narratives by Study

Study	No. of anidulafungin/ fluconazole-treated patients	No. of hepatic figures for anidulafungin produced (patients with 2-fold increase in transaminases)	No. of narratives for anidulafungin requested by Dr. [redacted]	No. of hepatic figures for fluconazole produced	No. of narratives for fluconazole requested by Dr. [redacted]
VER002-4	300/301	102	2	103	2
VER002-5	30	4	0	NA	NA
VER002-6	120	70	4	NA	NA
VER002-7	30	23	3	NA	NA
VER002-9	131/125	78	1	49	6
VER002-11	19	7	0	NA	NA
VER002-12	25	8	0	NA	NA
VER002-15	35	2	0	NA	NA
Total	690/426	294	10	152	8

Source: Adapted from Hepatology Experts Report, in submission 2005-05-27

Table 44 summarizes the cases that fulfilled the predefined criteria of ALT > x2ULN and total bilirubin >1.5 X ULN as well as the opinions of the hepatology expert, the investigator and the FDA clinical reviewer with regard to causation assessments. Cholestasis was not considered by the consultant and the clinical reviewer to reflect true hepatocellular injury. Patients who had predominant cholestasis and clear cases of shock liver were not regarded as cases of hepatocellular drug toxicity.

There were four Hy's rule cases in the anidulafungin group, and seven in the fluconazole group. Two of 294 (0.68%) cases among the anidulafungin-treated patients were considered by the clinical reviewer to be possibly related to anidulafungin and confounding factors that might account for the findings were present in both. One of 152 (0.66%) fluconazole-treated cases was considered by clinical reviewer to be possibly drug-related. The clinical reviewer and the hepatology expert came to a different conclusion with regard to causation assessment of one Hy's rule case, ID # 67-001. The hepatologist attributed the hepatic chemistry abnormalities in this case to be due to anidulafungin. The clinical reviewer and an FDA hepatologist concluded that tuberculosis drugs could have caused the hepatic chemistry abnormalities observed in this case, and therefore the case was confounded. A more detailed review of case #67-001 and all the cases in the hepatic safety analysis are included in Appendix A. Dr. Senior, hepatology expert at the FDA consulted on case #67-001, and his report is included in Appendix B.

Table 44: Summary of Cases and Causation Assessments

Patient ID # Study No.	age	sex	Study Drug Exposure	Prior and concomitant meds with potential for liver toxicity	Co morbid Disease	Causation Assessments and Comments Hepatologist	Investigator	FDA
Anidulafungin Cases								
13-008 VER002-4	53	M	100/50mg x 3 days	yes	AIDS TB Cor pulmonale	Unrelated Probable shock liver Hy's rule case	possibly related	Unrelated
16-003 VER002-4	35	M	100/50mg x 14days	yes	Disseminated TB Esophageal candidiasis	Unrelated Not Hy's rule	unrelated	Unrelated
001-002 VER002-6	37	M	150/75mg X 10 days	yes	Staph endocarditis candidemia	Unrelated Not Hy's rule	Unrelated	Unrelated
030-009 VER002-6	62	F	200/100mg X14 days	yes	Candidemia Respiratory arrest colon cancer	Multifactorial Not Hy's rule	Not stated	Multifactorial Unlikely related
033-002 VER002-6	75	M	150/75mg x 17 d	yes	Staph pneumonia, intestinal perforation Resp failure candidemia	Multifactorial Not Hy's rule	Not stated	Multifactorial Unlikely related
035-003 VER002-6	42	M	200/100mg x 11 d	yes	Surgery for colonic perforation Staph bacteremia Candidemia Alcoholic hepatitis	Unlikely related Not Hy's rule case	Unlikely related	Multifactorial Unlikely related
007-001 VER002-7	29	M	200/100mg X 38 days plus L-AmB	yes	Aspergillus endocarditis	Unlikely related Hy's rule case	Not stated	Multifactorial Unrelated
033-001 VER002-7	56	M	200/100mg X 28 days plus L-AmB	yes	Invasive Aspergillosis Acute leukemia	Related Not Hy's rule	Unrelated	Multifactorial Possibly related
067-001* VER002-7	33	F	200/100mg X 30 d	yes	Pulmonary aspergillosis Tuberculosis	Related Hy's rule case	Unrelated	possibly related but more likely

								to be due to TB drugs
41-006 VER002-9	46	M	200/100mg X 30 d	yes	Pulmonary aspergillosis	Unrelated Hy's rule case		Unlikely related
Fluconazole cases								
17-002 VER002-4	41	M	200mg/100mg x 14 days	yes	AIDS Esophageal candidiasis Disseminated TB	Unrelated Hy's rule case	unrelated	unrelated
18-003 VER002-4	39	M	200mg/100mg x14 days	yes	AIDS Disseminated TB Esophageal candidiasis	Unrelated Hy's rule	Not stated	unrelated
32-002 VER002-9	62	F	800/400mg X 2 d	yes	Pancreatic cancer Cardiac arrest	Unrelated Hy's rule case Probable shock liver	Not stated	unrelated
04-009 VER002-9	26	F	800/400mg x 26 d	yes	Crohn's disease Small bowel resection Cardiac arrest	Unrelated Hy's rule case Probable shock liver	Not stated	Unrelated
07-003 VER002-9	49	M	800/400mg x 21 d	yes	Colonic perforation	Not Hy's rule	Not stated	unrelated
11-004 VER002-9	24	F	800/400mg x 15 d	yes	Nasopharyngeal cancer Esophageal candidiasis	Not stated Hy's rule case	Possibly related	Inconclusive
18-010 VER002-9	74	M	800/400mg x 15 d	yes	Bladder cancer	Not stated Hy's rule case	Possibly related	Possibly related
20-010 VER002-9	62	M	800/400mg x 6 d		Bacterial sepsis Retroperitoneal bleed	Not stated Possible Hy's rule	unrelated	unrelated

*See Appendix A and B. Note: L-AmB = Liposomal Amphotericin B, AmBisome®

Conclusion

There were more Hy's rule cases in the fluconazole arm, seven versus four cases. Of the 690 patients with representative exposure to anidulafungin, the reviewer identified two cases of significant hepatic injury possibly related to anidulafungin. Both cases were confounded by concomitant intercurrent illness and drugs with potential for hepatotoxicity. The hepatic chemistry abnormalities resolved after drug discontinuation. Of the 426 fluconazole-treated patients, one cases of significant hepatic injury were considered possibly related to study drug by

the clinical reviewer. The frequency of liver injury was slightly less with anidulafungin- than fluconazole-treated patients, and cases could not be definitively attributed to anidulafungin.

Analysis of the hepatobiliary parameters for the two comparative studies

A second analysis of the hepatobiliary parameters for the two comparative studies was performed by the clinical reviewer. In the esophageal candidiasis study (VER002-4), of the 431 anidulafungin-treated patients and 426 fluconazole-treated patients, 283 patients and 281 patients, respectively were evaluable for all hepatic chemistry on-therapy. Of the131 anidulafungin-treated patients in the invasive candidiasis study (VER002-9), between 90 to 93 patients were evaluable for hepatic chemistry on-therapy depending on the parameter being measured. In the fluconazole arm, there were 82 to 84 of 125 patients who were evaluable for hepatic chemistry on therapy depending on the parameter being measured. Repeat hepatic chemistry testing was not available on all subjects for a variety of reasons including withdrawal from the study due to death or lost to follow up. Two dosing levels were pooled i.e. 50mg IV daily and 100mg IV daily. The study populations consisted of patients with AIDS and critically ill hospitalized patients, all of whom had multiple co-morbid diseases. Table 45 integrates hepatobiliary parameters on therapy from the two comparative phase 3 studies.

Table 45: Integrated Summary of Hepatobiliary Parameters from Comparative Phase 3 Data on Therapy (Study VER002=4 and study VER002-9)

Hepatic parameter	Anidulafungin	Fluconazole
ALT> X3 ULN	18/376 (4.8%)	27/364 (7.4%)
ALT > X5 ULN	6/376 (1.6%)	9/364 (2.5%)
ALT > 10 ULN	0/376 (0.0%)	1/364 (0.27%)
AST > X3 ULN	43/374 (11.5%)	39/364 (10.7%)
AST > X5 ULN	17/374 (4.5%)	14/364 (3.8%)
ALT > X3 ULN and bilirubin > X1.5 ULN	4/283 (1.06%)	2/277 (0.72%)

The numbers of patients with abnormal hepatic chemistry abnormalities in the anidulafungin- and fluconazole-treated patients were similar. There were more patients with abnormal hepatobiliary parameters in the esophageal candidiasis study at the lower dose (50mg IV daily) than in the invasive candidiasis study at the higher dose (100mg iv daily). For example, 2 of 18 patients in the anidulafungin arm who had ALT > x 3 ULN, were in the invasive candidiasis study; 1of 6 patients in the anidulafungin group with ALT > x 5 ULN, was in the invasive candidiasis study. The four anidulafungin-treated cases with ALT>3 XULN and total bilirubin > 1.5 x ULN are summarized in Table 45a.

Table 45a. **Anidulafungin cases with ALT>3 XULN and total bilirubin > 1.5 x ULN**

Patient ID # Study No.	Diagnosis	Comment on hepatic chemistry	Relationship to study drug by clinical reviewer
13-008 * VER002-4	Esophageal Candidiasis	Elevations in hepatic chemistry are most likely secondary to shock liver due to right heart failure	Unrelated
16-003* VER002-4	Esophageal candidiasis	Elevations in hepatic chemistry are most likely secondary to disseminated TB and TB drugs	Unrelated
41-006* VER002-9	Candidemia	Liver enzymes returned to normal despite continued treatment with anidulafungin	Unrelated
42-001 VER002-9	Candidemia	Hepatic transaminases and bilirubin were elevated at baseline and improved on anidulafungin	Unrelated

*See Appendix A for detailed discussion of these cases.

Conclusion
The percentage of biochemical hepatic abnormalities is similar for anidulafungin- and fluconazole- treated patients, see Table 45. The four anidulafungin patients with concurrent elevations of transaminases and bilirubin were considered to be unrelated to study drug upon detailed review as summarized above (Table 45a.)

11.1

11.2 Summary

In the preclinical studies, the majority of the hepatic adverse events in animals occurred at dosages 8 to 11-fold greater than those for the proposed dosage for esophageal candidiasis. Hepatic adverse events in preclinical studies were also found to be reversible upon cessation of drug administration. It is unlikely that any of these hepatic chemistry abnormalities were due to drug interactions because elimination of anidulafungin in preclinical studies was by chemical degradation indicating that the drug was not likely to interact with the metabolism of other drugs that might be used concomitantly with anidulafungin.
In Phase 1 studies in healthy volunteers, elevations in ALT levels tended to occur toward the end of the treatment period, were less than four times the upper limit of normal, were asymptomatic, and reversible off-therapy.
Phase 1 – 2 studies provided additional evidence of the hepatic safety of intravenous

anidulafungin. Results from clinical studies in patients with renal insufficiency (study VER002-3) and hepatic insufficiency (study VER002-2) found that no dosage adjustments were required to compensate for hepatic or renal dysfunction.

In a pharmacokinetic study of anidulafungin in neutropenic children (age 2 to 17y), there was no dose-limiting toxicity at the doses tested and that there were no dose- or age-dependent differences in clinical chemistry values, changes from baseline for hepatobiliary parameters, or hepatobiliary parameters of potential clinical significance.

Five major studies were included in the phase 2-3 program. There was a range of doses from 50mg to 100mg daily in these studies. Two studies had a dose of 50mg IV daily for 14 to 21 days, i.e. the esophageal candidiasis study VER002-4 and the refractory mucosal candidiasis study, (VER002-11). One phase 2 study, (VER002-6) in patients with invasive candidiasis had maintenance doses of 50, 75, or 100 mg/day for 15 to 42 days. Two studies, an invasive candidiasis study (VER002-9) and an invasive aspergillosis study (VER002-7) had a maintenance dose of 100mg IV daily for $\geq$ 14 days. There were no serious hepatobiliary events in the follow-up open-label study to study 9, i.e. VER002-9b.
One case in the invasive candidiasis study (VER002-9) experienced a 5-fold increase in serum ALT and a 1.6-fold increase in serum bilirubin seven days into treatment with anidulafungin. The bilirubin level returned to normal despite continuation of anidulafungin. No case from the invasive candidiasis study was found to be related to anidulafungin therapy. One patient in the invasive aspergillosis study experienced a 20-fold increase in hepatic transaminases that was attributed to anidulafungin. Following a review of this case, the clinical reviewer and FDA hepatologist concluded that anti-tuberculosis medications could have caused the hepatic chemistry abnormalities observed in this case, and therefore the case was confounded. A second case in the invasive aspergillosis study had abnormal liver transaminases at baseline, the elevations in transaminases were reversible following discontinuation of study drug; this was not a Hy's rule case. Many of the cases in these studies were confounded by severe underlying disease and concomitant medications with potential to cause hepatotoxicity.
Other than case #13-008, already reviewed in the original NDA 21-632, no similar cases of fulminant liver injury were observed in any other patient during the clinical development program of anidulafungin. This patient most likely died from shock liver due to right heart failure and did not represent a case of anidulafungin toxicity. Two cases with similar hepatic profiles were found in the fluconazole arm of the invasive candidiasis study; the liver injury in these cases was reported to be due to shock liver and unrelated to study drug.

In summary, a few cases of significant hepatic dysfunction and hepatitis, were reported in patients receiving anidulafungin in studies completed since the original NDA submission. However, a causal relationship to anidulafungin was not established. In the two comparative studies with fluconazole, both sets of data were confounded by co-morbid conditions and concomitant medications with potential for hepatotoxicity. No hepatic safety concerns emerged when compared to fluconazole. As with other FDA approved echinocandins, monitoring of hepatic function should be done at baseline and during anidulafungin therapy. Significant elevations in hepatic chemistry should prompt an assessment of the risks and benefits of continuing therapy.

12 RISK/BENEFIT ANALYSIS

Anidulafungin is a useful addition to the current antifungal armentarium for candidemia. Infection with non-albicans *Candida* species are increasing in hospitalized patients, and some of these species are less susceptible to fluconazole.

Echinocandins, including anidulafungin are fungicidal *in vitro* against *Candida* species including species that are less susceptible or resistant to azoles, such as *C. glabrata and C. krusei,* respectively. Anidulafungin has activity against fluconazole- resistant, and fluconazole-susceptible strains of *Candida* species, (Pfaller 1997, Vazquez 2005).

It must also be stated that a correlation between antifungal *in vitro* susceptibility testing and clinical outcome has not been adequately demonstrated. No cross resistance between anidulafungin and azoles or polyenes have been demonstrated *in vitro*, and therefore anidulafungin could be used for treatment of azole-resistant and polyene-resistant *Candida* species (Pfaller 1997, Steinbach 2004, Vazquez 2005).

Amphotericin B formulations have excellent fungicidal activity against *Candida* species but are associated with renal toxicity. Anidulafungin has an advantage over amphotericin B in patients with renal insufficiency. Anidulafungin is not metabolized by the kidney and has not been associated with renal toxicity. A dose adjustment is not required for renal insufficiency. This agent would be of benefit in a patient with renal insufficiency who is potentially at risk for developing renal toxicity from amphotericin B. A dose adjustment is required for azole drugs in patients with renal insufficiency. Intravenous voriconazole is contraindicated in patients with moderate or severe renal impairment.

Uniquely among the echinocandins, anidulafungin is eliminated almost exclusively by slow chemical degradation, and not by hepatic metabolism. Dose adjustments are not required in mild, moderate or severe hepatic insufficiency. The currently approved echinocandins have not been studied in severe hepatic insufficiency. A dose adjustment for moderate hepatic insufficiency is recommended for other approved echinocandins, caspofungin, and micafungin. As with echinocandin drugs, isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to anidulafungin has not been established.

It is recommended for echinocandins that patients who develop abnormal liver function tests during therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing therapy.

Anidulafungin has an advantage over some other echinocandins in that it does not interact with some of the immuosuppressive drugs commonly used in clinical practice. In drug interaction studies, there were no interactions between anidulafungin and tacrolimus or cyclosporine. Concomitant use of caspofungin and cyclosporine is not recommended. Monitoring of tacrolimus levels and appropriate tacrolimus dose adjustments are required for patients receiving caspofungin and tacrolimus. No drug interactions have been demonstrated between anidulafungin, and voriconazole, an antifungal triazole commonly used in clinical practice for invasive *Candida* infection and invasive Aspergillosis .

Anidulafungin was efficacious in the treatment of esophageal candidiasis, as demonstrated in VER002-4, the pivotal, phase 3, randomized, controlled, double-blind, double-dummy trial. In this population, most of which had AIDS, the primary analysis of efficacy demonstrated that

anidulafungin is at least as efficacious as fluconazole, as assessed by endoscopic success at the end of therapy (97.2% in the anidulafungin; 98.8% in the fluconazole group, treatment difference -1.6%; (95% CI -4.1, 0.8). A high relapse rate off- therapy was demonstrated in this study. Anidulafungin was as effective as the comparator agent during the 14-21 day treatment period but was associated with a significantly higher rate of relapse at two weeks post therapy. Consideration of the relapse rates off-therapy should be taken into account when considering anidulafungin as initial therapy.

Anidulafungin has shown efficacy in other forms of invasive candidiasis. In a randomized controlled clinical trial of anidulafungin in patients with candidemia and other invasive *Candida* infections, anidulafungin had statistically superior anti-*Candida* activity over fluconazole at all time points. In the anidulafungin arm, 96 patients (75.6%) had a global success versus 71 patients (60.2%) in the fluconazole arm. The between group difference in global success rate (anidulafungin minus fluconazole) was 15.42% (95% CI 3.85, 26.99). The majority of study subjects were critically ill patients (~90%) with candidemia. Patients were treated with a 200mg IV loading dose followed by 100mg IV daily i.e. double the proposed dose for treatment of esophageal candidiasis study.

There were no major safety concerns for this dose of anidulafungin compared to fluconazole. Most patients did not experience adverse events related to study medication. The two most common related adverse events for anidulafungin were hypokalemia (3.1%) and diarrhea (3.1%). For fluconazole, the two most common related adverse events were increased hepatic enzyme (7.2%) and increased blood alkaline phosphatase (4.0%). In this study the hepatic toxicity profile of anidulafungin was comparable with that of fluconazole.

In the era of combination antifungal therapy, the lack of drug-drug interactions with amphotericin B formulations and voriconazole is advantageous.

Anidulafungin is intravenous product only (same as all other approved echinocandins), which potentially limits its use to hospitalized patients.

In summary, anidulafungin has a favorable risk/benefit ratio in the treatment of esophageal candidiasis. It has shown efficacy in esophageal candidiasis, and in candidemia. Safety concerns are mainly related to hepatic effects and infusion reactions. Anidulafungin appears to be similar to other echinocandins in its hepatic and overall safety profile. As with other approved echinocandin drugs, isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to anidulafungin has not been established. Monitoring of hepatic function is recommended for patients receiving anidulafungin.

13 APPENDIX A

13.1 Study VER002-9b

This was an open-label continuation of the invasive candidiasis study, VER002-9. There were 33 patients enrolled in the study. The purpose of this Phase 3, open-label study was to evaluate the safety and efficacy of anidulafungin in patients with candidemia and other forms of invasive candidiasis. Eligible patients included those who were receiving fluconazole prophylaxis, or for whom fluconazole was otherwise relatively contraindicated, and were therefore ineligible for enrollment in the double-blind VER002-9 study. All patients were eligible for this study after the double-blind study was closed to enrollment.

Table 1 Comparison of VER002-9 and VER002-9B

	VER002-9	VER002-9B
	Randomized, double blind, comparative	Open label, noncomparative, extension study
Disease	Invasive candidiasis	Invasive candidiasis
Sites	US, Canada, Europe	US , Canada
Subjects enrolled	256	33

Study Objective
The primary objective was to evaluate the safety and efficacy of 100 mg daily of anidulafungin in the treatment of patients with a diagnosis of candidemia and/or other forms of invasive candidiasis.

Inclusion Criteria
Inclusion criteria were the same as for study VER002-9 as well as at least one of the following criteria that made patients ineligible for enrollment in the double-blind study, VER002-9.

- Had received prophylactic administration of fluconazole, itraconazole, or voriconazole ≥ one week within 30 days prior to enrollment;
- Were receiving and were to continue to receive terfenadine and cisapride
- Had a known *Candida krusei* infection;
- Had a known hypersensitivity to azole therapy

Exclusion Criteria
Patients who received greater than 72 hours of systemic antifungal therapy for the *Candida* infection for which they were enrolled. In study VER002-9 the cut off period was 48 hours. Patients with *Candida krusei* were not excluded.

Patient Disposition
Of the 33 enrolled, 22 completed the study including follow-up. Reasons for study discontinuations are listed in Table 2.

Study Endpoints
See review of study VER002-9

Schedule of Monitoring
See review of Study VER002-9

Study Populations

ITT: All patients who received at least one dose of study medication were included in the intent to treat (ITT) population.
MITT: The primary efficacy population was the Microbiological-ITT population. This population included all patients who received at least one dose of study medication and who had a positive culture from a normally sterile site at baseline for *Candida* species, preferably within 96 hours before entry into the study.
Efficacy Evaluable: The Efficacy Evaluable population was a subset of the Micro-ITT population. Patients in the efficacy evaluable populations had both clinical and microbiological data available for analysis at entry and test of cure visits. There were five distinct groups in the efficacy evaluable population: Efficacy evaluable at Day 10 of IV therapy, at the end of IV therapy, at the end of all therapy (oral and/or IV), at 2-week follow-up, and at 6-week follow-up.

Clinical outcome and Response
The Investigator was to assign a clinical response at:
- Day 10 of IV therapy
- End of IV therapy (primary time point)
- End of oral therapy (if applicable)
- 2-week FU
- 6-week FU

Study Endpoints

The primary endpoint is the same as VER002-9, i.e. the global response in the Micro-ITT population at the end of IV therapy. The secondary endpoints are similar to study VER002-9. Prevention of Late Complications: The number of patients who developed endophthalmitis and the number of patients who had global success at the 2-week FU and then had a positive *Candida* culture (blood or other normally sterile site) by the time of the 6-week FU were summarized.

Patient Disposition

The Micro-ITT population was comprised of 31 patients (93.9%). The efficacy evaluable population at the end of IV therapy was a subset of the Micro-ITT population.
A total of 17 (51.5%) patients were evaluable for efficacy at the end of IV therapy.

Table 2

Population	**Anidulafungin**	**Reasons for exclusion**
ITT [a]	**33 (100%)**	
Excluded	2	Did not have a positive baseline culture for *Candida*
Micro-ITT	**31 (93.9%)**	
Excluded [b]	1	Clinical response of indeterminate at end of IV therapy
	13	≥ 3 days of prior antifungal therapy and was not a clinical failure
Total Excluded	14	
Efficacy Evaluable @ end of IV therapy (Primary time point)	17 (51.5%)	
Efficacy Evaluable at 2 -week and 6 -week follow-up	14 (42.4%)	Death and lost to follow up. See Table 3

a: Denominator for all % calculations is N of ITT.
b: For patients with multiple reasons for exclusion from a population, only the primary reason was tabulated.
c: Patients were excluded from the Micro-ITT population if no baseline culture for *Candida* from a normally sterile site was obtained within 5 days of the first dose of study medication.
Adapted from Data from Section 14.1, Table 1.3.2.

TABLE 3. PATIENT DISPOSITION AND REASONS FOR WITHDRAWAL

Category Event		n (%)
Total enrolled		33
Intent-to-Treat		33
Total completed the study through 6 week follow-up		22 (66.7)
Total discontinued from study prior to 6 week follow-up		11 (33.3)
Death		7 (21.2)
Patient lost to follow-up		4 (12.1)
Total completed full course of study medication[a]	25 (75.8)	
Total withdrawn from study medication[b]	8 (24.2)	
Adverse Event		4 (12.1)
Patient Withdrew Consent		1 (3.0)
Worsening Clinical Status/Lack of Efficacy		2 (6.1)
Investigator Discretion		1 (3.0)

NOTE: Percentages are based on the ITT population.

a: "Total completed full course of study medication" refers to completion of IV and oral (if applicable) study medication.

b: For each patient who withdrew from study medication, only 1 reason (the primary) for withdrawal is tabulated.

Source: Data from Section 14.1, Table 1.1.

Demographics

Demographic characteristics for the Micro-ITT population are presented in Table 4. There were more males than females, and most patients were white. The average age of the population was 54.5 years. Approximately 20% of the patients had Apache II scores > 20, indicative of a sick population often found in intensive care units. Two patients were neutropenic (ANC ≤ 500). There were no notable differences in demographic and baseline characteristics between the ITT population and the Micro-ITT population.

TABLE 4. PATIENT DEMOGRAPHY AND BASELINE CHARACTERISTICS (MICRO-ITT POPULATION)

Demography	N=31
Gender, n (%)	
Male	20 (64.5)
Female	11 (35.5)
Age, years	
Mean (SD)	54.5 (16.5)
Median	59
Min - Max	23 - 83
Ethnic Origin, n (%)	
White	20 (64.5)
Black/African American	4 (12.9)
Other	7 (22.6)
Apache II Score	
≤20, n (%)	25 (80.6)
> 20, n (%)	6 (19.4)
Mean (SD)	14 (7.5)
Median	13
Min - Max	2 - 27
Absolute Neutrophil Count, cells/mm3	
> 500, n (%)	29 (93.5)
≤ 500, n (%)	2 (6.5)

Adapted from Section 14.1, Table 1.4.1

TABLE 5. BASELINE CHARACTERISTICS: COMORBIDITIES AND RISK FACTORS, Micro-ITT.

Characteristic Detail	N = 31 n (%)
Comorbid Diseases Assoc. with IC, n (%)[a]	
Endocrine/Metabolic Disorders	17 (54.8)
Recent Surgical History	16 (51.6)
Bacterial Sepsis	14 (45.2)
Neoplastic Disease	9 (29.0)
Genitourinary	6 (19.4)
Hematopoietic/Lymphatic	3 (9.7)
Rheumatologic	2 (6.5)
Transplantation	1 (3.2)
Other	25 (80.6)
Invasive Candidiasis Risk Factors, n (%)[a]	
Central venous catheter	26 (83.9)
Broad-spectrum antibiotics	24 (77.4)
Recent surgery	16 (51.6)
Underlying malignant condition	12 (38.7)
Recent hyperalimentation	8 (25.8)
Immunosuppressive therapy	6 (19.4)
Receipt of a transplant	1 (3.2)
Other	2 (6.5)
Catheter and IC, n (%)	
Invasive Candidiasis related to IV Catheter?[b]	N=31
Yes	16 (51.6)
If yes, catheter removed?[b]	N=16
Yes	15 (93.8)

a: Patients may have had more than one
b: Per Investigator assessment
Note: The number (%) of patients with neoplastic diseases, surgery within the past 7 days, and transplants (comorbid conditions) does not exactly match the number (%) of patients with malignancies, recent surgery, and receipt of a transplant (risk factors) because of Investigator discretion in determining what situations were considered risk factors.
Source: Adapted from Section 14.1, Table 1.4.1.

Efficacy Results

Global response in the Micro-ITT population is presented. In the primary efficacy analysis, a total of 21of 31 patients (67.7%) had a global success at the end of IV therapy. Indeterminate responses were considered to be failures.

Table 6. Global response in the Micro-ITT population at the end of IV therapy

Response	N = 31
Outcome	n (%)
Success	21 (67.7)
Failure	10 (32.2)

Source: Adapted from Section 14.2, Table 2.1.1.

In the Micro-ITT population at the end of IV therapy, five patients had an indeterminate global response. Reasons for an indeterminate response included withdrawal from the study or from study medication. Reasons for withdrawal included an adverse event (3 patients), withdrawal of consent (1 patient), and investigator discretion (1 patient).

Global responses at secondary time points

Table 7. Global response in Micro-ITT population at secondary time points

Secondary Timepoint	
Response	
Outcome	n (%)
End of Oral Therapy	N=6
Success	5 (83.3)
Failure	1 (16.7)
End of All Therapy	N=31
Success	21 (67.7)
Failure	10 (32.2)
2-Week Follow-Up	N=31
Success	18 (58.1)
Failure	13 (41.9)
6-Week Follow-Up	N=31
Success	18 (58.1)
Failure	13 (41.9)

Source: Adapted from Section 14.2, Table 2.2.1

Microbiology

Global success for all species occurred in 20/28 (71%) patients. The microbiological success was higher than clinical success in this patient population. Eradication or presumed eradication of the baseline pathogen occurred in 25/31(80.6%) of patients, Table 9.

Global Response by Baseline Pathogen at the End of IV Therapy

TABLE 8. GLOBAL SUCCESS AT END OF IV THERAPY BY PATHOGEN (MICRO-ITT POPULATION)

Baseline Species	n/N (%)
All species	20/28 (71.4)
Candida albicans	7/11 (63.6)
Non-*albicans* species	13/17 (76.5)
Candida glabrata	8/9 (88.9)
Candida parapsilosis	3/4 (75.0)
Candida tropicalis	2/3 (66.7)
Candida krusei	0/1 (0.0)

Note: N=Number of patients with a single baseline pathogen.
Source: Adapted from Section 14.2, Table 2.13.

TABLE 9. PATIENT-LEVEL MICROBIOLOGICAL RESPONSE AT THE END OF IV THERAPY (MICRO-ITT POPULATION)

Response	N = 31
Outcome	n (%)
Success	25 (80.6)
Eradication	22 (71.0)
Presumed Eradication	3 (9.7)
Failure	6 (19.4)
Persistence	3 (9.7)
Super-infection	2 (6.5)
Indeterminate	1 (3.2)

Source: Data from Section 14.2, Table 2.7

Three patients had a persistent infection with a baseline pathogen at the end of IV therapy. Though there are no established breakpoints for these organisms, based on published literature the MIC values baseline and during therapy are low and therefore acquired antifungal resistance does not explain persistence of infection in these patients. The pathogen level microbiological response for *C. albicans* and *C. glabrata* was 12/13 (92.3%) and 18/21(85.7%), respectively. Patient #38-301 had proven *C. krusei* fungemia at the time of death following 14 days of therapy. Blood cultures were negative from day 2 through to day 8, and became positive with *C. krusei* from day 9 to 14.

TABLE 10. PATIENTS WITH MICROBIOLOGICAL PERSISTENCE AT THE END OF IV THERAPY (MICRO-ITT POPULATION)

Patient	Number of Days of IV Therapy	Site of Infectiona	Baseline Pathogen	Rel Day of Last Positive Cultureb	Baseline Anidulafungin MIC (mg/L)	Catheter Removed
12-301*	9	Blood	*C. glabrata*	8	0.004c	Yes
20-302	10	Blood	*C. albicans*	8	≤ 0.002d	Yes
38-301*	14	Blood	*C. krusei*	16 (+2)	0.015d	Yes

a: All had multiple positive baseline cultures.
b: In baseline site.
c: MIC at end of IV therapy was 0.008 mg/L.
d: MIC at end of IV therapy was the same as baseline.
* patient died
Source: Data from Appendix16.2.1, Listing 1.1; Appendix 16.2.4, Listing 2.8; Appendix 16.2.6, Listings 4.3 and 4.4; Appendix 16.2.8, Listing 6.8

Table 11. Prevention of Late Complications

Prevention of Complications	Anidulafungin (N=31) n (%)
	N = 31
Developed endophthalmitis during study *	1 (3.2)
	N = 8
Positive *Candida* culture from a sterile site at 6 weeks [1]	0

[1]Only include patients that are global success at 2 weeks and have a 6 week culture done within the 6 week visit window (regardless of baseline Candida species).

*Patient 12-305 received 3 days of anidulafungin which was stopped due to an accelerated junctional rhythm and was stopped due to investigator discretion. The patient had a history of atrial fibrillation. The patient had a lapse in antifungal therapy for 3 days and was then commenced on fluconazole. Endopthalmitis was diagnosed on day 2 of fluconazole therapy. Blood cultures were positive for *C. albicans and C glabrata* on Nov 9th and 10th, and no growth on the 13th, 14th, 15th and 22nd of November, 2004.

Medical officer's comment
This case of endophthalmitis may not be attributable to a failure of anidulafungin therapy due to the 72 hour lapse in antifungal therapy.

Global success based on central catheter removal status
A total of 16 of 31 (51.6%) patients had fungemia related to a central catheter. 15/16 (93.7%) had the catheter removed. One had the central catheter changed over a guide wire.

SAFETY
The median exposure to study drug was 14 days in the ITT population. Twenty- six (78.8%) patients received IV anidulafungin and 7(21.2%) patients received anidulafungin followed by oral fluconazole.

Table 12. Extent of exposure to study drug

Number of Days of IV Study Drug Category or Statistic	(N=33) n (%)
3 to 10	9 (27.3)
11 to 14	12 (36.4)
15 to 21	9 (27.3)
22 to 28	3 (9.1)
Mean	13.85
SD	5.68
Median	14.00
Minimum, Maximum	3, 28

Exposure to IV study drug is calculated as Stop date – Start date + 1 day.
Source:Data from Section 14.3, Table 3.1.1.

Adverse Events
Serious adverse events were reported in 57.6% of patients. Two patients had a serious adverse event that was thought to be related to study drug, and both cases were confounded by co-morbid conditions and concomitant medications. Approximately 33% of patients had an adverse event reported as possibly or probably related to study drug. Two (6.1%) of patients had drug discontinued due to an adverse event. There were no cases of QT prolongation, hepatic failure or anaphylaxis due to study drug. There were seven deaths in the study, Table 15. Following a review of the case reports none of the deaths were found to be related to anidulafungin

TABLE 13. OVERALL SUMMARY OF ADVERSE EVENTS (ITT POPULATION)

Patients with:	(N=33) n (%)
≥1 AE	33 (100.0)
≥1 AE of mild severity	28 (84.8)
≥1 AE of moderate severity	27 (81.8)
≥1 AE of severe severity	16 (48.5)
≥1 AE related to study drug	11 (33.3)
≥1 AE leading to study drug discontinuation	2 (6.1)
≥ 1 related AE leading to study drug discontinuation	1 (3.0)
≥ 1 SAE	19 (57.6)
≥ 1 related SAE	2 (6.1)
Death	7 (21.2)

Note: A patient who experienced multiple events was counted once for "Patients with at least one AE".
Source: Data from Section 14.3, Table 3.5.

All Cause Mortality

Seven (21.2%) patients died during the study period and 26 (78.8%) patients survived. The median time to death was 13 days. Death was associated with invasive candidiasis in one case per the investigator assessment. Two patients had an autopsy, and neither had histopathologic or culture evidence of invasive candidiasis. Two patients had evidence of *Candida* on culture at the time of death- these 2 patients did not have an autopsy.

Table 14. Patients with positive cultures at time of death

Patient ID #	Culture/day	Stated Cause of death	Day of death [1]
02-302	*C. krusei* On Day 35 +18	Acute renal failure	Day 39 (+22)
38-301	*C. krusei* On Day 16 +2	Hodgkin's disease/ T cell leukemia	Day 16 (+2)

[1] Study day of death is relative to start date of study drug. If death occurred after the end of treatment, then an additional number of days post-therapy will be included and designated by a plus(+) in front of the number e.g., 12(+5).

Table 15. All Cause Mortality

Patient ID	Treatment Arm	Date of Death	Study Day [1]	Cause of Death	Attributable to IC/Candidemia **Investigator**	Attributable to IC/Candidemia **FDA reviewer**	Culture Status at Death	Autopsy Performed	Evidence of Candida
02-301	Anidulafungin	[redacted]	8(+1)	right heart failure secondary to lung disease	No	No	Growth	Yes	No
02-302	Anidulafungin	[redacted]	39(+22)	acute renal failure	Yes	Yes	Growth	No	
12-301	Anidulafungin	[redacted]	10(+1)	cardiorespiratory arrest	No	Yes	Unknown *	No	
20-301	Anidulafungin	[redacted]	13(+3)	cardiac arrest	No	No	No Growth	No	
24-301	Anidulafungin	[redacted]	4(+1)	pseudomonas sepsis	No	No	No Growth	Yes	No
38-301	Anidulafungin	[redacted]	16(+2)	hodgkin's disease, t-cellleukemia	No	No	Growth	No	
61-301	Anidulafungin	[redacted]	22(+1)	heart failure-sepsis-renal failure	No	No	No Growth	No	

[1] Study day of death is relative to start date of study drug. If death occurred after the end of treatment, then an additional number of days post-therapy will be included and designated by a plus(+) in front of the number e.g., 12(+5).
* patient 12-301 has *C. glabrata* fungemia 2 days prior to day of death

Patient ID # 02-302; This was a 50 year old male who presented with an obstructed bowel on [redacted]. The patient was admitted to the study with an APACHE II score of 27, critically ill. On [redacted], anidulafungin was administered for treatment of *C. albicans* isolated from a central catheter blood culture. The patient developed a seizure after anidulafungin infusion on day 11 of IV anidulafungin therapy. On day 16 [redacted]) of IV therapy, blood cultures (peripheral & central catheter) grew *C. parapsilosis*. Amphotericin B –lipid-complex was commenced. On [redacted] the patient developed respiratory distress and hypotension. On [redacted] blood cultures were negative and Amphotericin B –lipid-complex was stopped due to renal failure. Blood cultures on [redacted] were positive for *C. krusei* and *S. aureus*. The investigator attributed the cause of death to bacteremia and fungemia. No autopsy was performed.

Medical officer comment

The MO agrees that the bacteremia and fungemia was the most likely cause of death in this patient.

Patient ID # 12-301

This was a 38-year-old white female with metastatic adenocarcinoma who was admitted into the study with an Apache II score of 19. She was hospitalized on [redacted] for hyponatremia, dehydration and sepsis. Blood cultures from the [redacted] remained positive for *C. glabrata*. She expired of cardio-respiratory arrest on [redacted]

Medical officer's comment

The C. glabrata fungemia most likely contributed to the cause of death in this case.
The seven deaths were considered by the medical reviewer to be unrelated to anidulafungin.

All Adverse Events

The most frequently reported adverse events were a raised alkaline phosphatase, nausea, hypoglycemia, hypokalemia, and pyrexia.

Table 16. All Adverse events reported in the ITT population

	(N = 33)
Adverse Event	n (%)
Alkaline phosphatase increased	9 (27.3)
Nausea	8 (24.2)
Hypoglycemia	6 (18.2)
Hypokalaemia	6 (18.2)
Pyrexia	6 (18.2)
Abdominal distension	5 (15.2)
Hypotension	5 (15.2)
Vomiting	5 (15.2)
ALT increased	4 (12.1)
Anaemia	4 (12.1)
AST increased	4 (12.1)
Clostridium colitis	4 (12.1)
Constipation	4 (12.1)
Dyspnoea	4 (12.1)
Fluid overload	4 (12.1)
Gastritis	4 (12.1)
Headache	4 (12.1)
Insomnia	4 (12.1)
Thrombocytopenia	4 (12.1)
Abdominal pain	3 (9.1)
Anxiety	3 (9.1)
Back pain	3 (9.1)
Bacteraemia	3 (9.1)
Bradycardia	3 (9.1)
Chest pain	3 (9.1)
Cough	3 (9.1)
Diarrhoea	3 (9.1)
Hypomagnesaemia	3 (9.1)
Sepsis	3 (9.1)
Urinary tract infection	3 (9.1)
Atrial fibrillation	2 (6.1)
Blood creatinine increased	2 (6.1)
Cardiac arrest	2 (6.1)
Cardio-respiratory arrest	2 (6.1)
Cellulitis	2 (6.1)
Cholecystitis	2 (6.1)
Confusional state	2 (6.1)
Convulsion	2 (6.1)
Depression	2 (6.1)
Dizziness	2 (6.1)
Enterococcal bacteremia	2 (6.1)
Fall	2 (6.1)
Flank pain	2 (6.1)
Hyperkalaemia	2 (6.1)

Hypophosphataemia	2 (6.1)
Hypovolaemia	2 (6.1)
Infusion site reaction	2 (6.1)
Leukocytosis	2 (6.1)
Loose stools	2 (6.1)
Metabolic acidosis	2 (6.1)
Necrosis	2 (6.1)
Oedema periorbital	2 6.1
Pain in extremity	2 (6.1)
Pericardial effusion	2 (6.1)
Pleural effusion	2 (6.1)
Rash	2 (6.1)
Rash pruritic	2 (6.1)
Rectal haemorrhage	2 (6.1)
Renal insufficiency	2 (6.1)
Rigors	2 (6.1)
Skin laceration	2 (6.1)
Systemic *Candida*	2 (6.1)
Urinary retention	2 (6.1)
Wheezing	2 (6.1)
Wound infection *Staphylococcus*	2 (6.1)

Source: Data from Section 14.3, Table 3.7.

Related adverse events are summarized in table 17.

Table 17. **Related Adverse events (ITTpopulation)**

Adverse Event	(N = 33) n (%)
Patients with at least one related AE	11 (33.3)
Total number of related AEs[a]	16 (4.8)
ALT increased	1 (3.0)
AST increased	1 (3.0)
Back pain	1 (3.0)
Blood ALKP increased	1 (3.0)
Blood bilirubin increased	1 (3.0)
Blood creatinine increased	1 (3.0)
Constipation	1 (3.0)
Convulsion	1 (3.0)
Diarrhoea	1 (3.0)
Flushing	1 (3.0)
Hypokalaemia	1 (3.0)
Loose stools	1 (3.0)
Platelet count decreased	1 (3.0)
Rash maculopapular	1 (3.0)
Rash pruritic	1 (3.0)
Thrombocytopenia	1 (3.0)

Note: If a patient had multiple occurrences of the same event, the event with the least complimentary relationship is presented and the patient was counted once for the event.
a: Numerator and denominator are AEs/total AEs.
Data from Section 14.3, Table 3.10.

Overdosage

One patient (56-301) received an accidental overdose of 400 mg anidulafungin as a loading dose. The patient was asymptomatic, but had a minimal transient elevation of bilirubin. Total bilirubin parameters were as follows: 1.9 mg/dL at baseline/screening (normal range 0.1 – 1.1 mg/dL); 2.1 mg/dL on study day 2; 1.2 mg/dL later on study day 2; 0.9 mg/dL on study day 3; 0.2 mg/dL on study day 7. The patient did not experience any hypersensitivity reactions of rash, dyspnea, hypotension, urticaria,

This was a 37 yo white male who underwent a colon resection/colostomy for a perforated diverticulum and required surgical interventions for an anastomtic leak on study day, -4,-3,-2, and -1 (staged abdominal repair). Peritoneal fluid grew *C. albicans*.

Medical officer's comment

Transient rises in bilirubin are not uncommon in surgical ICU patients who have had multiple abdominal surgical interventions and concomitant antibacterial drugs.

Serious Adverse Events

The most common serious adverse events were cardio-respiratory arrest, convulsion, fluid overload, and renal insufficiency.

Table 18.

SERIOUS ADVERSE EVENTS

Serious Adverse Event	(N = 33) n (%)
Cardio-respiratory arrest	2 (6.1)
Convulsion	2 (6.1)
Fluid overload	2 (6.1)
Renal insufficiency	2 (6.1)
Accidental overdose	1 (3.0)
Adult T-cell lymphoma/leukemia	1 (3.0)
Blood creatinine increased	1 (3.0)
Candida sepsis	1 (3.0)
Cardiac arrest	1 (3.0)
Cardiac failure	1 (3.0)
Chest pain	1 (3.0)
Cholecystitis	1 (3.0)
Escherichia bacteremia	1 (3.0)
Fall	1 (3.0)
Gastric perforation	1 (3.0)
Gastrointestinal hemorrhage	1 (3.0)
Haemodialysis	1 (3.0)
Hodgkin's Disease recurrent	1 (3.0)
Hypovolaemia	1 (3.0)
Mental status changes	1 (3.0)
Pneumonia aspiration	1 (3.0)
Pseudomonal sepsis	1 (3.0)
Renal failure acute	1 (3.0)
Respiratory distress	1 (3.0)
Sepsis	1 (3.0)
Urinary retention	1 (3.0)
Ventricular fibrillation	1 (3.0)

Source: Data from Section 14.3 Table 3.14.

Related Serious Adverse Events

Two patients in the study had a serious adverse event and both recovered.

Table 19. Related Serious Adverse Events

Patient ID	Sex	Age	SAE	Start Day*
02-302	Male	50	Convulsion	11
25-304	Male	48	Blood creatinine increased	4 (+1)

*Relative to start day of study medication with an additional "(+X)" to indicate days after stopping study medication. Source: Data from Appendix 16.2.7, Listing 5.5.

Two patients in the study had a serious adverse event and both recovered. Both cases were critically ill and had confounding factors that made attribution to anidulafungin therapy inconclusive.
One patient, ID #25-304, developed increased creatinine on day 3 of anidulafungin therapy. This was thought to be related to anidulafungin by the investigator. However, on review of this case, the clinical reviewer found that this case had abnormal renal function prior to anidulafungin therapy and the increased creatinine could also be associated with muscle injury due to a lower limb degloving injury and fracture, and limb surgeries.

Patient 25-304	**Study Day ***	**Creatinine (mg/dL)**	**BUN (mg/dL)**
Normal Range		**0.8-1.3**	**8.0-22.0**
Screen	1	1.0	22
End of IV	3	1.7 H CS	27 H
2 week FU	18 (+15)	1.7 H CS	21
6 week FU	52 (+49)	1.1	19

The second patient, ID 02-302, (liver disease and acute bowel obstruction) was admitted to the study with an Apache score of 27. During hospitalization, he experienced hypotension and renal failure with subsequent transfer to the intensive care unit for intubation and hemodialysis. He was commenced on anidulafungin therapy for *C. albicans* candidemia. He had a seizure following anidulafungin infusion on study day 11; on the same day, the patient developed respiratory acidosis, pulmonary edema and sepsis related to candidemia due to *C. parapsilosis*. All of these concomitant events could have contributed to seizure activity in this patient.

Discontinuations from study drug

Two patients discontinued study drug due to an adverse event.

Table 20. Adverse events leading to discontinuation from study drug

Patient ID	Sex	Age (years)	Event	Start Day*	Severity	Outcome
02-302	M	50	*Candida* sepsis	16	Severe	Ongoing
25-304	M	48	Blood creatinine increased	4 (+1)	Moderate	Recovered

* Relative to start day of study medication with an additional "(+X)" to indicate days after stopping study medication.
Source: Adapted from Data from Appendix 16.2.4, Listing 2.1, Appendix 16.2.7, Listing 5.4.

Summaries for these patients, ID # 02-302, and 25-304 are discussed above under the section , Related Serious Adverse Events." Both cases were confounded and could not be definitively attributed to anidulafungin.

Possible Infusion and Hypersensitivity Events

Table 21. Possible infusion events during IV therapy (ITT population)

Event	N = 33 n (%)
Dyspnea	4 (12.1)
Flushing / Hot flushes	1 (3.0)

Source: Data from Section 14.3, Table 3.7, and Appendix 16.2.7, Listing 5.3

Table 22. Possible hypersensitivity during IV therapy (ITT)

Event	N = 33 n (%)
Pruritus	1 (3.0)
Rash[a]	4 (12.1)

a: includes all forms
Source: Data from Section 14.3, Table 3.7 and Appendix 16.2.7, Listing 5.3

Medical officer comment
Flushing/ hot flushes of the skin have been previously reported with other echinocandins. See integrated analysis of safety for further information re infusion associated reactions.

Electrocardiography findings - Adverse events
No QT abnormalities were documented during therapy. Two female patients, aged 32 and 38yo had EKG abnormalities thought to be unrelated to anidulafungin. Both patients were critically ill and received several concomitant medications as well as mineral supplements (calcium gluconate and potassium acetate). The AE was on going at the end of the study and study drug was not discontinued.

Hepatobiliary Adverse Events

Three (9.1%) patients had hepatobiliary adverse events. See results for patient ID #25-304 who experienced a transient rise in total bilirubin following an overdosage of study drug.

Table 23. Hepatobiliary Adverse Events

Patient ID	Event	Intensity	Study Drug?	Action Taken	Outcome
02-302	Cholecystitis	Moderate	Unlikely	Non-pharm Rx added, New drug Rx added	Ongoing
07-302	Biloma	Mild	No	None	Ongoing
52-301	Cholecystitis	Moderate	No	Non-pharm Rx added, New drug Rx added, New or prolonged hospitalization	Recovered

Source: Data from Section 14.3, Table 3.6 and Appendix 16.2.7, Listing 5.3.

Laboratory Adverse Events

Hematology

Table 24. Percentage (%) of patients with potentially clinically significant changes in hematology values from baseline

Parameter	Day 3	On Therapy[a]	End of IV Therapy	End of Oral Therapy	2 Week Follow-up	6 Week Follow-up
Hemoglobin	N=30	N=27	N=32	N=6	N=23	N=18
Low, Decrease (n,%)	0	3 (11.1)	1 (3.1)	0	0	1 (5.6)
Hematocrit	N=30	N=27	N=33	N=6	N=23	N=18
Low, Decrease (n,%)	0	3 (11.1)	1 (3.0)	0	0	1 (5.6)
Platelet Count	N=30	N=27	N=33	N=6	N=23	N=18
Low, Decrease (n,%)	2 (6.7)	0	2 (6.1)	0	1 (4.3)	1 (5.6)
WBC	N=30	N=27	N=33	N=6	N=23	N=18
High, Increase (n,%)	0	3 (11.1)	2 (6.1)	0	0	0
Lymphocytes	N=26	N=26	N=29	N=6	N=21	N=16
Low, Decrease (n,%)	1 (3.8)	1 (3.8)	2 (6.9)	0	0	0
Bands	N=20	N=23	N=25	N=5	N=16	N=12
High, Increase (n,%)	1 (5.0)	1 (4.3)	0	0	0	0

a: Includes patients with a value after Day 3 but before End of IV Therapy.
Note: N is the number of patients included in the analysis for the specified parameter at the specified visit. Percentages are based on the number of patients in the ITT population who have a baseline value and a post-baseline value for the specified parameter at the specified visit. Post-baseline potentially clinically significant changes still within normal range are not included.
Data from Section 14.3, Table 3.20.

Table 25. Percentage (%) of patients with potentially clinically significant changes in chemistry values from baseline

Parameter	Day 3	On Therapy[a]	End of IV Therapy	End of Oral Therapy	2 Week Follow-up	6 Week Follow-up
Creatinine	N=31	N=28	N=33	N=6	N=24	N=17
High, Increase (n,%)	0	0	1 (3.0)	0	0	0
BUN [b]	N=30	N=28	N=33	N=6	N=24	N=17
High, Increase (n,%)	0	0	0	0	1 (4.2)	0
AST	N=23	N=26	N=28	N=6	N=17	N=17
High, Increase (n,%)	0	1 (3.8)	0	0	0	1 (5.9)
Alkaline Phosphatase	N=23	N=26	N=28	N=6	N=17	N=17
High, Increase (n,%)	1 (4.3)	4 (15.4)	7 (25.0)	1 (16.7)	5 (29.4)	3 (17.6)
Glucose	N=31	N=28	N=33	N=6	N=23	N=16
Low, Decrease (n,%)	0	0	0	0	1 (4.3)	0
Potassium	N=31	N=28	N=33	N=6	N=24	N=17
High, Increase (n,%)	0	0	0	1 (16.7)	0	0
Low, Decrease (n,%)	1 (3.2)	1 (3.6)	0	0	0	1 (5.9)
CO_2	N=30	N=28	N=33	N=6	N=24	N=17
Low, Decrease (n,%)	0	0	1 (3.0)	0	0	0

a: Includes patients with a value after Day 3 but before End of IV Therapy.
b: If BUN was not available then urea value was used.
Note: N is the number of patients included in the analysis for the specified parameter at the specified visit.
Percentages
are based on the number of patients in the ITT population with a baseline value and a post-baseline value for the specified parameter at the specified visit. Post baseline potentially clinically significant changes still within normal range are not included.
Data from Section 14.3, Table 3.23.

Hepatic Chemistry

No patient, at any time during the study, had ALT > 5 x ULN or had AST > 10 x ULN.
No patient developed ALT >3 x ULN + Total Bilirubin >1.5 x ULN during the study. Four patients had abnormal hepatic chemistry at baseline

Table 26. Number (%) of patients with abnormal hepatic chemistry parameters

Parameter Criterion	Baseline	Day 3	On Therapy*	End of IV Therapy	End of Oral Therapy	2-Week Follow-up	6-Week Follow-up
Patients with ALT >3xULN + T. Bili. >1.5xULN	N=33 1 (3.0)	N=23 0	N=26 0	N=28 0	N=6 0	N=17 0	N=17 0
Patients with ALT >3-5xULN	N=33 1 (3.0)	N=23 0	N=26 0	N=28 0	N=6 0	N=17 0	N=17 0
Patients with AST >3-5xULN AST >5-10xULN	N=33 0 1 (3.0)	N=23 1 (4.3) 0	N=26 2 (7.7) 0	N=28 0 0	N=6 0 0	N=17 0 0	N=17 1 (5.9) 0

* "On Therapy" includes patients with a value after Day 3 but before End of IV Therapy.
Note: Percentages are based on the number of patients in the ITT population who have appropriate laboratory values at the specified visit. N is the number of patients in the analyses for the specified parameters at the specified visit.
Source: Data from Section 14.3, Table 3.24.

Table 27. Summary of Transitions In Hepatobiliary Parameters from Baseline at any Study Visit (ITT Population)

Baseline Category	≤3xULN	>3-5xULN	>5-10xULN	>10xULN
ALT	N=33	N=0	N=0	N=0
<=3xULN	32 (97.0)	0	0	0
>3-5xULN	1 (3.0)	0	0	0
AST	N=29	N=4	N=0	N=0
<=3xULN	28 (96.6)	4 (100.0)	0	0
>3-5xULN	0	0	0	0
>5-10xULN	1 (3.4)	0	0	0
Alkaline Phosphatase	N=24	N=2	N=5	N=2
<=3xULN	24 (100.0)	1 (50.0)	3 (60.0)	1 (50.0)
>3-5xULN	0	1 (50.0)	2 (40.0)	1 (50.0)

Note: "N" is the number of patients with a value for baseline and at least one on-treatment value (irrespective of study visit) for the specified parameter. All percentages are based on the presented "N" values.
Source: Data from Section 14.3, Table 3.25.

Table 28. Hepatic Chemistry findings reported as adverse events (ITT)

Adverse Event	(N = 33) n (%)
Blood ALKP increased	9 (27.3)
ALT increased	4 (12.1)
AST increased	4 (12.1)
Blood bilirubin increased	1 (3.0)

Data from Section 14.3, Table 3.6.

Most patients had baseline ALT, AST, and ALKP values ≤ 3 x ULN that remained in this range throughout the study. Six of eight patients with raised alkaline phosphatase had elevated alkaline phosphatase levels at baseline. The medical officer concluded that these elevations were unlikely to be to study drug. See hepatic safety analysis for entire data base for further analysis of hepatic events.

TABLE 48. PATIENTS WITH ABNORMAL TRANSITIONS IN HEPATOBILIARY PARAMETERS

Patient ID	Sex	Age	Abnormal Parameter	Test Result [a]	Baseline Result (Normal Range)	Day of Onset [b]	Day of Resolution[c]
02-302	M	50	ALKP (>3-5 X ULN)	449	96 (50-130)	14	Ongoing
02-305	M	38	ALKP (>10-20X ULN)	1678	451 (50-130)	26 (+11)	Ongoing
02-306	M	66	ALKP (>10-20X ULN)	1659	308 (50-130)	21 (+4)	Ongoing
07-302	M	57	ALKP (>5-10X ULN)	1054	288 (30-120)	15 (+1)	Ongoing
12-304	M	63	AST (>3-5 X ULN)	149	96 (15-46)	3	35 (+14)
20-301	M	59	AST (>3-5 X ULN)	118	61 (0-37)	5	7
20-302	F	32	ALKP (>5-10X ULN)	600	149 (39-117)	58 (+48)	Ongoing
			AST (>3-5X ULN)	98	11 (0-31)	58 (+48)	Ongoing
25-302	F	46	ALKP (>5-10X ULN)	915	620 (50-135)	15 (+1)	Ongoing
25-304	M	48	ALKP (>5-10X ULN)	724	433 (50-135)	18 (+15)	Ongoing
38-301	F	23	ALKP (>5-10X ULN)	774	92 (38-126)	14	Died
52-301	M	67	AST (>3-5 X ULN)	116	21 (5-35)	36	43 (+1)

a: Highest recorded test result

b: Number of days since the first dose of study drug/+ number of days after the last dose of study drug

c: Day that test result returned to a value within the normal range

Note: Narratives for all other patients' enzyme elevations are in Section 14.3.2.

Data from Appendix 16.2.8, Listing 6.5.

Safety Conclusions
Anidulafungin was generally well tolerated in this critically ill population.

Conclusions
The efficacy and safety results in this study were similar to the comparative randomized study, VER002-9. The results are supportive of the data in the comparative study.

APPENDIX B

Appears This Way
On Original

22 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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/s/

Elizabeth OShaughnessy
2/17/2006 02:46:11 PM
MEDICAL OFFICER

Leonard Sacks
2/17/2006 03:02:32 PM
MEDICAL OFFICER

TEAM LEADER REVIEW
OF COMPLETE RESPONSE

Applicant: Vicuron/Pfizer

Application number: 21,632

Generic Name: Anidulafungin

Proposed Trade Name: [illegible]

Pharmacologic Category: Anti-fungal

Dosage Form: Vials for injection

Route of Administration: Intravenous

Date of Submission: May 27, 2005

PDUFA goal date: November 27,2005

Medical officer: Leonard Sacks

Anidulafungin is an injectable echinocandin that has been developed for the treatment of Candida infections. A prior new drug application for this product for the indication of esophageal candidiasis was deemed approvable, pending satisfactory demonstration of hepatic safety and ancillary efficacy data (see approvable letter May 21, 2004). In a complete response, the applicant has satisfactorily addressed these concerns.

- A new randomized comparative study of anidulafungin in the treatment of invasive candidasis (Ver 002-9) provided adequate ancillary evidence of anti-candida activity. Anidulafungin was statistically superior to fluconazole in study Ver002-9.
- A comprehensive review of hepatic safety across all studies in the NDA including 292 new anidualfungin-treated patients not previously submitted revealed the following:
    - One case of liver failure in a patient with multiorgan failure due to causes other than the study drug
    - Ten of the 690 anidulafungin treated patients and 8 of the 426 fluconazole treated patients were identified with ALT>=2xULN and concurrent bilirubin >=1.5x ULN. After excluding patients with predominant cholestasis or clear cases of shock liver (not reflective of drug-related hepatocellular injury), 4 anadulafungin-treated and 7 fluconazole treated cases remained. Upon review of these patient narratives, 2 anadulafungin-treated cases and one fluconazole treated case were considered possibly drug related hepatocellular injury, but confounded by concurrent disease or concomitant therapy. The potential for liver injury is addressed in the precautions section of the label (see below).
- Based on higher relapse rates for esophageal candidiasis treated with anidulafungin compared with fluconazole in the initial submission, the applicant accepted the Division's recommendation that anidulafungin be given a second line indication for esophageal candidiasis. The recommended labeling emphasizes the need to consider high relapse rates when selecting anidulafungin as initial therapy for esophageal candidiasis.
- [redacted]

The efficacy of anidulafungin in esophageal candidiasis was previously reviewed (See NDA review, Dr Ibia). Satisfactory efficacy was demonstrated at the test of cure visit although relapse rates after completion of therapy were higher for patients treated with anidulafungin than for those treated with fluconazole.

Synopsis of safety and efficacy in invasive candidiasis

The applicant performed a prospective randomized study of anidulafungin compared to fluconazole in the treatment of patients with invasive candidiasis.

Two hundred and fifty six patients were randomized to receive anidulafungin (200mg loading dose then 100mg IV daily) or fluconazole (400mg IV daily). Study drug was to

be given for at least 10 days, following which oral fluconazole days could be substituted once the patients had shown a clinical and microbiological response.
One hundred and twenty seven patients who were evaluable for clinical and microbiological outcome received anidulafungin and 118 received fluconazole.
The diagnosis of invasive candidiasis in most patients was based on a positive blood culture (>90%). In 26 patients, positive cultures were obtained from a normally sterile site (mostly from peritoneal or pleural fluid), together with clinical signs of infection.
There were no cases of candida endophthalmitis, endocarditis or hepatosplenic candidiasis.
In both arms serious underlying illnesses were present including sepsis, cancer and post surgical complications.
A test of clinical and microbiological cure (global response) upon completion of IV therapy with the study drug demonstrated superiority of andulafungin when compared to fluconazole. This trend was sustained through 6 weeks of follow up.

Table 1: Global response at end of IV therapy in Micro ITT population*

	Anidulafungin	Fluconazole	Difference (95% CI)
Global success	96/127 (75.6%)	71/118 (60.2%)	15.42 (3.85, 26.99)

*all patients with a baseline isolate who received at least one does of study drug

Table 2: Global response at the end of IV therapy in efficacy evaluable population*

	Anidulafungin	Fluconazole	Difference (95% CI)
Global success at end of IV Rx	90/103 (87.4%)	68/91 (74.4%)	12.65% (1.66, 23.65)
Global success after 6 weeks of follow up	59/79 (74.7%)	43/69 (62.3%)	12.36 (-2.56, 27,29

* all patients with a baseline isolate who received at least one does of study drug and were evaluable at the follow up visit

One hundred and fifty five patients had central lines which were removed.
Of 7 patients in whom central lines were not removed, anidulafungin treatment resulted in a clinical cure in 3/3 and fluconazole in 3/4.

Microbiological efficacy:
Most cases were caused by *C. albicans*. Limited efficacy data was available for other candida species (see below)

GLOBAL SUCCESS AT END OF IV THERAPY BY PATHOGEN(MICRO-ITT POPULATION)

Baseline Species	**Anidulafungin** n/N (%)	**Fluconazole** n/N (%)

All species	92/119 (77.3)	65/106 (61.3)
Candida albicans	60/74 (81.1)	38/61 (62.3)
Non-*albicans* species	32/45 (71.1)	27/45 (60.0)
Candida glabrata	9/16 (56.3)	11/22 (50.0)
Candida tropicalis	13/14 (92.9)	4/8 (50.0)
Candida parapsilosis	7/11 (63.6)	10/12 (83.3)
Candida guilliermondii	2/2 (100.0)	--
Candida krusei	0/1 (0.0)	--
Candida lusitaniae	1/1 (100.0)	1/2 (50.0)
Candida famata	--	1/1 (100.0)

Note: N=Number of patients with a single baseline pathogen.

Safety

In this study, the safety of anadualfungin was similar to the safety of fluconazole (see review by Dr O'Shaughnessy). The most frequent adverse events seen on anidulafungin, regardless of attributability included hypokalemia (25.2%), nausea (24.4%) and diarrhea (18%). In particular no serious cases of hepatic injury were seen.

Synopsis of integrated hepatic safety data

In order to identify all cases with potentially significant hepatic injury among patients treated with multiple therapeutic intravenous doses of anidulafungin, the applicant in consultation with FDA applied a strategy to screen all reported liver function tests in the NDA for elevations of ALT, AST, bilirubin or alkaline phophatase >2XULN. Among 690 patients treated with multiple IV doses of anidulafungin >=50mg/day and 426 patients treated with fluconazole >=100mg per day, 294 patients (42.6%) and 152 patients (35.6%) were respectively identified using this screening criterion.

From these, 10 of the 690 anidulafungin treated patients and 8 of the 426 fluconazole treated patients were identified with ALT>=2xULN and concurrent bilirubin >=1.5x ULN. After excluding patients with predominant cholestasis or clear cases of shock liver (not reflective of drug-related hepatocellular injury), 4 anadulafungin-treated and 7 fluconazole treated cases remained. Upon review of these patient narratives, 2 anadulafungin-treated cases and one fluconazole treated case were considered possibly drug related hepatocellular injury, but confounded by concurrent disease or concomitant therapy.

These findings, together with previously recognized animal findings, and mild transient hepatic enzyme elevations seen in healthy volunteer studies, form the basis for recommending the following labeled precaution.

> Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with [ ] In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with [ ], clinically significant hepatic abnormalities have occurred. Isolated cases of significant hepatic dysfunction, [ ] in patients; a causal relationship to [ ] has not been established.

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/s/

Leonard Sacks
11/25/2005 02:07:54 PM
MEDICAL OFFICER

Applicant: Vicuron/Pfizer

Application number: NDA 21-632

Generic Name: Anidulafungin

Proposed Trade Name: [ ]

Pharmacologic Category: Anti-fungal

Dosage Form: Vials for injection

Route of Administration: Intravenous

Date of Submission: May 27th, 2005

PDUFA goal date: November 27th, 2005

CLINICAL REVIEW COMPLETE RESPONSE NDA 21-632

DRUG NAME: Anidulafungin

CLINICAL REVIEWER: Elizabeth M. O'Shaughnessy, M.D.

Division of Special Pathogens and Transplant Products

Table of Contents

EXECUTIVE SUMMARY

Recommendation on Approval

The submitted material constitutes a complete response to the action letter of May 2004. From a clinical perspective, anidulafungin can be approved for the indication of esophageal candidiasis. The additional safety data provided in the complete response is supportive of the safety data provided in the original NDA 21-362. The additional efficacy data in the complete response adequately addresses the FDA's request for additional efficacy data in another form of invasive *Candida* infection.

Brief Overview of Background

The division had two main concerns regarding the original NDA 21-632, i.e. that a satisfactory risk- benefit ratio had not been shown for the use of anidulafungin as first-line therapy for esophageal candidiasis (study VER002-4) because of the higher relapse rate at two week follow-up in the anidulafungin treated patients compared to the fluconazole treated patients. From a safety standpoint, there may have been a signal for hepatoxicity based on one case in the anidulafungin treated group. Therefore, the division requested additional clinical data to further characterize the safety and efficacy of anidulafungin in invasive candidiasis.

To address the FDA's concerns, the sponsor submitted data from a large, adequate and well-controlled clinical trial in patients with invasive candidiasis as the pivotal study in the complete response submission. A hepatologist's safety report and an integrated summary of safety across the entire clinical program were also submitted. The sponsor addressed the concern regarding relapse rates off- therapy by requesting a second-line indication for anidulafungin in esophageal candidiasis.

Overview of Invasive Candidiasis Study, VER002-9

This is a phase 3, double-blind, randomized, multi-center study of the safety and efficacy of anidulafungin vs. fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis and prevention of complications.
Patients with candidemia and other forms of invasive candidiasis who met the inclusion and exclusion criteria were randomized (1:1 ratio) to treatment with either anidulafungin IV (200mg loading dose followed by 100mg daily maintenance dose) or fluconazole IV (800mg loading dose and 400mg maintenance dose).
The main criteria for inclusion were: *Documentation of Candida infection by:* 1) Candidemia: at least one blood culture positive for yeast (in the absence of other demonstrated foci of infection); OR 2) other forms of invasive candidiasis: positive culture for yeast from a specimen from a normally sterile site with or without a positive blood culture; positive yeast culture from a newly-placed drain in a normally sterile site; OR 3) any positive blood culture for yeast plus ophthalmic examination consistent with *Candida* endophthalmitis. AND *Clinical features by at least one of the following:*

fever; hypothermia; systolic blood pressure of less than 100 mmHg or a decrease in systolic blood pressure of at least 30 mmHg from baseline; signs or symptoms of candidemia/invasive candidiasis; radiologic findings consistent with a diagnosis of invasive candidiasis. AND *expected hospitalization for at least 3 days.*

Main criteria for exclusion were: 1) Received > 48 hours of systemic antifungal therapy for the *Candida* infection for which they were enrolled. 2) Received prophylactic administration of fluconazole, itraconazole, or voriconazole for more than one week within 30 days prior to enrollment. 3) Known *Candida krusei* infection or suspected *Candida* osteomyelitis, endocarditis, or meningitis. 4) Had abnormal pre-specified liver tests: ALT or AST > 10 x ULN; total bilirubin > 5 x ULN. 5) Life expectancy ≤ 72 hours.

Patients were stratified according to their APACHE II score (≤ 20 and > 20) and absolute neutrophil count (≤ 500 and > 500/mm^3). Study drug was to be administered for minimum treatment duration of 14 days. The maximum treatment duration of study drug was not to exceed 42 days. Qualifying patients in either group could be switched to oral fluconazole after at least 10 days of IV therapy.

Efficacy was evaluated based on clinical and microbiological responses. The primary efficacy endpoint was the global response (combined clinical and microbiological) in the microbiological intent-to-treat (Micro-ITT) population at the end of IV therapy. Safety was evaluated by the collection and analysis of data on adverse events (AEs), clinical laboratory tests, 12-lead ECGs, and temperature. An independent Data Safety Monitoring Board (DSMB) was formed to review safety data.

Efficacy

There were 127 patients in the anidulafungin arm, and 118 patients in the fluconazole arm in the primary efficacy population, Micro-ITT population. The study population comprised of equal numbers of males and females. The average age of the anidulafungin-treated patients was 57 years compared with 59 years for the fluconazole-treated patients. Common co-morbid diseases for both treatment groups included endocrine/metabolic disorders (~50%), bacterial sepsis and recent surgical history (both ~40%), and neoplastic diseases (~20%).

The majority of patients in the study (>90%) of patients had candidemia. Approximately 50% of patients had candidemia related to a central venous catheter.

A global response to treatment was a combined clinical and microbiological response. Anidulafungin was found to be superior to fluconazole (75.6% versus 60.2%), (CI 15.42% (3.85-26.99) for the treatment of invasive candidiasis/candidemia in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population. Anidulafungin-treated patients had higher rates of global, clinical, and microbiological success at all time points on therapy and at the end of therapy. In all secondary efficacy analyses, anidulafungin was superior to (end of IV therapy, end of all therapy and 2-week FU time points), or at least as effective as (end of oral therapy and 6-week FU time points), fluconazole consistent with the primary efficacy analysis.

GLOBAL RESPONSE AT END OF IV THERAPY (MICRO-ITT POPULATION)

	Anidulafungin	Fluconazole		
Response	(N = 127)	(N = 118)	Between-Group	
Outcome	n (%)	n (%)	Difference[a]	(95% CI)
Success	96 (75.6)	71 (60.2)	15.42%	(3.85 , 26.99)
Failure	31 (24.4)	47 (39.8)		

a: Anidulafungin minus fluconazole. Source: Data from study report VER002-9, Section 14.2, Table 2.1.1

This study provided satisfactory additional evidence of the efficacy of anidulafungin for invasive *Candida* Infection.

Dosing
The proposed dose of anidulafungin is 100mg IV loading dose followed by 50mg IV daily maintenance dose. Please see Dr. E. Ibia's original review of NDA21-632 for further details.

Safety
No major safety concerns emerged during the review of the pivotal invasive candidiasis study. In this study, the dose (100mg IV daily) of anidulafungin was double the dose (50mg IV daily) administered in the esophageal candidiasis study.
Fewer anidulafungin-treated patients (30, 22.9%) than fluconazole-treated patients (39, 31.2%) died during and shortly after the study. The proportion of patients with study drug related adverse events was similar, approximately 25% in the two treatment arms. Fewer anidulafungin-treated patients (15, 11.5%) than fluconazole-treated patients (27, 21.6%) experienced an adverse event that led to discontinuation of study drug. Serious adverse events were reported by 49.6% and 56.8% of patients respectively, in the anidulafungin and fluconazole treatment groups. Serious adverse events were considered by the investigator to be possibly related to treatment for two patients in each study arm. In the anidulafungin arm there was one case of atrial fibrillation and one patient with a convulsion. The clinical reviewer concluded that study drug attribution in both of these cases was unlikely. No cases of anaphylaxis, or QT prolongation occurred.

Hepatic adverse events were more common in the fluconazole arm of the study. No cases of hepatic failure occurred in the study. There were 5(3.8%) patients in the anidulafungin group and 8 (6.3%) patients in the fluconazole group who reported clinical adverse events categorized under the hepatobiliary category. Four of these events were severe in intensity and all four occurred in fluconazole-treated patients. One hepatic AE that was considered possibly related to study drug occurred in an anidulafungin-treated patient (ongoing cholestasis in a patient with disseminated candidiasis). However, this case was confounded because both disseminated candidiasis and concomitant medications could have caused the hepatic abnormalities that were observed.
The safety data suggests that anidulafungin at a dose of 100mg IV daily has a safety profile similar to that of fluconazole 400 mg IV daily in a population of patients with invasive candidiasis, mostly candidemia.
Similar to other approved echinocandins, it is important to monitor hepatic chemistry during therapy with anidulafungin. Patients who develop abnormal liver function tests during therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy.

Overview of Study of Azole Refractory Mucosal Candidiasis
In this open label study of refractory oropharyngeal and esophageal candidiasis, 12 patients with endoscopically proven disease (EC) were identified among the 19 patients enrolled. Review of the individual cases indicated that only 5 of the 12 patients had received an adequate trial of azole therapy, defined as fluconazole 200 mg x 14 days, and were refractory to treatment at the time that they entered the study and were switched to anidulafungin. The remaining seven

patients either had inadequate prior azole therapy or experienced recurrent disease after successful treatment with fluconazole rather than refractory disease.
In the five evaluable patients with refractory EC, complete endoscopic resolution occurred in 2 patients and improvement was seen in 3 patients, although symptoms were recorded as cured in all 5 patients. Microbiological eradication was documented in the two patients who were cured and persistence was seen in the remaining three patients.

Hepatic Safety Across The Clinical Development Program

Exposure to multiple IV doses of Anidulafungin
In the clinical program, there were 690 patients who received multiple IV doses of anidulafungin at ≥50 -100mg/day, and 426 patients received multiple doses of fluconazole at ≥ 100mg per day. A total of 292 of the 690 anidulafungin-treated patients were from studies completed after the submission of the original NDA 21-632. Most of these patients received at least two weeks of therapy.

Cases of hepatic dysfunction
There were no cases of hepatic failure in the new studies completed since the original NDA 21-632. Of the 690 anidulafungin-treated and 426 fluconazole-treated patients who had repeated IV doses, 294 (42.6%) and 152 (35.7%) patients respectively had a two- fold elevation in AST, ALT, ALKP, or total bilirubin. Patients who had baseline hepatic chemistry abnormalities were included. The elevations in hepatic transaminases tended to be gradual and to resolve off therapy. These abnormalities were observed at twice the dose proposed for the treatment of esophageal candidiasis. Many of the cases were confounded by intercurrent illness and concurrent medications.
A hepatology consultant (Dr [redacted] selected cases conforming to the conservative criteria of an ALT rise to > 2 X ULN, **and** concomitant or up to one month delayed rise in bilirubin >1.5 X ULN as representing potential hepatocellular injury. Ten of 690 (1.4%) anidulafungin-treated patients and 8 of 426 (1.9%) fluconazole-treated patients were identified according to these criteria. The individual case reports for these patients were reviewed by the clinical reviewer. Patients who had predominant cholestasis and clear cases of shock liver were not regarded as cases of drug-induced hepatocellular injury.
Following exclusion of these, there were four Hy's rule cases in the anidulafungin group, and seven in the fluconazole group. Two of 294 (0.68%) cases among the anidulafungin-treated patients were considered by the clinical reviewer to be possibly related to anidulafungin and confounding factors that might account for the findings were present in both. One of 152 (0.66%) fluconazole-treated cases was considered by clinical reviewer to be possibly drug-related.
Many of the patients in the clinical studies were critically-ill. The majority of these patients had co-morbid conditions and concomitant medications that could affect hepatic function. Many of the patients had abnormal baseline hepatic chemistry.

A recommendation regarding monitoring of liver function is included in the current proposed label, similar to that in the labels for other FDA approved echinocandins.
In summary, a few cases of significant hepatic dysfunction, or hepatitis were reported in patients receiving anidulafungin during the clinical development program. However, a causal relationship to anidulafungin was not established.
As with other FDA approved echinocandins, monitoring of hepatic function should be monitored at baseline and during anidulafungin therapy. Significant elevations in hepatic chemistry should prompt an assessment of the risks and benefits of continuing therapy.

Risk /Benefit Analysis

Anidulafungin has a favorable risk/benefit ratio in the treatment of esophageal candidiasis.
It has shown efficacy in esophageal candidiasis, and in candidemia. Safety concerns are mainly related to hepatic effects. Information on the hepatic safety of this drug from a review of the complete response, including 292 new patients treated with anidulafungin who were not included in the original NDA, did not reveal any cases of significant hepatic dysfunction where a causal relationship to anidulafungin could be established. These cases were confounded by co-morbid conditions and concomitant medications. Anidulafungin appears to be similar to other echinocandins in its hepatic and overall safety profile.
Anidulafungin has an advantage over some other echinocandins in that it does not interact with a number of immunosuppressive drugs commonly used in clinical oncology and organ transplant medicine. For example, concomitant use of caspofungin and cyclosporine is not recommended. Monitoring of tacrolimus levels and appropriate tacrolimus dose adjustments are required for patients receiving caspofungin and tacrolimus. Monitoring of sirolimus levels is recommended for patients receiving sirolimus and micafungin. In drug interaction studies, there were no interactions between anidulafungin was combined with tacrolimus or cyclosporine. No drug interactions have been demonstrated between anidulafungin and voriconazole. In the era of combination antifungal therapy, this lack of interaction with a commonly prescribed triazole such as voriconazole is advantageous. Please refer to the original review of NDA 21-632 for additional information on risk/benefit analyses in HIV patients with esophageal candidiasis.

High relapse rates seen in the original submission remain a concern, see table below.
Consideration of the relapse rates off-therapy in the esophageal candidiasis study should be taken into account when considering anidulafungin as initial therapy.

Endoscopic Success and Relapse Rate in the Clinically Evaluable Population in Study VER002-4

Response	Anidulafungin N= 231	Fluconazole N= 236	Treatment difference	95% CI
Endoscopic Success n, (%)	225 (97.4)	233 (98.7)	-1.3%	-4.2%, 1.6%
Failure n, (%)	6 (2.6)	3 (1.3)		
Endoscopic Relapse off-therapy. n/N (%)	120/225 (53.3%)	45/233 (19.3%)	34	(25.3, 42.7)

INTRODUCTION

Drug Established Name: Anidulafungin
Trade Name: [ ]
Drug Class: Echinocandin
Proposed Indication: Esophageal Candidiasis

An "approvable" letter for the indication of esophageal candidiasis was sent to the sponsor, Vicuron Pharmaceuticals Inc. on May 21st, 2004. The sponsor submitted a complete response to the approvable letter on May 27th, 2005. This document is a review of the sponsor's complete response. The division had two major concerns regarding the original NDA 21-632, i.e. that a satisfactory risk benefit ratio had not been shown for the use of anidulafungin as first-line therapy for esophageal candidiasis (study VER002-4) because of the higher relapse rate at two week follow-up in the anidulafungin treated patients compared to the fluconazole treated patients. From a safety standpoint, there may have been a possible signal for hepatoxicity based on one case in the anidulafungin group. Therefore, the sponsor was asked to provide additional data on the safety profile of anidulafungin and also to provide further evidence of the efficacy of anidulafungin in invasive *Candida* infection.
In the approvable letter, the FDA stated that this deficiency may be addressed by providing the following:

- *"In order to address the concern regarding hepatic toxicity you must provide additional clinical data to further characterize the safety of anidulafungin. This information should be from clinical studies evaluating anidulafungin at doses and durations that equal or exceed the esophageal candidiasis regimen.*
- *In order to address the concern regarding the efficacy of anidulafungin, you must provide additional clinical data to address the observed high relapse rate and/or provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent. This concern may be addressed by submitting results from one or both of the following types of studies:*

  - *An adequate and well- controlled study evaluating alternative regimens of anidulafungin to reduce the relapse rates in patients with esophageal candidiasis. This study would need to demonstrate both efficacy at the end of therapy and durability of response at the two-week follow-up visit to support the labeling of anidulafungin as initial therapy in esophageal candidiasis.*

AND/OR

  - *An adequate and well- controlled study demonstrating the efficacy of anidulafungin in another infection due to Candida spp. This study would provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent; however, it would not support labeling of anidulafungin as initial therapy in esophageal candidiasis because this type of study would not address the high relapse rate observed in study VER002-4."*

In response to the approvable letter (5/21/2004), the sponsor took the alternative option of, *"An adequate and well-controlled study demonstrating the efficacy of anidulafungin another infection due to Candida spp. This study would provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent; however, it would not support labeling of anidulafungin as*

initial therapy in esophageal candidiasis because this type of study would not address the high relapse rate observed in studyVER002-4."
Table 1a summarizes the sponsor's response to the deficiencies listed in the "approvable" letter, May 2004. Table 1b summarizes the list of studies submitted.

Table 1a

FDA requirements regarding deficiencies in NDA 21-632 as listed in approvable letter, May 2004.	**Complete Response from Sponsor**
To address concern regarding possible hepatoxicity, additional safety data was requested.	Hepatic safety data from: • Study VER002-9: A Phase 3, Double-Blind, Randomized, Multi-Center, Study of the Safety and Efficacy of **Anidulafungin vs. Fluconazole** in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications. • Safety reports for study, VER002-7, 11, 12, 13, and 15. • Hepatologist's expert report for studies: VER002-4, VER002-5, VER002-6, VER002-7, VER002-9, VER002-12, VER002-13, and VER002-15. • Integrated summary of hepatic safety and all safety data across the entire clinical development program for anidulafungin.
To address FDA request for additional evidence of efficacy in another form of invasive candidiasis	VER002-9: A Phase 3, Double-Blind, Randomized, Multi-Center, Study of the Safety and Efficacy of **Anidulafungin vs. Fluconazole** in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications. VER002-11: A Phase 2 Open Label Study of the Safety and Efficacy of Intravenous Anidulafungin as a Treatment for Azole-Refractory Mucosal Candidiasis.
To address FDA concern regarding the relapse rate off therapy	A claim for a second line indication for esophageal candidiasis following the division's statement that further data on efficacy would not address the high relapse rate in study VER002-4 (NDA21-632), and thus would not support labeling as initial therapy.

Table 1b: Studies submitted in Complete Response

VER002-7	An Open Label Non-Comparative Study of the Safety and Efficacy of Intravenous Anidulafungin Plus AmBisome® [(Amphotericin B) Liposome for Injection] as a Treatment for Invasive Aspergillosis
VER002-9	A Phase 3, Double-Blind, Randomized, Multi-Center, Study of the Safety and Efficacy of Anidulafungin vs. Fluconazole in the Treatment of Patients with Candidemia and Other Forms of Invasive Candidiasis and Prevention of Complications.
VER002-11	A Phase 2 Open Label Study of the Safety and Efficacy of Intravenous Anidulafungin as a Treatment for Azole-Refractory Mucosal Candidiasis
VER 002-12	Phase 1/2 Study of the Safety, Tolerance, and Pharmacokinetics of Anidulafungin in Immunocompromised Children with Neutropenia
VER 002- 13	Phase 1, Double-Blind, Multiple Dose, Randomized, Crossover, Pharmacokinetic Interaction Study Between VFEND(Voriconazole) and Anidulafungin
VER002-15	Phase 1, Open-Label, Single-Sequence, Pharmacokinetic Interaction Study Between Oral Tacrolimus (Prograf®, Fujisawa Healthcare, Inc.) and Intravenous Anidulafungin in Healthy Male Subjects
VER002-4 (post hoc analysis)	A post hoc analysis of the original NDA 21-632: A Phase 3 Randomized, Double-Blind, Double-Dummy Non-Inferiority Study of the Safety and Efficacy of IntravenousAnidulafungin vs. Oral Fluconazole in the Treatment of Patients with Esophageal Candidiasis

Pivotal study

Study VER002-9 is the pivotal study in the complete response. Efficacy and safety data including hepatic safety is reviewed for this study, VER002-9. The majority (~90%) of the study subjects in this study were critically ill patients with candidemia. Patients in this study received double the dose of anidulafungin administered in the esophageal candidiasis study in the original NDA 21-632.

Additional Safety Data

Additional safety data is provided in smaller studies VER002-7, VER002-11, VER002-12, VER002-13, and VER002-15, and VER002-9b. Studies VER002-7 and VER002-11 were on going at the time of the original NDA, and 120 -day safety updates from these two studies were previously reviewed. Study VER002-11, is an open-label non-comparative trial of anidulafungin in refractory esophageal and oropharyngeal candidiasis. The sponsor has not sought the indication of *refractory* esophageal or oropharyngeal candidiasis. VER002-9b is an open-label continuation of the pivotal invasive candidiasis study (VER002-9) and was submitted as part of NDA 21-948. Study VER002-12, is a pharmacokinetic study in a neutropenic pediatric population; the differences in dosage and population in this study is not comparable to the

original NDA (an adult population with invasive esophageal candidiasis (mostly AIDS). The sponsor has not sought a pediatric indication in the current label. Studies VER002-13, and VER002-15 are drug interaction studies of anidulafungin combined with voriconazole or tacrolimus, respectively. Safety data provided is mainly for drug combinations; independent safety data for anidulafungin alone is limited due to the nature of the studies.

Appears This Way
On Original

BACKGROUND RELATED TO NDA 21-632

To support the proposed indication in the original NDA 21-632 submitted in 2003, the sponsor presented data from:

- a large, adequate and well-controlled study in patients (mostly AIDS) with esophageal candidiasis, studyVER002-4. The proposed dose and duration was 100 mg intravenously of anidulafungin on the first day of therapy followed by 50 mg intravenously daily for 14 to 21 days. In addition to this pivotal study, the applicant presented supportive data from three smaller phase 2 studies as follows:
- a dose–ranging study of 36 patients with esophageal candidiasis randomized to receive one of two doses of anidulafungin smaller than the dose used in the pivotal study.
- an on-going (in 2003), open-label, non-randomized study of anidulafungin 100/50 mg IV daily for 14 to 21 days for the treatment of fluconazole-refractory mucosal candidiasis (data from 5 patients are included in the NDA (2 of these 5 patients had esophageal candidiasis) of a planned total enrollment of 20 patients).
- an open label, randomized, dose-ranging study that enrolled 120 patients (40 on each of the three arms) with invasive candidiasis (nearly 90% with candidemia alone) treated with anidulafungin doses of 100/50 mg, 150/75 mg, or 200/100 mg intravenously daily for a minimum duration of 14 days and up to 42 days. (Most of these patients were immunocompromised.

Summary of efficacy findings of original clinical reviewer for NDA 21-632
The primary clinical reviewer for the phase 3 esophageal candidiasis study NDA 21-632 concluded that at the end of therapy, anidulafungin met the protocol specified endpoint with 97.8% endoscopic success in the evaluable patients at the end of therapy compared to 98.7% for fluconazole. The following table from the original review of NDA21-632 summarizes the clinical response in patients with esophageal candidiasis.

Table 27 from original review: **Clinical Response at End of Therapy and Follow-Up in Clinically Evaluable Patients**

		Anidulafungin	Fluconazole	Treatment difference	95% CI	p-value[1]
Clinically evaluable at end of therapy population		249	255			
End of therapy visit	Success n, (%)	246 (98.8)	254 (99.6)	-0.8%	-2.4%, 0.7%	
	Cure	242 (97.2)	250 (98.0)			
	Improvement	4 (1.6)	4 (1.6)			
	Failure n, (%)	3 (1.2)	1 (0.4)			
Clinically evaluable at follow-up population		233	229			
Follow-up visit	Success n, (%)	130 (55.8)	190 (83.0)	-27.2%	-35.2%, -19.2%	< 0.001
	Cure	125 (53.6)	186 (81.2)			
	Improvement	5 (2.1)	4 (1.7)			
	Failure n, (%)	103 (44.2)	39 (17.0)			
	Failure	100 (42.9)	38 (16.6)			
	Indeterminate	3 (1.3)	1 (0.4)			

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 24 of Study Report).

Clinical response at end of therapy in clinically evaluable populations

The original reviewer concluded that "Clinical success rates in the clinically evaluable patients at EOT were very high for arms, 98.8% and 99.6% for anidulafungin and fluconazole arms, respectively. Majority of the patients on both arms were clinical cures (97.2% and 98.0% for anidulafungin and fluconazole arms, respectively). Clinical response rates in the clinically evaluable patients at follow up remained durable at 83.0% for fluconazole, but less durable for anidulafungin (55.8%). The difference between these response rates was -27.2% with a 95% confidence interval around the difference -35.2% and -19.2% ($p < 0.001$)." (Source: original review of NDA 21-632)."

"Additional efficacy data from an ongoing phase 2 study, VER002-11 in refractory esophageal candidiasis (5 patients) was supportive of the activity of anidulafungin and results were consistent with findings from the larger phase 3 study in NDA 21-632."
(Source: original review of NDA 21-632).

Clinical response at follow-up in clinically evaluable populations

Anidulafungin was statistically significantly inferior to fluconazole in the proportion of patients with sustained success at follow-up. At the two week post-therapy follow-up visit anidulafungin was found to be statistically significantly inferior to fluconazole for the endpoint of endoscope success 39.0% (anidulafungin) vs. 69.1% (fluconazole), Table 27. The majority of patients were HIV- infected patients not on HAART.

The original reviewer commented that, "*The clinical course of disease for patients with esophageal candidiasis can be a course of relapsing or recurrent disease over the weeks to months following successful treatment, particularly in a population such as was studied in trial that received very limited treatment for AIDS before and during the trial*".

Mycological response in patients with Esophageal Candidiasis

The mycological responses at follow-up paralleled clinical and endoscopic responses at the follow-up time point. Successful mycological outcome (proven eradication and presumed eradication) were 54.2% (96/177) and 76.4% (136/178) on the anidulafungin and fluconazole arms respectively. Table x is from the original review, NDA21-632.

***Table 37 from original review*: Per-Pathogen Mycological Outcome at End of Therapy in Mycologically Evaluable Population**

		Anidulafungin	**Fluconazole**
All species	N	189	198
	Success n, (%)	165 (87.3)	186 (93.9)
	Proven eradication	161 (85.2)	182 (91.9)
	Presumed eradication	4 (2.1)	4 (2.0)
	Failure n, (%)	24 (12.7)	12 (6.1)
	Proven persistence	24 (12.7)	12 (6.1)
	Presumed persistence	0	0
C. albicans	N	177	182
	Success n, (%)	155 (87.6)	172 (94.5)
	Proven eradication	152 (85.9)	168 (92.3)
	Presumed eradication	3 (1.7)	4 (2.2)
	Failure n, (%)	22 (12.4)	10 (5.5)
	Proven persistence	22 (12.4)	10 (5.5)
	Presumed persistence	0	0
C. non-*albicans*	N	12	16
	Success n, (%)	10 (83.3)	14 (87.5)
	Proven eradication	9 (75.0)	14 (87.5)
	Presumed eradication	1 (8.3)	0
Failure n, (%)		2 (16.7)	2 (12.5)
Proven persistence		2 (16.7)	2 (12.5)
Presumed persistence		0	0

Source: Adapted from Applicant's Submission (NDA21-632, Study VER002-4 Table 28 of Study Report)

The proven eradication rates were higher in the fluconazole arm than in the anidulafungin arm (87.3% versus 93.9%). The eradication rates for non-*albicans* species were higher in the fluconazole arm; non-*albicans* species accounted for 6.3%, and 8.1% of the isolates in the anidulafungin and fluconazole arms, respectively.

INVASIVE CANDIDIASIS STUDY VER002-9

This is a phase 3, double-blind, randomized, multi-center, study of the safety and efficacy of anidulafungin vs. fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis and prevention of complications.

Efficacy Conclusions

Anidulafungin was found to be statistically superior to fluconazole in the primary efficacy analysis. There were 127 patients in the anidulafungin arm and 118 patients in the fluconazole arm in the primary efficacy population in the anidulafungin arm, 96 patients (75.6%) had a global success versus 71 patients (60.2%) in the fluconazole arm. The between group difference in global success rate (anidulafungin minus fluconazole) was 15.42% (95% CI 3.85, 26.99). A global success was defined as a combined clinical and microbiological success.

Clinical review methods

Clinical, safety, and laboratory data was reviewed as well as individual case reports for all deaths and serious adverse events including hepatic serious adverse events. The currently approved labels for two echinocandins, micafungin and caspofungin were reviewed. The majority of tables and some text in the review are taken directly from the applicant's study report.

Overview of Study VER002-9
This phase 3, double-blind (third-party unblinded) randomized, multi-center, comparative study enrolled and treated 256 patients, 131 received 100 mg IV anidulafungin, and 125 received 400 mg IV fluconazole for 14 to 42 days, in the ITT population. Candidemia was present in more than 90% of patients in both study arms. Approximately half of all patients had invasive candidiasis related to an IV catheter per investigator attribution. Most patients had a single baseline pathogen; *Candida albicans* and *Candida glabrata* were the baseline pathogens most frequently isolated.

Protocol Objectives

Primary objective:

- to determine if anidulafungin is at least as effective as fluconazole with respect to the global response (combined clinical and microbiological response at the end of IV therapy) for the treatment of patients with a diagnosis of candidemia and/or other forms of invasive candidiasis

Secondary objectives:

- to compare anidulafungin with fluconazole in this patient population for safety profile, the prevention of late infections and the clinical and microbiological efficacy at various time points

Study Design

As described previously, this study is a phase 3, double-blind, randomized, multi-center, study of the safety and efficacy of anidulafungin vs. fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis. All patients were to receive the study medication for minimum treatment duration of 14 days from the time of the last negative culture and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Total treatment duration was not to exceed 42 days.
Patients in either group were permitted to switch to oral fluconazole (400 mg/daily) after at least 10 days of IV treatment if the following criteria were met,

- the patient was afebrile for at least 24 hours;
- the patient was able to tolerate oral medications;
- the last blood culture was negative for *Candida* species;
- reduction of signs and symptoms of the *Candida* infection such that the investigator felt it was appropriate to switch to oral fluconazole (oral fluconazole was not to be given as prophylaxis).

The patients were followed for safety through the 6-week follow-up (FU) visit.

Randomization and stratification
Patients were stratified by APACHE II score and absolute neutrophil count. Patients were randomly assigned in a 1:1 ratio.

Dosage
The dose of anidulafungin (200mg loading dose/100mg daily) selected for this study was determined by phase 1 dose-ranging studies in healthy subjects, and by a phase 2, dose-ranging study (VER002-6) of anidulafungin in patients with invasive candidiasis, Table 2. The dose of fluconazole 400mg IV daily used is the highest approved dose for invasive fungal infections.

TABLE 2. GLOBAL SUCCESS IN VER002-6

	Anidulafungin Dose			
Population	50 mg/day	75 mg/day	100 mg/day	All Patients
Time point	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Micro-ITT				
End of Therapy	25/37 (68)	30/40 (75)	27/39 (69)	82/116 (71)
2-week Follow-up	14/37 (38)	23/40 (58)	20/39 (51)	57/116 (49)
Efficacy Evaluable				
End of therapy	21/25 (84)	27/30 (90)	25/28 (89)	73/83 (88)
2-week Follow-up	13/18 (72)	22/26 (85)	20/24 (83)	55/68 (81)

Data from VER002-6 Clinical Study Report Appendix 14 and Appendix 18

Medical officer's comment:
The dose of anidulafungin (200mg IV loading dose followed by 100mg IV daily) in this study is twice the dose (100mg IV loading dose followed by 50mg daily) used in the original esophageal candidiasis study, VER002-4. The original clinical reviewer for NDA21-632 commented that the dose in the esophageal candidiasis study may have been too low based on subsequent data from dose ranging studies.

Study Sites
Study sites were located in six countries: 33 in the United States, 8 in Canada and 4 in Europe. Forty-seven of 70 investigators enrolled patients. The majority of patients were enrolled in the United States. The number of treated patients by country was USA (185), Canada (59), Belgium (2), Germany (3) and Italy (6) and Netherlands (1). The largest number of patients (25) was enrolled at a single site in Canada.

Inclusion Criteria
Patients were eligible to participate in the study if they met the following inclusion criteria.
1. Diagnosis of candidemia or other forms of invasive candidiasis from a blood culture or a culture of a specimen from a normally sterile site, preferably taken within 96 hours before study entry. The diagnosis was to be based on the following,

- Candidemia defined as at least one blood culture positive for yeast (in the absence of other demonstrated foci of infection).
- Other forms of invasive candidiasis defined as a positive culture for yeast from a specimen from a normally sterile site with or without a positive blood culture; positive yeast culture from a newly-placed drain in a normally sterile site; or any positive blood culture for yeast plus ophthalmic examination consistent with *Candida* endophthalmitis. Positive yeast cultures from urine or a positive yeast culture from sputum (including those obtained by bronchoalveolar lavage or an endotracheal aspirate) did not qualify as a positive culture.

AND
At least one of the following:

- A fever defined as an oral/tympanic temperature ≥ 100.4°F (38.0°C), rectal temperature ≥101.4°F (38.6°C) or an axillary temperature ≥ 99.4°F (37.4°C)
- Hypothermia defined as a temperature less than 96.8°F (36.0°C)

- A systolic blood pressure of less than 100 mm Hg or a decrease in systolic blood pressure of at least 30 mm Hg from baseline
- Signs or symptoms of candidemia/invasive candidiasis
- Radiologic findings consistent with a diagnosis of invasive candidiasis

2. Male or female ≥ 16 years of age. Some sites may have enrolled patients ≥ 18 years of age only.
3. Willing and able to give signed informed consent, or have a legally authorized representative who was willing and able to give consent.
4. Reliable and willing to make themselves available for the duration of the study and to abide by the study restrictions.
5. Expected hospitalization for at least three days.

Exclusion Criteria

Patients were excluded from this study if any of the following criteria were present:
1. Female patients who were pregnant, lactating, or planning a pregnancy during the course of the study, or who were of child bearing potential and not using an acceptable method of birth control (i.e. surgically sterile, intrauterine device, oral contraceptive plus barrier contraceptive, hormone delivery system *plus* barrier contraceptive or condom in combination with contraceptive cream, jelly or foam). Patients were to continue contraceptive methods during the study and for at least 30 days after receiving their last treatment.
2. Patients who received greater than 48 hours of systemic antifungal therapy for the *Candida* infection for which they were enrolled.
3. Patients who failed antifungal therapy with any systemic antifungal for this episode of candidiasis/candidemia. Recurrence within 2 weeks was considered failure of previous therapy.
4. Patients who received prophylactic administration of fluconazole, itraconazole, or voriconazole for more than one week within 30 days prior to enrollment.
5. Patients who had received and who were to continue to receive terfenadine or cisapride.
6. Patients who had, at any time, previously received anidulafungin.
7. Known *Candida krusei* infection.
8. Patients with any of the following abnormal laboratory values: Bilirubin > 5 times the upper limit of normal (ULN), AST or ALT > 10 times the ULN.
9. Patients who required continued treatment with another systemic antifungal agent [oral nonabsorbable azoles (e.g., clotrimazole troches) were permitted].
10. Patients with poor venous access that would preclude IV drug delivery or multiple blood draws.
11. Patients with a known hypersensitivity to echinocandin therapy or azole therapy.
12. Patients who participated in a study of an investigational drug or device (without any FDA approved indications) within four weeks of study entry. The investigational use of antiretroviral agents and the investigational use of licensed agents were permitted if the patient was on a stable regimen for four weeks prior to study start.
13. Life expectancy ≤ 72 hours.
14. Patients on hemodialysis unable to tolerate the volume of fluid in the placebo infusion on non-dialysis days.
15. Patients with suspected *Candida* osteomyelitis, endocarditis, or meningitis.

16. Patients with prosthetic devices at a suspected site of infection were excluded unless the device was removed at study entry or soon after randomization. [Hemodialysis shunts (AV fistulae) could remain in situ)].
17. Patients with a prosthetic heart valve or vascular graft suspected to be the site of the *Candida* infection and positive blood cultures.

Medical officer's comments
The inclusion criteria were adequate to include patients with invasive candidiasis and to exclude patient with colonization with Candida species. Patients with known Candida krusei infection were excluded because of its resistance to fluconazole. It is appropriate to exclude patients with culture positive urine and sputum including BAL cultures as these cultures are often due to yeast colonization, and not true infection with Candida. "A positive yeast culture from a newly-placed drain in a normally sterile site" is an inclusion criterion; positive cultures from newly placed drains may not always indicate a true Candida infection, however the numbers of cultures from newly placed drains in this study are small and do not affect the overall results.

Duration of treatment

Treatment was for a minimum of 14 days to maximum of 42 days. Treatment could switch to oral fluconazole following ≥ 10 days of IV therapy. If patients had a fluconazole-nonsusceptible baseline *Candida* strain other than *C. krusei,* the investigator determined if the patient should continue on the study medication.

Schedule of Monitoring

Table 3 : Schedule of monitoring for study patients	STUDY SCHEDULE*									
	Screen[1]	**Daily through EOT**	**D3**	**D4**	**D7**	**Day 10**	**D8-D41**	**End of IV Therapy**	**End of Oral Therapy (if applicable)**	**Follow-up Visit Week 2 (± 2 days)**	**Long term Follow-up Week 7 (± 1 wk)**
Informed Consent	X										
Medical and Medication History, APACHE II	X										
Physical Examination[2]	X										
Temperature	X	X								X	X
Assessment of clinical signs & symptoms of											
	X					X		X	X	X	X
Candida infection											
Serum Pregnancy Test[4]	X										
Fundoscopic Exam	X[3]							X[3]	X[3]	X[3]	X
Standard 12 lead ECG[5]	X		X								
Blood Cultures[6]	X		X		X	X[7]	X[7]	X	X	X	X
Specimen Culture[7]	X	X									
CBC with Diff[8]	X		X		X		X[8]	X[8]	X[8]	X[10]	X[10]
Chemistry Panel [9]	X		X		X		X[9]	X[9]	X[9]	X[10]	X[10]
Saliva Samples[11]	X			X							
Sampling for Assays for Glucan and *Candida* DNA						X	X				
	X		X								
DNA[12]											
Study Medication		X	X								
Adverse Events		X	X							X	X

1. Screening procedures/assessments were completed before the first dose of study medication.
2. Could occur within 72 hours before the first dose of study medication.
3. Completed only if the baseline fundoscopic examination was positive for endophthalmitis.
4. A serum pregnancy test was performed before the first dose of study medication on women of childbearing potential.
5. ECGs were done before the first dose of study medication and on Day 3, 0-3 hours after the completion of the infusion.

6. *Table 3 contd.*	Screening blood cultures were obtained on all patients. If the screening blood culture was >24 hours before study entry, blood cultures were repeated at baseline. If the screening blood culture was <24 hours before study entry, the baseline blood cultures did not need to be repeated. Blood cultures were be repeated on Day 3, 7, and every three days until negative while on study medication and as clinically indicated
7.	Cultures of other normally sterile sites as clinically indicated.
8.	Hematology: CBC with differential count (RBC, WBC, absolute neutrophil count, platelet count, hemoglobin, hematocrit)
9.	Serum Chemistry: Creatinine, BUN (urea), AST, ALT, alk phos, total bilirubin, albumin, CO2 , NA, K, CL, glucose.
10.	Hematology and Chemistry tests were repeated at the follow-up visits if clinically significantly abnormal on the last day of study medication.
11.	At selected sites, patients had saliva samples obtained at baseline and anytime following the Day 4 dose.
12.	Blood specimens were collected at baseline, Day 3, Day 7, and weekly until the end of study medication and on the last day of study medication.

Screening Blood Cultures

Two aerobic blood cultures from 2 different sites were performed at screening on all patients. Peripheral venipuncture was the preferred method for obtaining blood cultures. If the patient had an indwelling central venous catheter, one blood culture was from a peripheral site if at all possible; the other culture could be drawn from one lumen of the catheter.
Baseline Cultures (other than blood): These were obtained as clinically indicated. The type/site of the culture, the culture results, and date of the culture used for entry into the study were recorded in the case report form.
On-Study Cultures: Blood cultures were obtained on Day 3, Day 7, and every 3 days thereafter until negative while on study medication; at the end of IV therapy; at the end of oral therapy; and at the 2-week and 6-week FU visits from the end of therapy. Additional cultures could be obtained at the Investigator's discretion as clinically indicated. For patients whose baseline isolates (or histological evidence of infection) was obtained from samples other than blood, culture or histology from the same site was repeated as clinically indicated.

Medical officer's comment
The procedures used for obtaining blood cultures in this study are consistent with current guidelines. Current guidelines for suspected iv catheter-related infection state that two blood cultures should be drawn for culture with a least one set drawn percutaneously, (Mermel 2001). A negative blood culture drawn through an i.v. catheter is helpful for excluding catheter-related blood stream infection; in a study of hospitalized patients, catheter and percutaneous blood cultures had a positive predictive value of 63% and 73%, but had a greater negative predictive value of 99% and 98%, respectively, for IV catheter related infection, (de Jardin 1999).

Central Venous Catheter Management
The relationship between the catheter and the invasive candidiasis was based on the investigator's assessment. Insertion and removal dates as well as catheter cultures from insertion site and catheter tip were documented. Central venous catheter removal was guided by currently published recommendations, (Walsh 2002 and Mermel 2001). Current data indicate that catheter removal should generally be considered early in the management of candidemia.

Medical officer's comment
It is not clear what criteria the investigator used to establish the candidemia was catheter- related. The numbers of patients with catheters and the rates of catheter removal were balanced between study arms.

Withdrawal from Study

Patients were free to withdraw from the study at any time for any reason.
Only those patients who died, were lost to follow-up, or refused any further contact with respect to the study was prematurely withdrawn from the study. Patients withdrawn from the study were not replaced, regardless of the reason for withdrawal.

Discontinuation from Study Medication

Patients could have been discontinued from study medication for any of the following reasons: any adverse event (AE); patient noncompliance or unwillingness to comply with the procedures required by the protocol; worsening clinical status (lack of efficacy); absence / presence of certain pathogens; or request by the patient (withdrawal of consent), investigator, or Vicuron.

Study Populations

ITT: All patients who received at least one dose of study medication were included in the intent to treat (ITT) population.
MITT: The primary efficacy population was the Microbiological-ITT population. This population included all patients who received at least one dose of study medication and who had a positive culture from a normally sterile site at baseline for *Candida* species, preferably within 96 hours before entry into the study.
Efficacy Evaluable: The Efficacy Evaluable population was a subset of the Micro-ITT population. Patients in the efficacy evaluable populations had both clinical and microbiological data available for analysis at entry and test of cure visits. There were five distinct groups in the efficacy evaluable population: Efficacy evaluable at Day 10 of IV therapy, at the end of IV therapy, at the end of all therapy (oral and/or IV), at 2-week follow-up, and at 6-week follow-up.

Safety population

All safety analyses were conducted in the ITT population.

Study Endpoints

Primary Endpoint
The primary efficacy endpoint was the global response (based on the clinical and microbiological responses) at the end of IV therapy in the Micro-ITT population.

Patients were assigned a **global response** in the Micro-ITT population as follows:
Success: required both a clinical and microbiological success as described below

Clinical Success

- Cure: Resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or oral fluconazole required to complete the course of therapy. OR
- Improvement: Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or additional oral fluconazole required.

AND

Microbiological success

- Eradication (documented or presumed): Culture was negative for all *Candida* species present at baseline (documented), or culture data were not available for a patient with a successful clinical response (presumed).

Failure:

Clinical failure

- No significant improvement in signs and symptoms, or death due to the *Candida* infection.

Microbiological failure

- Documented or presumed persistence or recurrence of baseline *Candida* infection;superinfection with a new *Candida* species while on study medication; emergence of a new *Candida* species at an original site of infection or at distant, sterile site after study medication completion.
- The sponsor considered the following patients "indeterminate" and evaluated them as failures,
    - patients who received fewer than 3 doses of study medication
    - death not due to the *Candida* infection;
    - withdrawal from study medication for reasons other than failure

Medical officer's comment
In the efficacy evaluable population, the same criteria of success and failure were applied, except that patients with an "indeterminate" response were excluded from the evaluation.

Microbiological Response at the Baseline Pathogen Level

Success:

- Eradication (documented or presumed): Culture was negative for the *Candida* species present at baseline (documented), or culture data were not available for a patient with a successful clinical response (presumed).

Failure:

- Persistence (documented or presumed): The baseline *Candida* species was present in repeat cultures (documented), or culture data were not available for a patient with a clinical response of failure (presumed).
- Recurrence (documented or presumed): The baseline *Candida* species isolated following eradication (documented), or culture data were not available for a patient with a clinical response of failure after a previous response of success (presumed).
- Indeterminate: culture data were not available for a patient with a clinical response of indeterminate.

Secondary Endpoints

Global response at all secondary time points in the Micro-ITT population
Global response at the end of IV therapy in the modified Micro-ITT population
Global response at all time points in the efficacy evaluable population
Clinical response at all time points in the Micro-ITT and efficacy evaluable populations
Patient level microbiological response at all time points in the Micro-ITT and efficacy evaluable populations
Pathogen level microbiological response in the Micro-ITT and efficacy- evaluable populations at the end of IV therapy and 2 week FU time points only.
Death directly attributable to invasive candidiasis/candidemia and all cause mortality

Data Integrity

A total of seven patients in the fluconazole arm were unblinded. None of the patients in the anidulafungin arm were unblinded. Five were unblinded by investigator request and two were accidentally unblinded. Two patients were not protocol evaluable.

Table 4. UNBLINDED PATIENTS

Patient ID	Treatment	Efficacy Evaluable Status
Reason for the Unblinding		
Randomization fax accidentally sent to study coordinator		
25-001	FLU	Yes, study coordinator not involved in efficacy assessment*
73-001	FLU	Yes, study coordinator not involved in efficacy assessment*
Per Investigator request for patients with clinical failure		
02-012	FLU	Yes, not a protocol violation
39-001	FLU	Yes, not a protocol violation
71-001	FLU	Yes, not a protocol violation
Per Investigator request for patients with serious adverse events		
10-002	FLU	No, received only 1 dose of study drug
31-002	FLU	No, received only 1 dose of study drug

* Both study coordinators were removed from care of unblinded patients

Data from Section 16.2.3, Listing 1.5

Efficacy Results

Patient Disposition

Table 5.

Population	**Anidulafungin**	**Fluconazole**	**Reasons for exclusion**
ITT [a]	**131 (100%)**	**125 (100%)**	
Excluded	4	7	Did not have a positive baseline culture for *Candida*
Micro-ITT	**127 (96.9%)**	**118 (94.4%)**	
Excluded [b]	13	12	< 7 days of IV therapy and did not have a clinical response of failure
	7	10	Clinical response of indeterminate at end IV therapy
	3	2	≥ 3 days of prior antifungal therapy
	1	1	Violation of inclusion/ exclusion criteria w/o waiver
	0	2	Patient unblinded and not a clinical failure
Total Excluded	28	34	
Efficacy Evaluable @ end of IV therapy (Primary time point)	103 (78.6%)	91 (72.8%)	
Efficacy Evaluable at 6 Week Follow-up	79 (60.3)	69 (55.2)	See Table 6

a Denominator for all % calculations is N of ITT population in each treatment arm.
b. For all patients who had multiple reasons for exclusion, only the primary reason is listed

The primary efficacy population, the Micro-ITT population, included all patients who received at least 1 dose of study medication and who had a positive culture from a normally sterile site at baseline for *Candida* species. The Micro-ITT population was comprised of 245 patients; 127 (127/131, 96.9%) in the anidulafungin arm and 118 (118/125, 94.4%) in the fluconazole arm.

The Efficacy Evaluable population at the end of IV therapy was a subset of the Micro-ITT population. The percentage of patients evaluable for efficacy was (103)78.6% for the anidulafungin arm compared with 91(72.8%) for the fluconazole arm. Twenty-eight patients in the anidulafungin arm and 34 in the fluconazole arm had protocol violations that led to exclusion from the efficacy evaluable population and the end of IV therapy, Table 5.

Withdrawal from Study

More patients in the fluconazole treatment group in the fluconazole arm withdrew during the six week study periods compared to the anidulafungin treatment group.

Table 6. PATIENT DISPOSITION AND REASONS FOR WITHDRAWAL DURING STUDY PERIOD		
Category	Anidulafungin	Fluconazole
Event	N (%)	N (%)
Intent-to-Treat	131	125
Total completed the study through 6 week follow-up	94 (71.8)	80 (64.0)
Total discontinued from study prior to 6 week follow-up	37 (28.2)	45 (36.0)
Reasons for discontinuation from study prior to 6 week follow-up		
Death	29 (22.1)[a]	38 (30.4)[b]
Patient lost to follow-up	8 (6.1)	7 (5.6)

NOTE: Denominator for all % calculations is N of ITT population in each treatment arm.

a: Patient 27-003 died after the 6-week follow-up period and is not included in this table.
b: Patient 40-014 was counted as completing the study through the 6-week follow-up period on the CRF termination page with a completion date of 11 Aug 2004, although the patient died on the same day and was counted in the number of deaths in the time to death (Section 11.4.8) and safety (Section 12.4) sections.

Table 7. PATIENT DISPOSITION AND REASONS FOR WITHDRAWAL FROM STUDY MEDICATION

Category	Anidulafungin	Fluconazole
Event	N (%)	N (%)
Intent-to-Treat	131	125
Total completed full course of study medication[a]	97 (74.0)	77 (61.6)
Total withdrawn from study medication[b]	34 (26.0)	48 (38.4)
Reasons for withdrawal from study medication		
Adverse Event	12 (9.2)	21 (16.8)
Patient Withdrew Consent	5 (3.8)	4 (3.2)
Patient Noncompliant	1 (0.8)	0
Worsening Clinical Status/Lack of Efficacy	11 (8.4)	16 (12.8)
Investigator Discretion	5 (3.8)	5 (4.0)
Vicuron's Request	0	1 (0.8)[c]
Patient Lost To Follow-Up	0	1 (0.8)

a: Total completed full course of study medication- refers to completion of IV and oral (if applicable) study medication. Note: *Not all patients went onto oral therapy following IV therapy.*
b: For each patient who withdrew from study medication, only 1 reason (the primary) for withdrawal is tabulated.
c: Patient 07-008 had study medication discontinued by Sponsor request due to a diagnosis of cryptococcal meningitis.
Source: Table modified from Section 14.1, Table 1.1.

Medical officer's comment

More patients in the fluconazole arm prematurely discontinued study medication for an adverse event: 21(16.8%) vs. 12 (9.2%) or for lack of efficacy 16 (12.8%) vs. 11(8.4%) compared with the anidulafungin arm, respectively. Withdrawals from study are discussed in more detail in the safety evaluation sections.

Protocol violations in the ITT population

Overall, the most common violation was an indeterminate clinical response at 6-week follow-up visit and indeterminate clinical response at 2-week follow-up visit for patients in both study arms. Slightly more patients in the fluconazole arm compared to anidulafungin arm, 28 (21.4 %) vs. 38 (30.4 %) respectively, had an indeterminate clinical response at the 2 week follow up time point, and at the 6 week follow-up i.e. 36 (27.5%) vs. 43 (34.4%), respectively.

TABLE 8. SUMMARY OF PROTOCOL VIOLATIONS AND DEVIATIONS (INTENT-TO-TREAT POPULATION)

Category	Anidulafungin (N=131)		Fluconazole (N=125)	
Event	n	(%) [a]	n	(%) [a]
Protocol Violations [b]				
Violation of inclusion/exclusion criteria and no waiver granted	1	(0.8)	2	(1.6)
< 7 days of IV therapy and did not have a clinical response of failure	14	(10.7)	16	(12.8)
> 24 h of concomitant systemically absorbed antifungals & not a failure	15	(11.5)	14	(11.2)
Absence of a positive baseline culture for *Candida* spp	4	(3.1)	7	(5.6)
Clinical response of indeterminate at Day 10	21	(16.0)	21	(16.8)
Clinical response of indeterminate at End of IV Therapy	18	(13.7)	26	(20.8)
Clinical response of indeterminate at End of Oral Therapy		0	5	(4.0)
Clinical response of indeterminate at 2 Week Follow-up Visit	28	(21.4)	38	(30.4)
Clinical response of indeterminate at 6 Week Follow-up Visit	36	(27.5)	43	(34.4)
Day 10 clinical assessment not done within Days 9 to 11	1	(0.8)		0
Patient unblinded and not a clinical failure		0	2	(1.6)
Patient received at least 3 days of prior antifungal medication and was not a clinical failure	4 (3.1)		3 (2.4)	
Protocol Deviations [b]				
No Diagnosis Of Candidemia Or Other Forms Of Invasive Candidiasis	4	(3.1)	1	(0.8)
Patient who received greater than 72 hours of prior systemic antifungal therapy	1	(0.8)	2	(1.6)
Bilirubin >5 times the upper limit of normal	1	(0.8)	4	(3.2)
Prosthetic devices at a suspected site of infection		0	2	(1.6)
Prosthetic heart valves or vascular grafts and positive blood cultures.	1	(0.8)	2	(1.6)

a: Denominator for % calculations is N of ITT

b: This table includes all protocol violations and deviations, whether or not they affect evaluability.

For patients with more than one violation and/or deviation, all violations and/or deviations were tabulated

Source: Data from Section 14.1, Table 1.3.1.

Baseline characteristics of the Micro-ITT population.

Demographics

Table 9. CHARACTERISTICS (MICRO-ITT POPULATION)

	Anidulafungin	Fluconazole
Gender, n (%)	N = 127	N = 118
Male	65 (51.2)	60 (50.8)
Female	62 (48.8)	58 (49.2)
Age, years	N = 127	N = 118
Mean (SD)	57 (17.1)	59.2 (16.5)
Median	59	57.5
Min - Max	16 - 89	24 - 91
Ethnic Origin, n (%)	N = 127	N = 118
White	92 (72.4)	87 (73.7)
Black/African American	23 (18.1)	25 (21.2)
Other	12 (9.4)	6 (5.1)
Weight, kg	N = 127	N = 117
Mean (SD)	76.4 (25.5)	76.3 (22.5)
Median	70.4	72.7
Min - Max	35 196.5	40.8 - 159
Apache II Score	N=127	N=118
< 20, n (%)	101 (79.5)	98 (83.1)
> 20, n (%)	26 (20.5)	20 (16.9)
Mean (SD)	15 (7.7)	14.4 (6.8)
Median	14	13
Min - Max	2 - 42	3 - 36
Absolute Neutrophil Count, cells/mm^3	N=127	N=118
> 500, n (%)	124 (97.6)	114 (96.6)
< 500, n (%)	3 (2.4)	4 (3.4)
Mean (SD) [a]	8110.6 (5589.6)	8197.4 (6440.5)
Median [a]	7342.8	6600
Min Max [a]	0 - 26800	0 - 33840

a: For one patient, only ANC category (>500, □500) was known, and therefore this patient was excluded from this summarization of ANC count.
Source: Data from Section 14.1, Table 1.4.1.

All demographic characteristics were well balanced between the two treatment arms. Most patients were white >70%, ≤25% black patients and ≤12% of patients of other ethnic origins. Approximately 20% of anidulafungin-treated patients and 17% fluconazole-treated patients had Apache II scores > 20, indicative of a sick population often found in intensive care units.
Few neutropenic patients were enrolled in this study. Less than 4% of patients in both arms were neutropenic (ANC ≤500). Approximately 20% of anidulafungin-treated patients and 17% fluconazole-treated patients had Apache II scores > 20, indicative of a critically ill population.

Medical Officer's comments

The results of the study may not be applicable to neutropenic patients because of the small numbers of patients with neutropenia in the study.

Underlying disease and risk factors for invasive candidiasis

The study population was well balanced with regard to co morbid conditions and risk factors for invasive candidiasis. There was a 9% difference between the two arms for immunosuppressive therapy; 18 (14%) anidulafungin-treated patients versus 27 (23 %) fluconazole-treated patients received immunosuppression, (p=0.099 by Fisher's exact test). There were more diabetic patients in the anidulafungin arm, 34% versus 25%. Approximately ≤ 10 % of patients had hematopoeitic disorders. Approximately 5 % of patients had transplants, mostly solid organ transplants. Two patients in each arm had bone marrow transplants. In patients who were diagnosed with catheter related invasive candidiasis, catheter removal was more frequent in the anidulafungin arm, 95.2% versus 85.9%. There was no statistically significant difference between these baseline characteristics. See Dr. Dixon's statistical review for further detail.

Table 10. BASELINE CHARACTERISTICS: COMORBIDITIES AND RISK FACTORS (MICRO-ITT POPULATION)

	Anidulafungin	Fluconazole
Characteristic	N = 127	N = 118
Detail	n (%)	n (%)
Comorbid Diseases Assoc. with IC, n (%)		
Endocrine/Metabolic Disorders	68 (53.5)	57 (48.3)
Bacterial Sepsis	58 (45.7)	49 (41.5)
Recent Surgical History	50 (39.4)	55 (46.6)
Neoplastic Disease	28 (22.0)	27 (22.9)
Genitourinary	17 (13.4)	17 (14.4)
Hematopoietic Lymphatic	13 (10.2)	12 (10.2)
Rheumatologic	7 (5.5)	6 (5.1)
Transplantation	7 (5.5)	4 (3.4)[a]
Other	78 (61.4)	80 (67.8)
Invasive Candidiasis Risk Factors, n (%)		
Central venous catheter	99 (78.0)	92 (78.0)
Broad-spectrum antibiotics	88 (69.3)	82 (69.5)
Recent surgery	53 (41.7)	51 (43.2)
Recent hyperalimentation	31 (24.4)	31 (26.3)
Underlying malignant condition	28 (22.0)	25 (21.2)
Immunosuppressive therapy	18 (14.2)	27 (22.9)
Receipt of a transplant	6 (4.7)	4 (3.4)[a]
Other	16 (12.6)	14 (11.9)
Catheter and IC, n (%)		
Invasive Candidiasis related to IV Catheter [b]	N = 127	N = 118
Yes	63 (49.6)	64 (54.2)
If yes, catheter removed[b]	N = 63	N = 64
Yes	60 (95.2)	55 (85.9)

Abbreviation: IC = invasive candidiasis.

a: Five fluconazole-treated patients had transplant in their medical history. For 1 of these patients, the transplant was recorded under "other" rather than "transplant."
b: Per Investigator assessment
Note: The number (%) of patients with neoplastic diseases, recent surgery, and transplants (comorbid conditions) does not exactly match the number (%) of patients with malignancies, recent surgery, and receipt of a transplant (risk factors) because of Investigator discretion in determining what situations were considered risk factors.
Source : Data from Section 14.1, Table 1.4.1.

Prior Antifungal Therapy

In the ITT population, the two arms were well balanced with regard to use of prior antifungal drugs. A large number of patients (>70%) in both arms had fluconazole therapy in the 48hr period prior to the start of the study, Table 11. Patients who received more than 48 hours of systemic antifungal therapy were excluded from the study, as well as those who received prophylactic antifungals for more than 7 days within the 30 days prior to the study. Antifungal agents other than fluconazole were administered to small numbers of patients prior to the study. Six patients received Amphotericin B formulations prior to study in both groups. All patients were evaluable.

Table 11. ANTIFUNGAL MEDICATIONS TAKEN PRIOR TO STUDY THERAPY (ITT POPULATION)

Antifungals, systemic	Prior
Drug	n (%)
Anidulafungin (N=131)	
Any systemic antifungal	93 (71.0)
Fluconazole	82 (62.6)
Caspofungin	8 (6.1)
Amphotericin B, liposome	3 (2.3)
Amphotericin B	3 (2.3)
Voriconazole	1 (0.8)
Fluconazole (N=125)	
Any systemic antifungal	94 (75.2)
Fluconazole	86 (68.8)
Caspofungin	5 (4.0)
Amphotericin B, liposome	1 (0.8)
Amphotericin B	5 (4.0)
Voriconazole	0
Itraconazole	1 (0.8)
Flu cytosine	0

Source: Adapted from Data from Section 14.1, Tables 1.8.1 and 1.8.2.

Sites of infection

The majority > 90% of patients had candidemia. The remainder of patients had *Candida* infection in sterile sites such as peritoneal fluid/ abscess, pancreas, skin, kidney, eye and other sites.

Baseline Fungal Cultures
In the Micro-ITT population, 53 (41.7%) patients and 36 (30.5%) of patients in the anidulafungin group and the fluconazole group, respectively, had a single positive culture at baseline. Sixty-seven (52.8%) in the anidulafungin arm and 71 (60.2%) in the fluconazole arm had multiple positive blood cultures at baseline. The majority of patients, 93.7% and 89.8% had a single baseline pathogen in the anidulafungin and fluconazole arms, respectively. The percentages were similar in the two arms for the efficacy evaluable population at the end of IV therapy, and during follow-up.

Medical officer's comment
Screening blood cultures had to be taken within 24 hours of study entry. If screening blood cultures were taken within > 24 hours of study entry, blood cultures were repeated.

Baseline Microbiology

The distribution of baseline pathogens is similar between the two treatment arms. The relative proportion of isolates is consistent with the Candida species found in hospitalized patients. In the Micro-ITT population, *C. albicans* accounted for 61.6% of the total number of Candida isolates, i.e. 63.8 % of isolates in the anidulafungin arm and 59.3% in the fluconazole arm. These percentages did not change significantly in the efficacy evaluable population at end of IV therapy. There was a higher number of *Candida glabrata* (fluconazole known to have higher MIC against this species) in the fluconazole Micro-ITT population and efficacy evaluable population at the end of IV therapy. *Candida parapsilosis* (anidulafungin known to have higher MIC against this species) was lower in the anidulafungin arm compared to the fluconazole arm. The number of isolates is small for these two species in each arm. It must be emphasized that a correlation between antifungal MIC and clinical outcome has not been established.

TABLE 12. PER-PATIENT DISTRIBUTION OF BASELINE PATHOGENS

Population	Anidulafungin	Fluconazole	Total
Species	N (%)	N (%)	N (%)
Micro-ITT	N=127	N=118	N=245
Candida albicans	81 (63.8)	70 (59.3)	151 (61.6)
Candida glabrata	20 (15.7)	30 (25.4)	50 (20.4)
Candida parapsilosis	13 (10.2)	16 (13.6)	29 (11.8)
Candida tropicalis	15 (11.8)	11 (9.3)	26 (10.6)
Candida lusitaniae	1 (0.8)	2 (1.7)	3 (1.2)
Candida guilliermondii	2 (1.6)	0	2 (0.8)
Candida krusei	2 (1.6)	0	2 (0.8)
Candida famata	0	1 (0.8)	1 (0.4)
Candida spp.	1 (0.8)	0	1 (0.4)
Efficacy Evaluable at End of IV Therapy	N=103	N=91	N=194
Candida albicans	66 (64.1)	56 (61.5)	122 (62.9)
Candida glabrata	16 (15.5)	22 (24.2)	38 (19.6)
Candida parapsilosis	11 (10.7)	15 (16.5)	26 (13.4)
Candida tropicalis	13 (12.6)	6 (6.6)	19 (9.8)
Candida lusitaniae	1 (1.0)	1 (1.1)	2 (1.0)
Candida guilliermondii	2 (1.9)	0	2 (1.0)
Candida famata	0	1 (1.1)	1 (0.5)
Candida spp.	1 (1.0)	0	1 (0.5)

N = number of patients in the respective population.
The sum of the percent column for each population may be >100% due to some patients presenting with more than one pathogen at baseline.
Source: Data from Section 14.1, Table 1.6.2.

Duration of therapy

Median exposure to IV study drug was 14 days for anidulafungin, and 11 days for fluconazole (in ITT population).

TABLE 39. EXTENT OF EXPOSURE (DAYS) TO IV STUDY DRUG (ITT POPULATION)

Number of Days of IV Study Drug Category or Statistic	Anidulafungin (N=131) n (%)	Fluconazole (N=125) n (%)
<3	5 (3.8)	8 (6.4)
3 to 10	35 (26.7)	46 (36.8)
11 to 14	46 (35.1)	36 (28.8)
15 to 21	36 (27.5)	24 (19.2)
22 to 28	6 (4.6)	9 (7.2)
29 to 35	3 (2.3)	1 (0.8)
36 to 42	0	1 (0.8)
>42	0	0
Mean	13.31	12.17
SD	6.19	6.51
Median	14.00	11.00
Minimum, Maximum	1,33	1,37

Exposure to IV study drug is calculated as Stop date Start date + 1 day.
Source: Data from Section 14.3, Table 3.1.1.

Primary Efficacy Analysis

Global responses (combined clinical responses and microbiological responses) were evaluated in the Micro-ITT and Efficacy Evaluable populations.

A. MICRO-ITT
There were 127patients in the anidulafungin arm, and 118 patients in the fluconazole arm in the Micro-ITT population.

Global Response at End of IV Therapy (primary time point)
In the anidulafungin arm, 96 patients (75.6%) had a global success versus 71 patients (60.2%) in the fluconazole arm. The between group difference in global success rate (anidulafungin minus fluconazole) was 15.42% (95% CI 3.85, 26.99). Anidulafungin was found to be superior to fluconazole in the primary analysis of efficacy. Global response at the end of IV therapy in the Micro-ITT population is presented in Table 13.

TABLE 13. GLOBAL RESPONSE AT END OF IV THERAPY (MICRO-ITT POPULATION)

	Anidulafungin	Fluconazole		
Response	(N = 127)	(N = 118)	Between-Group	
Outcome	n (%)	n (%)	Difference[a]	(95% CI)
Success	96 (75.6)	71 (60.2)	15.42%	(3.85 , 26.99)
Failure	31 (24.4)	47 (39.8)		

a: Anidulafungin minus fluconazole.
Source: Data from Section 14.2, Table 2.1.1.

Medical officer's comment
There is a statistically significant difference between the global success rate for fluconazole and anidulafungin at the end of IV therapy. This was not explained by differential activity against various Candida species, see Table 20. Anidulafungin is a fungicidal agent against most Candida species and fluconazole, similar to other azoles, is a fungistatic antifungal drug- this may account for inferior efficacy.

Failures and Indeterminate responses

Indeterminate responses are considered to be failures. There were 31 and 47 failures in the anidulafungin and fluconazole arm, respectively, Table 14; eighteen and 23 patients respectively had indeterminate responses. The reasons why a patient could be assigned a global response of "indeterminate" at the end of IV therapy were:

- received less than 3 doses of study medication
- death not due to the *Candida* infection
- withdrawal from study medication for reasons other than failure defined as worsening clinical status/lack of efficacy.

All patients with an indeterminate global response at the end of IV therapy were discontinued from study medication. The two most common reasons for discontinuation in both treatment arms was an adverse event, or death (not due to invasive candidiasis infection), Table 14, Table 15.

TABLE 14. GLOBAL RESPONSE AT END OF IV THERAPY (MICRO-ITT POPULATION)

Response Outcome	Anidulafungin (N = 127) N (%)	Fluconazole (N = 118) N (%)	Between-Group Difference	(95% CI)
Success	96 (75.6)	71 (60.2)	15.42%	(3.85 , 26.99)
Failure	31 (24.4)	47 (39.8)		
Observed Failure	13 (10.2)	24 (20.3)		
Indeterminate	18 (14.2)	23 (19.5)		

A: Anidulafungin minus fluconazole.
Source: Data from Section 14.2, Table 2.1.1.

TABLE 15. REASONS THAT PATIENTS HAD INDETERMINATE GLOBAL RESPONSES AT END OF IV THERAPY (MICRO-ITT POPULATION)

Reason [a]	Anidulafungin (N = 18)	Fluconazole (N = 23)
Withdrew from the study or study medication	18	23
Reason for withdrawal		
Adverse Event	11	16
Patient withdrew consent	4	4
Investigator Discretion	3	3
Death, not due to candidemia or invasive candidiasis	10	16
Received less than 3 doses of study medication	5	8

Data from Appendix 16.2.1, 16.2.7, Listing 1.1, Listing 1.2 , Listing 5.7

[a]*Note: Each patient is represented more than once in reasons for withdrawal.*

Global Response at Secondary Time Points in the Micro-ITT Population

At all secondary time points, anidulafungin was either superior to fluconazole or at least as effective as fluconazole for the proportion of patients with global success, Table 16 and Table 17.

Table 16. GLOBAL RESPONSE AT END OF IV THERAPY AND SECONDARY TIME POINTS IN THE MICRO-ITT POPULATION

Time point	**Anidulafungin**	**Fluconazole**	
Global Success (Micro-ITT)	N (%)	N (%)	Between-Group Difference (95%CI)
End of IV Therapy	96/127 (75.6)	71/118 (60.2)	15.42% (3.85 , 26.99)
End of Oral Therapy	31/33 (93.9)	28/33 (84.8)	9.09% (-5.60 , 23.79)
End of All Therapy	94/127 (74.0)	67/118 (56.8)	17.24% (5.49 , 28.99)
2-Week Follow-Up	82/127 (64.6)	58/118 (49.2)	15.41% (3.14 , 27.68)
6-Week Follow-Up	71/127 (55.9)	52/118 (44.1)	11.84% (-0.60 , 24.28)

TABLE 17. GLOBAL RESPONSE AT SECONDARY TIME POINTS (MICRO-ITT POPULATION)

Secondary Time point				
Response Outcome	Anidulafungin N (%)	Fluconazole N (%)	Between-Group Difference[a]	(95% CI)
End of Oral Therapy	N=33	N=33		
Success	31 (93.9)	28 (84.8)	9.09%	(-5.60 , 23.79)
Failure	2 (6.1)	5 (15.2)		
Observed Failure	2 (6.1)	1 (3.0)		
Indeterminate	0	4 (12.1)		
End of All Therapy	N=127	N=118		
Success	94 (74.0)	67 (56.8)	17.24%	(5.49 , 28.99)
Failure	33 (26.0)	51 (43.2)		
Observed Failure	15 (11.8)	24 (20.3)		
Indeterminate	18 (14.2)	27 (22.9)		
2-Week Follow-Up	N=127	N=118		
Success	82 (64.6)	58 (49.2)	15.41%	(3.14 , 27.68)
Failure	45 (35.4)	60 (50.8)		
Observed Failure	18 (14.2)	27 (22.9)		
Indeterminate	27 (21.3)	33(28.0)		
6-Week Follow-Up	N=127	N=118		
Success	71 (55.9)	52 (44.1)	11.84%	(-0.60 , 24.28)
Failure	56 (44.1)	66 (55.9)		
Observed Failure	21 (16.5)	28 (23.7)		
Indeterminate	35 (27.6)	38 (32.2)		

a: Anidulafungin minus fluconazole.
Source: Data from Section 14.2, Table 2.2.1 of submission

B. EFFICACY EVALUABLE POPULATION

There were 103 patients in the anidulafungin arm and 91 patients in the fluconazole arm in the efficacy evaluable population.

Global Response at End of IV Therapy

In the anidulafungin arm, 90 patients (87.4%) had a global success versus 68 patients (74.7%) in the fluconazole arm. The between group difference in global success rate (anidulafungin minus fluconazole) was 12.65% (95% CI 1.66, 23.65). Anidulafungin was found to be superior to fluconazole in this analysis of efficacy. Global response at the end of IV therapy in the efficacy evaluable population is presented in Table 18.

Medical officer's comment

In the efficacy evaluable populations, trends were consistent with those seen in the Micro-ITT population. At all time points, anidulafungin was either superior to fluconazole or at least as effective as fluconazole for the proportion of patients with global success.

Table 18. Global Response at all Time Points (Efficacy Evaluable Population)

TABLE 21. GLOBAL RESPONSE AT ALL TIMEPOINTS (EFFICACY EVALUABLE POPULATIONS)

Time point Response	Anidulafungin n (%)	Fluconazole n (%)	Between-Group Difference (%)[a]	(95% CI)
End of IV Therapy	N = 103	N = 91		
Success	90 (87.4)	68 (74.7)	12.65%	(1.66 , 23.65)
Failure	13 (12.6)	23 (25.3)		
End of Oral Therapy	N = 30	N = 27		
Success	28 (93.3)	26 (96.3)	-2.96%	(-14.38 , 8.46)
Failure	2 (6.7)	1 (3.7)		
End of All Therapy	N = 103	N = 87		
Success	88 (85.4)	64 (73.6)	11.87%	(0.37 , 23.37)
Failure	15 (14.6)	23 (26.4)		
2-Week Follow-Up	N = 88	N = 76		
Success	71 (80.7)	51 (67.1)	13.58%	(0.17 , 26.98)
Failure	17 (19.3)	25 (32.9)		
6-Week Follow-Up	N = 79	N = 69		
Success	59 (74.7)	43 (62.3)	12.36%	(-2.56 , 27.29)
Failure	20 (25.3)	26 (37.7)		

a: Anidulafungin minus fluconazole.
Data from Section 14.2, Table 2.3.1 and Table 2.4.

Antifungal medications taken during and after study therapy, (ITT population)
There were 35 (26.7%) patients in the anidulafungin treatment group and 42 (33.6%) in the fluconazole treatment group who received antifungal therapy after the study drug was completed. Two patients in the anidulafungin arm and two patients in the fluconazole arm received amphotericin B formulations during the study period. The majority of the patients had global, clinical, or microbiological failure at the end of study therapy. Some patients received antifungal therapy for prophylaxis or empiric therapy, Table 19.

Table 19: ANTIFUNGAL MEDICATIONS TAKEN DURING AND AFTER STUDY THERAPY (ITT POPULATION)

Antifungals, systemic	During	After
Drug	N (%)	N (%)
Anidulafungin (N=131)		
Any systemic antifungal	9 (6.9)	35 (26.7)
Fluconazole	3 (2.3)	23 (17.6)
Caspofungin	3 (2.3)	11 (8.4)
Amphotericin B, liposome	2 (1.5)	5 (3.8)
Amphotericin B	0	2 (1.5)
Voriconazole	1 (0.8)	1 (0.8)
Fluconazole (N=125)		
Any systemic antifungal	7 (5.6)	42 (33.6)
Fluconazole	1 (0.8)	23 (18.4)
Caspofungin	4 (3.2)	19 (15.2)
Amphotericin B, liposome	1 (0.8)	7 (5.6)
Amphotericin B	1 (0.8)	6 (4.8)
Voriconazole	0	2 (1.6)
Itraconazole	0	0
Flucytosine	0	1 (0.8)

Adapted from

Medical officer's comment
The numbers of patients who received antifungal therapy during or after the study period was balanced in both treatment groups.

Table 20. GLOBAL SUCCESS AT END OF IV THERAPY BY PATHOGEN (MICRO-ITT POPULATION)

Baseline Species	Anidulafungin n/N (%)	Fluconazole n/N (%)
All species	92/119 (77.3)	65/106 (61.3)
Candida albicans	60/74 (81.1)	38/61 (62.3)
Non-*albicans* species	32/45 (71.1)	27/45 (60.0)
Candida glabrata	9/16 (56.3)	11/22 (50.0)
Candida tropicalis	13/14 (92.9)	4/8 (50.0)
Candida parapsilosis	7/11 (63.6)	10/12 (83.3)
Candida guilliermondii	2/2 (100.0)	--
Candida krusei	0/1 (0.0)	--
Candida lusitaniae	1/1 (100.0)	1/2 (50.0)
Candida famata	--	1/1 (100.0)

Note: N=Number of patients with a single baseline pathogen.
Source: Data from Section 14.2, Table 2.12.

In the Micro-ITT patients with a single baseline *Candida* species, there was a significant difference in global success between the anidulafungin and fluconazole arms by pathogen isolated. Anidulafungin- treated patients had more global success than fluconazole-treated patients for all species of *Candida* except *C. parapsilosis*.
The majority of patients had infection with *C. albicans*; the outcome for these patients was 60/74 (81.1%), and 38/61 (62.3%) in the anidulafungin and fluconazole arms, respectively. The number of non-albicans *Candida* isolates is small in this study. Patients with *C. parapsilosis* infection had a global success of 63.6% compared to 83.3% in the fluconazole arm. The difference in global success was also noticeable for *C. tropicalis*; 13/14 (92.9%) and 4/8 (50.0%) in the anidulafungin and fluconazole arms, respectively. All but one of the *C. tropicalis* isolates were documented as sensitive to fluconazole.

Minimum Inhibitory Concentrations
For baseline isolates from the Micro-ITT population, the median MIC50 and MIC90 of anidulafungin were, respectively, 0.008 and 0.5 mg/L. For fluconazole, the corresponding values were 0.25 and 8 mg/L. These MIC ranges are consistent with published literature. Please refer to Dr. Steele-Moore's microbiology review for more detailed commentary.

Medical Officer's comment
Higher MIC -2 results were observed for anidulafungin against C. parapsilosis, and fluconazole against C. glabrata, than for most other species tested- this is consistent with published literature. There were more global successes in the fluconazole-treated patients with C. parapsilosis infection and more global success in the anidulafungin-treated patients for C. glabrata. C. parapsilosis is known to have higher MIC compared to C. albicans and most other species of Candida when tested against echinocandins. It

must be emphasized, however, that a correlation between MIC and clinical outcome has not been established.

Global Response by Source of *Candida* Infection

Candidemia

Given that approximately 90% of patients in each treatment group had candidemia only, results for these patients closely paralleled results for the overall population with global success observed for 88 (75.9%) patients in the anidulafungin arm and 63 (61.2%) patients in the fluconazole arm. The difference (anidulafungin minus fluconazole) between treatment groups in global success rate was 14.70% (95% CI: 2.48, 26.91). Anidulafungin was superior to fluconazole in this analysis.

Table 21.GLOBAL RESPONSES AT END OF IV THERAPY FOR PATIENTS WITH CANDIDEMIA [1] , MICROBIOLOGICAL INTENT-TO-TREAT POPULATION

Subgroup: Candidemia = Yes

	Treatment Group			
	Anidulafungin (N=116)	Fluconazole (N=103)	Between-Group Difference (%)	95% Confidence
Response	N (%)	N (%)	Anidulafungin - Fluconazole	Interval
Global Success [2]	88 (75.9)	63 (61.2)	14.70	(2.48 , 26.91)
Failure	12 (10.3)	23 (22.3)		
Indeterminate	16 (13.8)	17 (16.5)		

Source: Table 2.1.5 in submission

[1] Patients with candidemia only at baseline.
[2] A global success represents a clinical success and a patient microbiological success. A 95% confidence interval is based on the difference in success rates.

Other Forms of Invasive Candidiasis

Results were similar for the few patients with other forms of invasive candidiasis. Among the small number of patients with documented infections at a normally sterile site other than blood (with or without concomitant positive blood cultures), 8 (72.7%) patients receiving anidulafungin and 8 (53.3%) patients receiving fluconazole had global success at the end of IV therapy.

Global Response in Subgroups of the Efficacy Evaluable Population

A number of subgroups were analyzed for outcome based on the presence or absence of IV catheters, and disease severity related to APACHE score and immunosuppressive therapy.

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Global Response at End of IV Therapy by Catheter Removal Status

The numbers of IV catheter removals was well balanced between the two treatment arms. Therefore the global response was analyzed in patients who had catheters removed or left in place, and those who did not have an IV catheter. The global success rates were higher in the anidulafungin arm compared to the fluconazole arm.

Table 22.
Subgroup: Catheter Removal Status = Had catheter and it was removed

	Treatment Group		
	Anidulafungin (N=87)	Fluconazole (N=68)	Between-Group Difference (%)
Response	n (%)	n (%)	Anidulafungin - Fluconazole
Global Success *	74 (85.1)	50 (73.5)	11.53
Failure	13 (14.9)	18 (26.5)	

Subgroup: Catheter Removal Status = Had catheter and it was NOT removed

	Treatment Group		
	Anidulafungin (N=3)	Fluconazole (N=4)	Between-Group Difference (%)
Response	n (%)	n (%)	Anidulafungin - Fluconazole
Global Success *	3 (100.0)	3 (75.0)	25.00
Failure	0	1 (25.0)	

Subgroup: Catheter Removal Status = Did NOT have catheter

	Treatment Group		
	Anidulafungin (N=13)	Fluconazole (N=19)	Between-Group Difference (%)
Response	n (%)	n (%)	Anidulafungin - Fluconazole
Global Success *	13 (100.0)	15 (78.9)	21.05
Failure	0 (0.0)	4 (21.1)	

Source: VER002-9 Study report, Section 14.2.1, tables 2.3.9
* clinical and microbiological success

Outcomes in Special Populations

Results were similar for the low numbers of patients with other forms of invasive candidiasis. Among patients with documented infections at a normally sterile site other than blood (with or without concomitant positive blood cultures), 8 (72.7%) patients receiving anidulafungin and 8 (53.3%) patients receiving fluconazole had global success at the end of IV therapy, Table 23.

TABLE 23. GLOBAL SUCCESS AT END OF IV THERAPY FOR OTHER FORMS OF INVASIVE
CANDIDIASIS (MICRO-ITT POPULATION)

Baseline Site of Infection, n (%)	Anidulafungin N (%)	Fluconazole N (%)
Other Forms of Invasive Candidiasis	8/11 (72.7)	8/15 (53.3)
Peritoneal fluid and/or IA abscess	4/6 (66.7)	5/6 (83.3)
Pleural fluid	1/1 (100)	-
Pelvic abscess	-	1/2 (50.0)
Pancreas	-	0/3 (0.0)
Blood and peritoneal (and/or IA abscess)	2/2 (100)	0/2 (0.0)
Blood and pleural fluid	0/1 (0.0)	-
Blood and left thigh lesion biopsy	1/1 (100)	-
Blood and bile	-	1/1 (100)
Blood and renal	-	1/1 (100)

Abbreviation: IA = intra-abdominal.
Source: Adapted from Data from Appendix 16.2.6, Listing 4.3, Appendix 16.2.8, Listing 6.8

Sub Group Analysis based on Apache II Score

The APACHE (Acute Physiology, Age, and Chronic Health Evaluation) score is a severity of disease classification system. The APACHE system is designed to assess the severity of illness of patients in intensive care units (ICUs). APACHE II uses a point score based upon initial values of routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. An increasing score correlates with increased severity of disease. Anidulafungin had more global successes in the patients with APACHE II < 20. Results are similar to that in the global success rate at the end of IV therapy, the primary time point. The rates of global success were similar between the two arms in patients with APACHE II > 20, Table 24a, and Table 24b.

Table 24a
Global Responses At End of IV Therapy For Patients with APACHE II Score Subgroup
Microbiological Intent-To-Treat Population

Subgroup: Apache II Score = <= 20

Response	Treatment Group: Anidulafungin (N=101) n (%)	Treatment Group: Fluconazole (N=98) n (%)	Between-Group Difference (%) Anidulafungin - Fluconazole
Global			
Success [1]	82 (81.2)	60 (61.2)	19.96
Failure	9 (8.9)	18 (18.4)	
Indeterminate	10 (9.9)	20 (20.4)	

Source : Data from section 14.2.1, Table 2.1.7

Table 24b
Global Responses At End of IV Therapy For Patients with APACHE II Score Subgroup
Microbiological Intent-To-Treat Population

Subgroup: Apache II Score = > 20

Response	Treatment Group: Anidulafungin (N=26) n (%)	Treatment Group: Fluconazole (N=20) n (%)	Between-Group Difference (%) Anidulafungin - Fluconazole
Global			
Success [1]	14 (53.8)	11 (55.0)	-1.15
Failure	4 (15.4)	6 (30.0)	
Indeterminate	8 (30.8)	3 (15.0)	

Source: Data from section 14.2.1, Table 2.1.7

Outcomes in Patients on Immunosuppressive Therapy

Global success in patients with immunosuppressive therapy was similar in both arms, with slightly more global success in patients in the slightly more global success in the anidulafungin arm, Table 25.

Table 25. Global Response Patients who received Immunosuppressive Therapy Micro ITT Population

Treatment Group	Global Response End-of IV Therapy	n (%)
ANIDULAFUNGIN	Success	12 (66.7%)
	Failure	3 (16.7%)
	Indeterminate	3 (16.7%)
FLUCONAZOLE	Success	16 (59.3%)
	Failure	4 (14.8%)
	Indeterminate	7 (25.9%)

Source: Data from section 14.2.1, Table 2.23

Conclusions Regarding Efficacy Data in Study VER002-9

Anidulafungin was superior to fluconazole for the treatment of invasive candidiasis/candidemia in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population. In all secondary efficacy analyses, anidulafungin was superior to, or at least as effective as, fluconazole, consistent with the primary efficacy analysis. Anidulafungin-treated patients had higher rates of global, clinical, and microbiological success at all time points on therapy and at the end of therapy. Candidemia was present in more than 90% of patients in both study arms. Approximately half of all patients had invasive candidiasis related to an IV catheter. Most patients had a single baseline pathogen; *C. albicans* and *C. glabrata* were the baseline pathogens most frequently isolated.

- Anidulafungin (96/127, 75.6%) was superior to fluconazole (71/118, 60.2%) for the treatment of invasive candidiasis/candidemia in the primary efficacy analysis of global response at the end of IV therapy in the Micro-ITT population.
- At the end of IV therapy, 6.3% of patients treated with anidulafungin had a documented persistent *Candida* infection compared with 14.4% of patients treated with fluconazole.
- In all secondary efficacy analyses anidulafungin was superior to (end of IV therapy, end of all therapy and 2-week FU time points), or at least as effective as (end of oral therapy and 6-week FU time points), fluconazole which is consistent with the primary efficacy analysis.
- The results of the study may not be applicable to neutropenic patients due to the low numbers of patients with neutropenia in the study. Neutropenic patients accounted for 3 (2.4%), and 4 (3.4%) in the anidulafungin and fluconazole arms, respectively.

Safety Results

Safety Summary
In this study, no hepatic safety concerns emerged when compared to fluconazole. The safety data provided from patients with invasive candidiasis suggest that anidulafungin at a dose of 100 mg IV daily has a safety profile similar to and, in some instances, more favorable than that of fluconazole 400 mg IV daily.

- Adverse events rates were similar in the two treatment arms. AEs were reported by 130 (99.2%) patients in the anidulafungin arm and 122 (97.6%) patients in the fluconazole arm. The proportion of patients with related AEs was similar in the two treatment arms (approximately 25%). Fewer anidulafungin-treated patients (15, 11.5%) than fluconazole-treated patients (27, 21.6%) experienced an AE that led to discontinuation of study drug.
- Serious adverse events (SAEs) were reported by 49.6% of patients in the anidulafungin arm and 56.8% of patients in the fluconazole arm; however, SAEs were considered related to treatment for only 2 patients in each study arm. The three most common SAE in the anidulafungin arm were cardiac arrest, multiorgan failure and respiratory arrest, none of which were attributable to anidulafungin.
- There were 4 (3.1%) patients in the anidulafungin group and 7 (5.6%) patients in the fluconazole group who reported clinical AEs categorized under the hepatobiliary category. Only 4 of these events were severe in intensity and all 4 occurred in fluconazole-treated patients. One hepatic AE in anidulafungin-treated patient was considered possibly related to study drug.
  - Fewer anidulafungin-treated patients (15, 11.5%) than fluconazole-treated patients (27, 21.6%) experienced an AE that led to discontinuation of study drug.
  - No cases of hepatic failure, anaphylaxis, or QT prolongation occurred. The safety data show that anidulafungin at a dose of 100 mg daily has a safety profile similar to fluconazole 400 mg IV daily.
  - Deaths: Fewer anidulafungin-treated patients (30, 22.9%) than fluconazole-treated patients (39, 31.2%) died during and shortly after the study.

Exposure to Study Drug

A total of 89.3% and 84.8% of patients in the ITT population received anidulafungin and fluconazole, respectively for 1 to 3 weeks. Approximately, 62% and 48% of patients received anidulafungin and fluconazole respectively for 11 to 21 days. The mean length of exposure to anidulafungin and fluconazole was 13 days and 12.17, respectively. Most patients (> 70%) completed IV therapy and were not switched to oral therapy with fluconazole. Similar percentages of patients in each study arm switched to oral therapy, 26.0% in the anidulafungin arm and 28.8 % in the fluconazole arm. The mean exposure to fluconazole was 15.7days for the anidulafungin treatment group and 14.7 for the fluconazole treatment group.

Extent of exposure Study VER002-9

TABLE 26. EXTENT OF EXPOSURE (DAYS) TO IV STUDY DRUG (ITT POPULATION)

Number of Days of IV Study Drug Category or Statistic	Anidulafungin (N=131) N (%)	Fluconazole (N=125) N (%)
<3	5 (3.8)	8 (6.4)
3 to 10	35 (26.7)	46 (36.8)
11 to 14	46 (35.1)	36 (28.8)
15 to 21	36 (27.5)	24 (19.2)
22 to 28	6 (4.6)	9 (7.2)
29 to 35	3 (2.3)	1 (0.8)
36 to 42	0	1 (0.8)
>42	0	0
Mean	13.31	12.17
SD	6.19	6.51
Median	14.00	11.00
Minimum, Maximum	1,33	1,37

Exposure to IV study drug is calculated as Stop date Start date + 1 day.
Source: Data from Section 14.3, Table 3.1.1.

Adverse Events

The percentages of patients with ≥ 1 mild, moderate, or severe AE were similar for both treatment arms. Approximately 50% of patients in both arms had a severe adverse event. Approximately 25% of patients in both arms had an AE considered possibly or probably related to the study medication.

TABLE 27. OVERALL SUMMARY OF ADVERSE EVENTS (ITT POPULATION)
VER002-9

Patients with:	Anidulafungin (N=131) N (%)	Fluconazole (N=125) N (%)
≥ 1 AE	130 (99.2)	122 (97.6)
≥ 1 AE of mild severity	113 (86.3)	104 (83.2)
≥ 1 AE of moderate severity	106 (80.9)	98 (78.4)
≥ 1 AE of severe severity	65 (49.6)	68 (54.4)
≥ 1 AE related to study drug	32 (24.4)	33 (26.4)
≥ 1 AE leading to study drug discontinuation	15 (11.5)	27 (21.6)
≥ 1 related AE leading to study drug discontinuation	1 (0.8)	4 (3.2)
≥ 1 SAE	65 (49.6)	71 (56.8)
≥ 1 related SAE	2 (1.5)	2 (1.6)
Death	30 (22.9)[a]	39 (31.2)[b]

a: Includes 1 anidulafungin patient who died after the final (6-week follow-up) study visit.
b: Includes 2 patients in the ITT population who were not in the Micro-ITT population.
Note: A patient who experienced multiple events was counted once for Patients with at least one AE .
Source: Section 14.3, Table 3.5.

Withdrawals from Study

A total 9.2% of the anidulafungin patients and 16.8 % of the fluconazole patients withdrew for any adverse event. Approximately 6 % of patients in both arms were lost to follow up, Table 6 and Table 7.

Medical officer's comment

More patients withdrew from study in the fluconazole arm than in the anidulafungin arm, 45 (36%) versus 37(28%), respectively. Five patients who withdrew from study, (one patient in the anidulafungin arm and four of the patients in the fluconazole arm) did not receive study drug. The arms are not significantly different with regard to withdrawals from study.

Deaths

There were 68 deaths during the study, 29 of 131 (22%) anidulafungin-treated patients, and 39 of 125 (31%) fluconazole-treated patients. One anidulafungin treated patient died after the 6 week follow–up and was not included in withdrawals from study. Withdrawal from study due to death occurred in 29 (22.1%) in the anidulafungin arm and 38 (30.4%) in the fluconazole arm. In both the anidulafungin and fluconazole groups, cardiac arrest (2.9% anidulafungin, 5.6% fluconazole) was the most common adverse event resulting in death. Two of patients who died in the fluconazole arm never received a dose of study drug. There was no distinguishable pattern in the causes of death among anidulafungin-treated patients or between the anidulafungin and fluconazole treatment populations. Table 28 summarizes the cause of death for all individuals in both study arms.

Medical officer's comment

The case report forms for each of the 68 patients who died were reviewed. The clinical reviewer and the investigator concluded that the deaths in the study are unlikely to be related to anidulafungin or fluconazole.

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TABLE 28. PATIENT DEATHS

Treatment Arm Patient ID	Sex	Age (years)	Primary Cause	Days on Study Medication	Elapsed time* (days)
Anidulafungin					
01-001	M	60	Renal failure	6	1
03-002	M	79	Respiratory failure	1	0
04-007	F	51	Worsening of cervical cancer	36	15
07-001	F	73	Metastatic pancreatic cancer	11	7
10-001	F	59	Cardiac/pulmonary arrest	26	11
10-004	M	76	Cardiac arrest	35	21
10-009	M	66	Cardiac arrest	17	3
12-010	F	57	Withdrawal of care secondary to pseudomembranous colitis and sepsis	13	4
12-014	M	60	Renal failure	18	9
12-018	F	49	Multisystem organ failure	10	1
17-004	F	77	Sepsis	10	3
18-001	F	71	Sepsis	15	4
18-005	F	67	Worsening pancreatic cancer	28	14
19-001	F	59	Cardiac failure	10	1
20-004	M	83	Anoxic brain injury secondary to respiratory failure/arrest	33	18
20-008	F	33	Multisystem organ failure	21	10
31-005	M	78	Cardiopulmonary arrest	14	0
32-003	M	56	Worsening of multisystem organ failure	22	1
33-004	M	78	Sepsis due to candidemia	2	1
38-003	F	61	Cardiogenic/septic shock	2	1
40-001	M	77	Bacteremia	41	16
40-004	M	77	Cardiac and respiratory arrest	24	8
40-017	F	24	Respiratory failure	36	17
41-004	F	46	Cardiac arrest	36	22
41-011	M	76	Respiratory arrest	12	1
42-002	M	21	Chronic lung disease resulting from cystic fibrosis	68	42
47-001	M	65	Multiorgan failure	26	1
52-004	F	65	Respiratory failure	67	39
82-001	F	40	Intracerebral hemorrhage	24	7
27-003**	F	51	Respiratory Distress	10	48

Patient deaths continued

Fluconazole

01-002	M	84	Aspiration	34	14
04-002	M	56	Worsening of terminal lung/brain cancer- respiratory failure secondary to brain metastases	7	0
04-005	M	24	GI hemorrhage	31	17
04-010	M	62	Respiratory failure leading to death may have been caused by bacteremia or candidemia	6	1
10-002	F	54	Cardiac arrest	2	1
10-005	F	83	Cardiac arrest	31	17
10-008	F	64	Septic shock	21	8
11-002	F	56	Multiple myeloma, renal failure, bilateral pulmonary emboli, respiratory arrest	3	1
12-001	F	27	Worsening multiorgan failure	37	19
12-008	M	75	Withdrawal of care secondary to multisystem organ failure	16	1
12-009	F	74	Complications of blunt trauma	55	39
12-011	M	41	Multisystem organ failure	11	3
17-002	M	79	Multisystem organ failure	5	1
18-003	F	68	Worsening cholangiocarcinoma	72	30
20-002	M	74	Cardiac arrest	13	5
24-001	F	50	Possible cardiac arrest or pulmonary embolism	17	1
24-004	M	49	Anoxic brain injury, secondary to asystole with subsequent respiratory arrest	12	1
24-009	M	52	Worsening renal failure, worsening hyperkalemia and bacterial sepsis	8	1
24-012	F	34	Septic shock and polymicrobial bacteremia	17	1
24-013	F	57	Septic shock with multiple organ failure	4	1
25-001	M	54	Polymicrobial sepsis, AIDS, hepatitis C	38	21
30-001	F	73	Lung cancer	23	1
31-002	F	52	Bradycardia	3	2
32-002	F	62	Cardiac arrest	3	1
33-002	M	71	Worsening renal failure due to progression of metastatic prostate cancer	7	0
37-002	M	50	Multiple myeloma	37	13
38-007	M	70	Renal failure	50	36
39-002	M	51	Cardiac arrest and do not resuscitate	35	29
40-006	F	80	Sepsis	11	5
40-012	F	76	Acute renal failure	31	9
40-014	M	69	Respiratory failure	49	41
41-021	M	77	Bradycardia	12	1
46-002	F	45	Multiorgan failure and pulmonary arrest	14	3
47-002	M	65	Respiratory failure	14	0
52-001	M	86	Acute renal failure	43	27

Patient deaths continued-Fluconazole					
56-002	M	64	Respiratory failure	7	2
67-001	F	60	Worsening sepsis	9	1
73-001	M	81	Cardiac arrest	14	1
75-001	M	72	Septic shock	71	38

* Number of days elapsed between end of study therapy and death.
Source: Data from Appendix 16.2.4, Listing 2.1; Appendix 16.2.5, Listing 5.1; Appendix 16.2.7, Listings 5.6 and 5.7.
Deaths considered related to study drug by investigator = 0

All-Cause Mortality

The all cause mortality was lower in the anidulafungin treated patients, Table 29. The autopsy rate was very low in both treatment arms; 4 (13.8%) and 3(7.7%) in the anidulafungin and fluconazole treatment groups, respectively. At the time of death, 65% and 59% of patients had negative cultures for *Candida.*

Table 29. All Cause Mortality, Intent-To-Treat-Population

	Treatment Group Anidulafungin (N=131) N (%)	Fluconazole (N=125) N (%)
What was patient status at last contact? [1]		
Alive	102 (77.9)	86 (68.8)
Dead	29 (22.1)	39 (31.2)
Was the death directly attributable to invasive candidiasis / candidemia?		
No	27 (93.1)	34 (87.2)
Yes	2 (6.9)	5 (12.8)
What was the culture status at time of death? [2]		
No Growth	19 (65.5)	23 (59.0)
Growth	2 (6.9)	7 (17.9)
Unknown	8 (27.6)	9 (23.1)
Was an autopsy performed? [2]		
No	25 (86.2)	36 (92.3)
Yes	4 (13.8)	3 (7.7)
At autopsy, was there histopathology or culture evidence of Candida? [2]		
No	4 (13.8)	3 (7.7)
Yes	0	0

Source: section 14.2.1, Table 2.17.1
[1] Percentages are based on the N in each treatment arm.
[2] Percentages are based on the patients who died in each treatment arm.

1. **All Adverse events in the ITT population**

Adverse events that occurred more frequently in the anidulafungin arm included hypokalemia, nausea, vomiting, insomnia, hypertension, dyspnea, increased white blood cell count, and thrombocythemia. Adverse events that occurred more frequently in the fluconazole arm included anemia, pneumonia, abdominal pain, hyperkalemia, increased hepatic enzyme levels, back pain, anxiety, cardiac arrest, renal insufficiency, pulmonary edema, thrombocytopenia, rash, increased AST, and septic shock.

TABLE 30. ADVERSE EVENTS EXPERIENCED BY □ 5% PATIENTS IN EITHER STUDY ARM, Study VER002-9

	(ITT POPULATION) Anidulafungin (N = 131)	Fluconazole (N = 125)
Adverse Event	N (%)	N (%)
Hypokalaemia	33 (25.2)	24 (19.2)
Nausea	32 (24.4)	15 (12.0)
Diarrhoea	24 (18.3)	23 (18.4)
Bacteraemia	23 (17.6)	23 (18.4)
Pyrexia	23 (17.6)	23 (18.4)
Vomiting	23 (17.6)	12 (9.6)
Insomnia	20 (15.3)	12 (9.6)
Urinary tract infection	19 (14.5)	22 (17.6)
Hypotension	19 (14.5)	18 (14.4)
Alkaline phosphatase increased	15 (11.5)	14 (11.2)
Hypomagnesaemia	15 (11.5)	14 (11.2)
Hypertension	15 (11.5)	5 (4.0)
Dyspnoea	15 (11.5)	4 (3.2)
Oedema peripheral	14 (10.7)	16 (12.8)
Pleural effusion	13 (9.9)	11 (8.8)
Deep vein thrombosis	13 (9.9)	9 (7.2)
Anaemia	**12 (9.2)**	**20 (16.0)**
Constipation	11 (8.4)	14 (11.2)
Headache	11 (8.4)	10 (8.0)
White blood cell count increased	11 (8.4)	3 (2.4)
Confusional state	10 (7.6)	10 (8.0)
Sepsis	9 (6.9)	11 (8.8)
Hypoglycaemia	9 (6.9)	10 (8.0)
Cough	9 (6.9)	7 (5.6)
Pneumonia	**8 (6.1)**	**19 (15.2)**
Abdominal pain	**8 (6.1)**	**16 (12.8)**
Hyperkalaemia	**8 (6.1)**	**14 (11.2)**
Hyperglycaemia	8 (6.1)	8 (6.4)
Depression	8 (6.1)	5 (4.0)
Dehydration	8 (6.1)	2 (1.6)
Respiratory distress	8 (6.1)	2 (1.6)
Thrombocythaemia	8 (6.1)	1 (0.8)
Hepatic enzyme increased	**7 (5.3)**	**14 (11.2)**
Back pain	7 (5.3)	13 (10.4)
Decubitus ulcer	7 (5.3)	10 (8.0)
Chest pain	7 (5.3)	6 (4.8)
Leukocytosis	7 (5.3)	6 (4.8)
Blood creatinine increased	7 (5.3)	1 (0.8)
Anxiety	6 (4.6)	13 (10.4)

Rigors	**6 (4.6)**	**11 (8.8)**
Agitation	6 (4.6)	7 (5.6)
ALT increased	6 (4.6)	7 (5.6)
Staphylococcal bacteraemia	6 (4.6)	7 (5.6)
Cardiac arrest	5 (3.8)	11 (8.8)
Renal insufficiency	**5 (3.8)**	**11 (8.8)**
Renal failure acute	5 (3.8)	9 (7.2)
Hypothermia	5 (3.8)	8 (6.4)
Pulmonary oedema	**4 (3.1)**	**13 (10.4)**
Thrombocytopenia	**4 (3.1)**	**13 (10.4)**
Rash	4 (3.1)	11 (8.8)
Abdominal distension	4 (3.1)	8 (6.4)
Bradycardia	3 (2.3)	7 (5.6)
Dizziness	3 (2.3)	7 (5.6)
AST increased	**2 (1.5)**	**9 (7.2)**
Septic shock	**1 (0.8)**	**10 (8.0)**
Metabolic acidosis	**1 (0.8)**	**7 (5.6)**

Source: Data from Section 14.3, Table 3.7.

Medical officer's comment

The anidulafungin treatment group had more GI symptoms such as nausea and vomiting compared to the fluconazole treatment group. Diarrhea was similar between the groups. Hepatic enzymes were elevated more often in the fluconazole arm. Metabolic acidosis, pulmonary edema, renal failure, renal insufficiency and pneumonia were more common in the fluconazole arm. Sepsis and bacteremia was balanced between the two arms but septic shock was more common in the fluconazole arm. Based on this table, the overall impression is that the fluconazole patients may have been a slightly sicker group of patients.

2. Adverse Events Related to Study Drugs

Most patients did not experience adverse events related to study medication. The two most common related AEs for anidulafungin were hypokalemia (3.1%) and diarrhea (3.1%). For fluconazole, the two most common related AEs were hepatic enzyme increased (7.2%) and blood alkaline phosphatase increased (4.0%). Table 31 Hepatic enzymes including alkaline phospahatase were elevated in more patients receiving fluconazole IV therapy alone. Patients received a median of 11 to 14 days of IV therapy with either fluconazole or anidulafungin. Table 32

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TABLE 31. RELATED ADVERSE EVENTS EXPERIENCED BY □ 2 PATIENTS IN EITHER STUDY ARM (ITT POPULATION) ver002-9

Adverse Event	Anidulafungin (N = 131) n (%)	Fluconazole (N = 125) n (%)
Patients with at least one related AE	32 (24.4)	33 (26.4)
Total number of related AEs[a]	59 (4.7)	64 (4.8)
Hypokalaemia	4 (3.1)	3 (2.4)
Diarrhoea	4 (3.1)	2 (1.6)
ALT increased	3 (2.3)	4 (3.2)
Hepatic enzyme increased	2 (1.5)	9 (7.2)
Blood alk. phos. increased	2 (1.5)	5 (4.0)
Flushing	2 (1.5)	2 (1.6)
Blood bilirubin increased	2 (1.5)	1 (0.8)
Hypomagnesaemia	2 (1.5)	1 (0.8)
Electrocardiogram QT prolonged	2 (1.5)	0
Pruritus	2 (1.5)	0
AST increased	1 (0.8)	3 (2.4)
Deep vein thrombosis	1 (0.8)	3 (2.4)
Anaemia	0	2 (1.6)
Dizziness	0	2 (1.6)
Rigors	0	2 (1.6)

Note: If a patient had multiple occurrences of the same event, the event with the least complimentary relationship is presented and the patient was counted once for the event. Numerator and denominator are AEs/total AEs. Source: Data from Section 14.3, Table 3.10.

TABLE 32. RELATED ADVERSE EVENTS IN □ 2 PATIENTS IN EITHER STUDY ARM: ITT PATIENTS RECEIVING ONLY IV STUDY MEDICATION

Adverse Event	Anidulafungin (N = 97) n (%)	Fluconazole (N = 89) n (%)
Diarrhoea	4 (4.1)	0
Hepatic enzyme increased	2 (2.1)	7 (7.9)
Blood bilirubin increased	2 (2.1)	1 (1.1)
Hypokalaemia	2 (2.1)	0
Alanine aminotransferase increased	1 (1.0)	4 (4.5)
Blood alkaline phosphatase increased	1 (1.0)	3 (3.4)
Deep vein thrombosis	1 (1.0)	2 (2.2)
Flushing	1 (1.0)	2 (2.2)
Aspartate aminotransferase increased	0	3 (3.4)

Source: Data from Section 14.3, Table 3.20.

3. **Serious adverse events (SAEs)**

In the anidulafungin arm, 65(49.6%) had 89 SAEs compared with the fluconazole arm, in which 71(56.8%) had 111 SAEs. The three most common SAEs for patients treated with anidulafungin were cardiac arrest, multi-organ failure, and respiratory arrest. The three most common SAEs for patients treated with fluconazole were cardiac arrest, sepsis, and septic shock. SAEs with frequencies differing by at least 3% in the treatment arms were cardiac arrest, sepsis and septic shock, and acute renal failure; these SAEs were more frequent in the fluconazole arm.

TABLE 33. SERIOUS ADVERSE EVENTS IN □ 2 PATIENTS IN EITHER STUDY ARM: ITT PATIENTS VER002-9

	Anidulafungin (N = 131)	Fluconazole (N = 125)
Serious Adverse Event	n (%)	n (%)
Cardiac arrest	5 (3.8)	11 (8.8)
Multi-organ failure	4 (3.1)	5 (4.0)
Respiratory arrest	4 (3.1)	2 (1.6)
Sepsis	3 (2.3)	8 (6.4)
Respiratory failure	3 (2.3)	6 (4.8)
Bacteraemia	3 (2.3)	4 (3.2)
Abdominal pain	3 (2.3)	1 (0.8)
Respiratory distress	3 (2.3)	0
Pulmonary embolism	2 (1.5)	3 (2.4)
Renal insufficiency	2 (1.5)	3 (2.4)
Cardio-respiratory arrest	2 (1.5)	1 (0.8)
Hypotension	2 (1.5)	1 (0.8)
Mental status changes	2 (1.5)	1 (0.8)
Atrial fibrillation	2 (1.5)	0
Dehydration	2 (1.5)	0
Intestinal obstruction	2 (1.5)	0
Septic shock	1 (0.8)	8 (6.4)
Deep vein thrombosis	1 (0.8)	3 (2.4)
Bacterial sepsis	1 (0.8)	2 (1.6)
Convulsion	1 (0.8)	2 (1.6)
Pneumonia	1 (0.8)	2 (1.6)
Renal failure acute	0	6 (4.8)
Hyperkalaemia	0	3 (2.4)
Anaemia	0	2 (1.6)
Bradycardia	0	2 (1.6)
Hepatic enzyme increased	0	2 (1.6)

Source: Data from Section 14.3, Table 3.14.

Related Serious Adverse Events

Four patients (two patients per arm) in the study were assessed to have serious adverse events related to study drug. All patients recovered from the events. A brief synopsis of each case history is presented. Most of the events occurred following one week of therapy. There was no anaphylaxis described in the study.

Table 34. RELATED SERIOUS ADVERSE EVENTS

Patient ID	Study Arm	Sex	Age	SAE	Start Day*
04-003	Anid	66	M	Atrial fibrillation	2
12-007	Anid	49	F	Convulsion/seizure	6 (+1)
07-010	Flu	61	F	Deep vein thrombosis	15 (+1)
33-007	Flu	81	F	Hepatic enzyme increased	19

*Relationship to start day of study medication
Source: Data from Appendix 16.2.7, Listing 5.5.
A brief description of each patient except (33-007) is provided below. Full SAE narratives for these patients are available in Section 14.3.2.2

Overview of Case Histories

Anidulafungin (1 case)

Patient ID # 04-003
Adverse Event: Atrial Fibrillation
Relationship to Study Drug: Possibly Related, (investigator assessment)
Study Drug: Anidulafungin
This is a 66 year old black male with a history of myocardial infarction, coronary artery bypass graft surgery x 4, hypertension, dyslipidemia, COPD, diabetes mellitus and renal insufficiency. He was admitted with congestive heart failure and hypotension and required mechanical ventilation. He developed MRSE bacteremia and subsequently developed candidemia. A serious adverse event of atrial fibrillation was reported on study day 2. Two hours after the second infusion of anidulafungin the patient developed atrial fibrillation. The event resolved the same day. The patient continued to receive anidulafungin without the event reoccurring.

Medical officer's comment
This patient's underlying cardiac and pulmonary diseases are risk factors for atrial fibrillation; it is difficult to attribute any causality to study drug in this case.

Patient ID # 12-007
Adverse Event: Convulsion
Relationship to Study Drug: Possibly Related, (investigator assessment)
Study Drug: Anidulafungin
A 49 year old black female with a history of respiratory failure, ventilator associated pneumonia, pulmonary hypertension, acute renal failure on dialysis, and septic shock. She was admitted for hypoxia, respiratory distress and was placed on mechanical

ventilation. During her hospitalization, the patient developed ventilator- associated pneumonia, septic shock, multi-system dysfunction, pleural effusion, anemia, metabolic acidosis, connective tissue disorder, a sacral decubitus ulcer and candiduria and candidemia.
On study day 6 the patient developed questionable seizure activity, described as irregular, rhythmic jaw movements/mouth twitching, which occurred intermittently throughout the day. She remained responsive during these episodes. A brain CT scan and EEG were non-diagnostic, a neurology consultant questioned whether this event was a seizure. The patient was on imipenem/cilastatin for pseudomonas pneumonia during this time period. According to the investigator, the questionable seizure activity was "unlikely but possibly" related to study medication or possibly due to imipenem/cilastatin. Concurrent to this event, the patient had a respiratory acidosis and eventually required intubation. One month later, the patient experienced a grand mal seizure that was considered unlikely related to study drug.

Medical officer's comment
In this case, it appears that the actual diagnosis of seizure was in question. The patient has multiple risk factors for the development of seizure activity such as concurrent hypoxia, and metabolic acidosis. I agree with the investigators assessment that imipenem/ cilastatin could have contributed to seizure activity in this case.

Fluconazole cases (2 cases)

Patient ID # 33-007
Adverse Event: Elevated Liver Enzymes
Relationship to Study Drug: Possibly Related, (investigator assessment)
Study Drug: Fluconazole
This 81-year-old Black female had a significant medical history of hypertension, congestive heart failure, gastrointestinal cancer, breast cancer/mastectomy, dementia, bilateral renal stent placement and suspected retroperitoneal fibrosis. She was hospitalized on [ ] for impaired mental status. She was found to be in acute renal failure (creatinine 7.6 mg/dL, BUN 119 mg/dL) and urosepsis. She was treated with ampicillin, gentamicin, cefazolin, and aggressive rehydration. A renal ultrasound performed on [ ] revealed moderate right and mild left hydronephrosis. Blood and urine cultures on [ ] and [ ] were positive for Candida *albicans*. She received blinded study drug from 08June2004 to 25June2004. Her baseline alkaline phosphatase, ALT and AST values were within normal limits.
However on the last day of study drug these enzyme values were found to be elevated: alkaline phosphatase (alk Phos) 489 U/L (baseline 73 U/L); ALT 227 U/L (baseline 12 U/L); and AST 425 U/L (baseline 17 U/L). Oral fluconazole 400 mg daily began on 26June2004. Since the last day of study drug the enzyme values have been progressively decreasing. Fluconazole was completed on 02July2004. On 06July2004 the ALT was 72 U/L, alk phos 210 and the AST 43 U/L. The investigator considered the event of enzyme elevations to be fully resolved. Concomitant medications during study drug administration were doxycycline, cefazolin, potassium chloride, sulfamethoxazole,

metoprolol and diltiazem for hypertension, digoxin, Roxanol (morphine sulfate), and furosemide. According to the investigator, the event of increased hepatic enzymes was **possibly related** to the blinded study drug.

Medical officer's comment
The patient does not fulfill the criteria for Hy's rule. The fluconazole label carries a warning regarding hepatic toxicity. The patient was receiving ampicillin and cefazolin; both drugs can cause transient increases in SGOT, SGPT, and alkaline phosphatase levels. As with other cephalosporins, reports of hepatitis have been reported.

Patient ID # 07-010
Adverse Event: Deep Vein Thrombosis
Relationship to Study Drug: Possibly Related (investigator assessment)
Study Drug: Fluconazole
This is a 61 year old white female with a history of Crohns disease and numerous other medical complications. She was hospitalized for complications of Crohn's disease, and *C. difficile* colitis. She developed candidemia and received 14 days of fluconazole therapy during her 22-day hospitalization. On Day +1, the patient was readmitted for pain and swelling in the lower left leg. An ultrasound revealed a thrombus extending to her iliac vein. She responded to medical therapy, completely recovered and was discharged from the hospital. According to the investigator the event was related to the study medication and to the recent prolonged hospital stay.

4. Discontinuations from Study Medication

Fifteen (15 [11.5%]) patients in the anidulafungin arm and 27 (21.6%) patients in the fluconazole arm had AEs leading to discontinuation of study medication. In general, the most common adverse events leading to study drug discontinuation were multi-organ failure and systemic *Candida* infection for the anidulafungin arm. The most common adverse events leading to discontinuation were cardiac arrest and septic shock for the fluconazole arm. The investigator considered the event related to anidulafungin for one patient, and related to fluconazole for four patients. One patient, ID #03-004 discontinued anidulafungin due to moderately increased liver enzymes.

TABLE 10 RELATED ADVERSE EVENTS LEADING TO DISCONTINUATION OF STUDY DRUG

Treatment Patient ID	Sex	Age (years)	Event	Start Day*	Severity	Outcome
Anidulafungin						
03-004	M	63	Elevated liver enzymes	5 (+1)	Moderate	Recovered
Fluconazole						
04-016	F	77	Worsening of candidemia	3	Moderate	Recovered
23-004	F	45	Increased liver function tests	1	Moderate	Recovered
			Clogged hearing	2	Mild	Recovered
			Weakness	2	Mild	Recovered
			Chest tightness	2	Mild	Recovered
			Light Headed	2	Mild	Recovered
38-001	F	31	Rash	1	Severe	Ongoing
75-001	M	72	Elevated liver enzymes	33	Moderate	Ongoing

* Relative to start day of study medication with an additional "(+X)" to indicate days after stopping study medication.
Source: Data from Appendix 16.2.4, Listing 2.1, Appendix 16.2.7, Listing 5.4.

Anidulafungin (1 case)

Study patient, ID #03-004

This 63-year-old White male had a significant medical history of seizure disorder, poorly differentiated lymphoma (1986) that required resection of a lymphomatous abdominal mass and repeat radiation therapy. He also had a history of a lung abscess (1999), deep vein thrombosis (DVT) and pulmonary embolism [(PE) (2003)], hypothyroidism, and respiratory insufficiency that required tracheostomy in [ ] with reversal in [ ].

The patient was hospitalized on [ ] with pleural effusions and candidemia due to *C. albicans*. He was enrolled in VER002-9 for treatment of candidemia and received anidulafungin from [ ] when study medication was discontinued due to elevations in hepatic enzymes. The patient received cefepime, ([ ] The patient was also receiving phenytoin, primidone for seizure prophylaxis, and warfarin because of the prior DVT and PE. He continued on caspofungin from [ ] and fluconazole [ ] and then caspofungin from [ ]. He developed a DVT, and was subsequently discharged on [ ] The baseline AST =31 (9-45), and the highest AST =144 U/L on the 5th day of therapy. The

investigator stopped the drug on day 4 of anidulafungin therapy. The liver enzymes began to trend down within 24 hours after stopping drug and had completely resolved off anidulafungin at day 16. Cefepime therapy was stopped on [redacted], day 10.

Hepatic Chemistry, Patient ID #03-004

	[redacted] (day 1)	(day3)	(day 5)	(day 6)	(day 16).	[redacted] (day 42).
AST *U/L*	31	48	144	61	25	26
ALT *U/L*	37	57	125	91	20	26
ALKP *U/L*	139	132	275	288	200	133
Total bilirubin *mg/dl*	0.3	0.1	0.4	0.3	0.2	0.2
Albumin g/dl	2.2	2.2	1.9	2.2	2.0	2.9

Medical officer's comment
There was a gradual increase and decrease in hepatic transaminases. Concurrent therapy with cefepime could have contributed to the elevation in hepatic transaminases. Similar to other cephalosporins, cefepime can cause hepatic dysfunction and cholestasis. *It is reassuring that the elevation in liver enzymes was gradual and reversible.*

Fluconazole (2 cases)

Two of the study patients, ID #23-004, and ID #75-001 discontinued fluconazole due to elevated liver enzymes. Patient ID #23-004 recovered, and patient ID # 75-001 later died due septic shock 38 days after the end of the study period.

Patient ID # 75-001
A 72-year-old White male was hospitalized [redacted] for an aortic valve replacement. On the same day, he developed a cerebral infarction and was diagnosed with *Staphylococcus aureus* endocarditis. Post-surgical hospitalization was complicated by bacterial sepsis, septic shock, cortical adrenal insufficiency, acute tubular necrosis and renal failure that required hemodialysis. Other complications occurring during hospitalization included, splenic bleeding and splenectomy, a duodenal perforation requiring a partial duodenal resection, and episodes of atrial fibrillation. Blood cultures from an arterial line and cultures of peritoneal fluid were positive for *C. albicans* and *Enterococcus faecium*. He was then enrolled in VER002-9 for treatment of candidemia. He received intravenous fluconazole as study medication beginning [redacted] the patient experienced a rectal bleed that resolved in one day. On [redacted] he developed systemic inflammatory response syndrome that resolved following surgical evacuation of an abdominal hematoma and insertion of a drain.
Study medication was permanently discontinued on [redacted] (day 33) for elevated hepatic enzymes. Screening values for ALT and AST (23 U/L and 42 U/L, respectively) rose to 45 U/L and 69 U/L, respectively, by Day 22 [redacted] and increased further by [redacted] (80 U/L and 79 U/L, respectively). The investigator

considered the elevations to be ongoing at the end of the study (ALT: 54 U/L; AST: 51 U/L on [redacted]). Concomitant medications included flucloxacillin, dobutamine, norepinephrine, midazolam, nadroparin, hydrocortisone, morphine, metoclopramide, human insulin, amiodarone, potassium chloride, pantoprazole, fentanyl, propofol, ciprofloxacin, heparin, ipratropium bromide and teicoplanin. According to the investigator, the elevation in hepatic enzymes was possibly related to the study medication. The patient died 38 days after the end of the study due to septic shock, assessed to be unrelated to previous study drug therapy.

Patient ID # 75-001

	Screen, [redacted]	[redacted] day 22	[redacted] day 33	[redacted] day 47
AST U/L	42	69	79	51
ALT U/L	23	45	80	54
ALKP U/L	Not available			

Patient ID # 23-004

A 45 year old Black female with a significant history of hypertension, obesity, cocaine abuse, congestive heart failure, hypercholesterolemia, Type 2 diabetes mellitus [redacted], COPD, and respiratory failure [redacted] developed MRSA pneumonia in [redacted] and was hospitalized. She underwent thoracotomy open lung biopsy and lung lavage. In [redacted] she was diagnosed with lung cancer and interstitial lung disease. In addition, she developed bacterial sepsis that was treated with vancomycin in combination with other antibiotics (metronidazole, cefepime, cefazolin and gatifloxacin).

She developed candidemia due to *C. albicans* on [redacted] She received one dose of intravenous fluconazole and was then enrolled and randomized to fluconazole. She received IV fluconazole on [redacted] when study medication was discontinued due to moderate elevations in liver enzymes and a series of other mild, non-serious adverse events (i.e. clogged hearing, weakness, chest tightness, and light-headedness).

ALT and AST were elevated at baseline on [redacted] (55 and 78 U/L, respectively) and rose steadily beginning [redacted] to maximum values of 153 U/L over subsequent days. The investigator indicated that the elevations resolved by 30 March 2004. Values obtained for ALT and AST on 4 April 2004 were 40 and 36 U/L, respectively. According to the investigator, the elevation in hepatic enzymes and all of the other events that led to discontinuation of study medication were possibly related to treatment.

Medical Officers Comment

The gradual increase and decrease in hepatic transaminases are similar between fluconazole and anidulafungin in these three patients.

Hepatobiliary Adverse Events
(See also Hepatic Safety Review)

1. All Hepatic Adverse Events Reported
There were more hepatobiliary events in the fluconazole arm compared to the anidulafungin arm. A total of five anidulafungin treated patients and eight fluconazole treated patients had a hepatobiliary adverse event, Table. 36. Only one hepatic adverse event was considered possibly related to study drug. One patient in the anidulafungin arm (ID #37-003), developed cholestasis on Study Day 9. This case is described in further detail.

Table 36: All adverse events classified as hepatobiliary disorders in Study VER002-9

Treatment Patient ID	Event	Intensity	Related to Study Drug?	Action Taken	Outcome
ANID					
24-003	Cholecystitis	Moderate	No	Cholecystotomy	Recovered
37-003	Cholestasis	Moderate	Possibly	None	Ongoing
42-002	Hepatomegaly	Moderate	No	None	Ongoing
52-004	Cholecystitis	Mild	No	Surgery	Recovered
52-004	Jaundice	Moderate	No	None	Recovered
FLU					
12-011	Cholecystitis	Moderate	No	Non-pharm Rx added	Ongoing
24-008	Portal vein thrombosis	Moderate	No	New Drug Rx	Ongoing
24-012	Hyperbilirubinemia	Moderate	Unlikely	None	Ongoing
24-012	Hyperbilirubinemia	Severe	Unlikely	None	Ongoing
25-003	Cholestasis	Severe/SAE	No	Non-pharm Tx added	Recovered
32-002	Hepatic infarction	Severe	No	None	Recovered
39-002	Hepatic pain	Moderate	No	None	Ongoing
41-010	Gangrenous cholecystitis	Severe/SAE	Unlikely	New or prolonged hospitalization	Recovered

Data Source: VER002-9 CSR, Table 47.

Patient ID # 37-003

Adverse Event: Cholestasis

Relationship to Study Drug: Possibly Related

Study Drug: Anidulafungin

Patient 37-003 was a 53-year old white female with acute myelogenous leukemia, immunostimulant therapy, and disseminated candidiasis. The patient had undergone two rounds of inductive chemotherapy and one round of consolidation chemotherapy in the months preceding admission to the study. She received her first dose of anidulafungin on 18-Aug-2004. On Day 9 of therapy the patient was diagnosed with cholestasis that was considered as possibly related to study drug by the investigator. The patient completed the study. The cholestasis was ongoing at the time of the 6-week follow-up visit, 41 days after the last dose of study drug. Significant concomitant medications the patient received along with the study drug were: valsartan, estradiol, ciprofloxacin, acyclovir, omeprazole, filgrastim, phytomenadione, morphine, ceftriaxone sodium, diphenhydramine, piperacillin/tazobactam, lorazepam, diazepam, lidocaine, pethidine, vancomycin, paracetamol, and pamidronate sodium. Hepatobiliary parameters were as follows:

Hepatic Chemistry

	Study Day*	ALKP (IU/L)	AST (IU/L)	ALT (IU/L)	T. Bilirubin (mg/dL)
Normal Range		**0-120**	**10-32**	**0-30**	**0.3-1.8**
Screening	-1	ND	ND	ND	1.0
Screening	1	59	15	15	ND
Day 3	3	65	11	11	0.9
On Therapy	7	227 H CS	19	14	0.7
On Therapy	9	298 H CS	24	31 H	0.7
On Therapy	14	330 H CS	48 H	45 H	0.5
On Therapy	20	324 H CS	21	22	0.6
End-of-Therapy	28	287 H CS	12	7	0.5
2 Wk Follow-up	42 (+14)	412 H CS	21	20	0.6
6 Wk Follow-up	69 (+41)	360 H CS	38 H	13	0.4

Note: Abnormal values are flagged Low (L) or High (H), as appropriate, based on the normal range, and Clinically Significant (CS) if so designated by the investigator on the CRF.

ND = Not done.

* (-x) = number of days prior to the first dose of study drug; (x) = number of days since the first dose of study drug, i.e., since Day 1; (+x) = number of days after the last dose of study drug.

Data Source: VER002-9 CSR, Section 12.3.5.3.

Medical officer's comment

The elevated alkaline phosphatase is possibly related to the study drug, however a common abnormal finding in patients with chronic disseminated candidiasis is an increase in alkaline phosphatase. The level of alkaline phosphatase in some cases may exceed 10 - fold normal values. One could speculate that the patients underlying disseminated candidiasis may have been the cause of the abnormal alkaline phosphatase or at least contributing to the elevation in hepatic enzymes that was observed. (Masood 2004, Thaler 1988, Haron 1987, Talbot 1988).

2. Special Analysis Based On Hepatic Chemistry Parameters

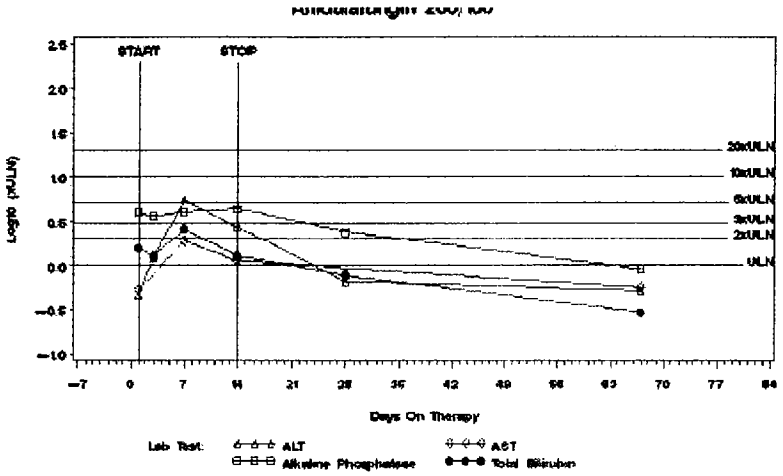
To address the FDA request for additional hepatic safety data the sponsor submitted a hepatologist's ([ ]) expert report covering eight studies. The findings in the report for this study of invasive candidiasis, VER002-9 are summarized.
To analyze the data, the hepatologist requested the following data in the following order:
1) Liver chemistry data from all clinical subjects who at any time experienced elevations ≥ 2 fold in any of the standard liver chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or bilirubin. These data were presented by graphing the serial value (expressed as log ULN on the y axis) versus time in study on the x-axis. *(This method of data presentation was first proposed by the FDA).*
2) Dr. [ ] then examined each subject graph and selected for further study any subject that fit the following conservative Hy's Rule definition:
ALT rise to > 2 X ULN, and concomitant or up to one month delayed rise in bilirubin > 1.5 X ULN.

There were more Hy's rule cases in the fluconazole arm. The hepatologist found one case in the anidulafungin arm and six cases in the fluconazole arm in the invasive candidiasis study(VER002-9). Case summaries for these patients are taken directly from the hepatologist's expert report.

Anidulafungin (1 case)

Patient ID #41-006:
This is a 46 year-old white male with a history of lymphoma, recent renal failure/insufficiency, node dissection, and splenectomy. At screening he presented with candidemia. He received study drug from 17-Oct-2003 to 30-Oct-2003. Prior and concomitant medications included ciprofloxacin, cefazolin sodium, vancomycin, cyclophosphamide, vinblastine, dexamethasone, and procarbazine.
He experienced a 5-fold increase in serum ALT and a 1.6-fold increase in serum bilirubin 7 days into treatment with anidulafungin. Serum alkaline phosphatase was elevated throughout treatment, but did not show much rise during treatment However, the bilirubin returned to normal despite continued treatment with anidulafungin, which is not consistent with severe drug induced liver injury. AST and ALT trended down between day 7 and Day 14 despite continued therapy with anidulafungin. The hepatologist concluded that this case was unrelated to anidulafungin.

Patient # 41-006	Oct 17th			Oct 30th			Upper Limit
Hepatic Parameter	Day 1	Day 3	Day 7	Day 14	Day 28	Day 67	Normal Range
Alk Phos	478	433	484	523	290	110	120 U/L
ALT	19	51 H	221	110	27	21	40 U/L
AST	19	ND	67	40	ND	20	35 U/L
Total Bilirubin	1.6	1.3	2.6	1.3	0.8	0.3	1 mg/dL



Fluconazole (6 cases)
Five cases fulfilled the criteria for Hy's rule. Two cases were characterized as ischemic liver injury. Definitive etiologies were not given for the other two cases but they were thought to be unrelated to fluconazole.
The two of these cases that were possibly related to fluconazole are summarized first.

1. Patient (ID #11-004): This is a 24 year old man who experienced 3-fold increases in both serum ALT and bilirubin ten days after termination of fluconazole therapy. Alkaline phosphatase was only elevated 1.5 fold at this time. The investigator considered this event possibly related to fluconazole.

2. Patient ID#18-010: This is a 74 year old man who experienced a 2.5 fold increase in ALT and a 2-fold increase in serum bilirubin at the end of two weeks of treatment with fluconazole. This event was thought by the investigator to be possibly related to fluconazole.

3. Patient ID #32-002 :This is a 62 year old woman who experienced a sudden and greater than 40-fold elevation in serum ALT and a > 5 fold elevation in bilirubin However, the patient experienced a cardiac arrest and the investigator felt the liver injury was due to **ischemic hepatitis**, which seems very likely.

4.Patient ID #04-009 is a 26 year old woman who also experienced a sudden elevation of > 20 fold elevation in serum ALT and a 2-fold elevation in serum bilirubin in the setting of a cardiac arrest. This **is a Hy's Rule case,** but it seems likely that the liver injury was **ischemic** in nature. This case also has biochemical similarities to the anidulafungin case 13-008 in the VER002-4 trial. Dr.[redacted] noted that this case was biochemically very similar to the index anidulafungin case ID #13-008 in the VER002-4 trial. *Note: Patient #13-008 died during the esophageal candidiasis study, VER-004.*

Please refer to page 116 of this document and the original review of NDA 21-632 for further detail on this case.

4. Patient ID #07-003: This is a 49 year old man who experienced a 4- and 2-fold increase in serum ALT and bilirubin, respectively. However, the serum alkaline phosphatase also rose, so this is not a Hy's Rule case.

5. Patient ID #20-010: This is a 62 year old man who experienced a 3-fold increase in serum bilirubin without a corresponding serum ALT recorded. However, serum AST rose > 4 fold so this case is included as a possible Hy's Rule case. This event was felt to be unrelated to fluconazole by the investigator but no other cause was assigned.

Clinical Laboratory Data

General safety - Serum Chemistry

There were no obvious differences in changes in creatinine, BUN and potassium levels between the two treatment arms, Table 39.

TABLE 37. NUMBER (%) PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHEMISTRY VALUES THAT WERE ALSO POTENTIALLY CLINICALLY SIGNIFICANT CHANGES FROM BASELINE, VER002-9

Parameter	Day 3	On Therapy[a]	End of IV Therapy	End of Oral Therapy	2 Week Follow-up	6 Week Follow-up
Anidulafungin						
Creatinine	N=123	N=104	N=114	N=30	N=89	N=71
High, inc(n,%)	1	2	2	0	0	0
BUN [a]	N=117	N=98	N=108	N=24	N=78	N=65
High, Increase (n,%)	0	1 (1.0)	1 (0.9)	0	0	1 (1.5)
Potassium	N= 123	N= 104	N= 118	N= 30	N= 90	N= 70
High, Increase (n,%)	0	1(1.0)	0	0	0	0
Low, Increase (n,%)	5(4.1)	5(4.8)	2(1.7)	0	1(1.1)	0
Fluconazole						
Creatinine	N=114	N=85	N=108	N=23	N= 74	N=56
High, inc(n,%)	1(0.9)	2 (2.4)	1(0.9)	0	1(1.4)	1(1.8)
BUN [a]	N=113	N=83	N=106	N=24	N=74	N=55
High, Increase (n,%)	0	2 (2.4)	2 (1.9)	0	1 (1.4)	0
Potassium	N=116	N=86	N=108	N= 24	N= 74	N= 56
High, Increase (n,%)	0	0	0	1 (4.2)	2 (2.7)	0
Low, Increase (n,%)	2 (1.7)	3 (3.5)	2 (1.9)	0	2 (2.7)	0

a: If BUN was not available then urea value was used.

Note: N is the number of patients included in the analysis for the specified parameter at the specified visit. Percentages are based on number of patients in the ITT population with a baseline value and a post-baseline value for the specified parameter at the specific Post baseline potentially clinically significant changes still within normal range are not included.

Source: Data from Section 14.3, Table3.27.

3. Significant Hepatic Chemistry Abnormalities

Hepatic Chemistry
A total of 20 anidulafungin patients and 27 fluconazole patients who had an ALT > X3ULN, an AST > X3 ULN, and/or an ALT > X3 ULN plus a total bilirubin >1.5 ULN. No anidulafungin-treated patient, at any time during the study, had ALT > 20 x ULN or an AST > 10 x ULN.

TABLE 38. NUMBER (%) OF PATIENTS WITH SPECIFIED ABNORMALITIES IN HEPATIC PARAMETERS DURING THE STUDY, VER002-9

Treatment Group Parameter Criterion	Baseline	Day 3	On Therapy*	End of IV Therapy	End of Oral Therapy	2-Week Follow-up	6-Week Follow-up
ANIDULAFUNGIN ARM							
Patients with ALT >3 x ULN + Total Bilirubin >1.5 x ULN	N=122 1 (0.8)	N=115 2 (1.7)	N=90 2 (2.2)	N=84 0	N=25 0	N=70 0	N=58 0
Patients with	N=128	N=116	N=93	N=87	N=25	N=71	N=61
ALT >3-5xULN	3 (2.3)	3 (2.6)	2 (2.2)	1 (1.1)	1 (4.0)	2 (2.8)	2 (3.3)
ALT >5-10xULN	2 (1.6)	1 (0.9)	1 (1.1)	0	0	1 (1.4)	0
ALT >10-20xULN	0	0	0	0	0	0	1 (1.6)
Patients with	N=127	N=115	N=91	N=88	N=25	N=70	N=61
AST >3-5xULN	4 (3.1)	1 (0.9)	2 (2.2)	1 (1.1)	2 (8.0)	2 (2.9)	1 (1.6)
AST >5-10xULN	2 (1.6)	1 (0.9)	0	0	0	0	1 (1.6)
FLUCONAZOLE ARM							
Patients with ALT >3 x ULN + Total Bilirubin >1.5 x ULN	N=117 3 (2.6)	N=102 2 (2.0)	N=82 0	N=88 2 (2.3)	N=23 0	N=62 0	N=50 0
Patients with	N=120	N=104	N=84	N=88	N=23	N=64	N=51
ALT >3-5xULN	8 (6.7)	5 (4.8)	3 (3.6)	4 (4.5)	0	0	0
ALT >5-10xULN	3 (2.5)	0	2 (2.4)	0	0	1 (1.6)	0
ALT >10-20xULN	0	1 (1.0)	0	0	0	0	0
ALT >20xULN	0	1 (1.0)	0	1 (1.1)	0	0	0
Patients with	N=120	N=105	N=83	N=90	N=23	N=65	N=50
AST >3-5xULN	7 (5.8)	4 (3.8)	4 (4.8)	4 (4.4)	0	0	0
AST >5-10xULN	2 (1.7)	2 (1.9)	0	2 (2.2)	0	0	0
AST >10-20xULN	0	1 (1.0)	0	0	0	0	0
AST >20xULN	0	1 (1.0)	0	1 (1.1)	0	0	0

* "On Therapy" includes patients with a value after Day 3 but before End of IV Therapy.

Note: Percentages are based on the number of patients in the ITT population who have appropriate laboratory values at the specified visit. N is the number of patients in the analyses for the specified parameters at the specified visit.

Source: Data from Section 14.3, Table 3.28. Table 58

Hepatobiliary Parameters

This table summarizes shifts from baseline in AST, ALT and Alkaline phosphatase for the two treatment arms. The majority (>96%) of patients in both arms had AST and ALT levels ≤ X3 normal at baseline. There were slightly more patients with abnormal baseline LFTs in the fluconazole arm compared to the anidulafungin arm, 96.1% versus 99.1%, respectively. There were more patients in the fluconazole arm with larger transitions in AST (X 3-5 ULN, and X 5-10 ULN), and ALT levels (X 3-5 ULN, and X 5-10 ULN).

TABLE 39. SUMMARY OF TRANSITIONS IN HEPATOBILIARY PARAMETERS FROM BASELINE AT ANY STUDY VISIT (ITT POPULATION)

	Parameter Range at Any Post-Baseline Study Visit							
Parameter	**Anidulafungin Arm**				**Fluconazole Arm**			
Baseline Category	≤ 3xULN	>3-5xULN	>5-10xULN	>10xULN	□ 3xULN	>3-5xULN	>5-10xULN	>10xULN
ALT	N=112	N=7	N=3	N=1	N=103	N=10	N=1	N=3
<=3xULN	111 (99.1)	5 (71.4)	3 (100.0)	0	99 (96.1)	5 (50.0)	0	2 (66.7)
>3-5xULN	1 (0.9)	1 (14.3)	0	1 (100.0)	3 (2.9)	3 (30.0)	1 (100.0)	1 (33.3)
>5-10xULN	0	1 (14.3)	0	0	1 (1.0)	2 (20.0)	0	0
AST	N=112	N=8	N=2	N=0	N=100	N=10	N=5	N=3
<=3xULN	109 (97.3)	7 (87.5)	1 (50.0)	0	98 (98.0)	6 (60.0)	3 (60.0)	2 (66.7)
>3-5xULN	2 (1.8)	1 (12.5)	1 (50.0)	0	1 (1.0)	3 (30.0)	2 (40.0)	1 (33.3)
>5-10xULN	1 (0.9)	0	0	0	1 (1.0)	1 (10.0)	0	0
Alkaline Phosphatase	N=99	N=15	N=6	N=2	N=97	N=8	N=10	N=1
<=3xULN	98 (99.0)	11 (73.3)	4 (66.7)	1 (50.0)	97 (100.0)	5 (62.5)	8 (80.0)	0
>3-5xULN	1 (1.0)	4 (26.7)	0	0	0	2 (25.0)	2 (20.0)	0
>5-10xULN	0	0	2 (33.3)	1 (50.0)	0	1 (12.5)	0	0
>10xULN	0	0	0	0	0	0	0	1 (100.0)

Note: "N" is the number of patients with a value for baseline and at least one on-treatment value (irrespective of study visit) for the specified parameter. All percentages are based on the presented "N" values.

Data from Section 14.3, Table 3.29. Table 59

VITAL SIGNS

There were no obvious differences in vital signs between the two treatment groups.

Cardiac Safety, QT prolongation

In the clinical safety database, there were 4 patients with an AE of QT prolongation. Three of the 4 patients received anidulafungin (Patients 02-008, 04-014 and 33-008) and the fourth patient received fluconazole (Patient 30-001). Centralized ECG reading by an independent expert cardiologist did not confirm any QT abnormalities for the 3 patients treated with anidulafungin.
Patient ID #02-008 was a 59 year-old female with bacterial sepsis, diabetes mellitus, stroke and peritoneal dialysis for chronic renal failure. Baseline ECG was reported as abnormal.
Patient ID #04-014 was a 63-year-old female who was ventilator dependent upon enrollment into the study following a cardiac arrest. Past medical history included marked hypertension. On Study Day 3, QT prolongation was reported as possibly related to blinded study medication. This patient was on numerous concomitant medications including levofloxacin, which can cause QT abnormalities.
Patient 33-008 was a 57-year-old female who had bacterial sepsis, renal failure, and an Apache II score of 18 at baseline. Past medical history included coronary artery disease, angioplasty with stents and CABG. Anidulafungin was administered for 14 days. On Study Day 3, mild QT prolongation was reported as unlikely to be related to study drug.

Standard 12-lead EKGs were recorded for 245 patients. EKGs were done at screening and on day 3 of the study. Five patients in the fluconazole arm had a protocol violation, i.e. no EKG pre-therapy. Twenty-six patients (13 patients in each arm) did not have an EKG on therapy. Paired EKGs were recorded for 214 patients. Paired EKGs with pre and on-therapy QT measurements were done for 202 patients. A cardiology expert analysis of these EKGs found that exposure to anidulafungin fluconazole had a slight effect on heart rate (-5 and -3msec respectively). These drugs did not elicit any effect on atrioventricular conduction (PR interval) and on intraventricular conduction (QRS interval). The effect on QTcF (Fredericia correction) was close to 0.0 msec for anidulafungin, and was 6.1msec for fluconazole for the 202 patients.
In the full data set, 2 patients in the anidulafungin arm had a QTC over 500msec (i.e.515 and 516msec, respectively) and they both had abnormal baseline QT intervals (491, and 484msec, respectively. There was no significant increase in QT interval after drug exposure. Related clinical adverse events of QT prolongation were not confirmed by a cardiology expert.
In summary, cardiology experts found no clinically significant electrophysiological effect on EKG morphology by anidulafungin.

Review of Specific Organ Systems

Renal adverse events

Renal SAEs were experienced by 2.9% of patients in the anidulafungin group and 7.2% of patients in the fluconazole group. None of these renal SAEs were considered treatment-related.

Anaphylaxis

No anaphylaxis was reported in this study.

Medical officer's comment
A case of anaphylaxis due to caspofungin has been reported in the published literature, (The Medical letter, 2001).

Neurological Adverse Events

Convulsions were reported by 2.5% of anidulafungin-treated patients and 1.6% of fluconazole-treated patients. In one case, the investigator reported that the convulsion maybe possibly related to anidulafungin. The case is described below.

Patient 12-007 (Candidemia: *C. glabrata*)
A 49 year old black female with a history of respiratory failure, ventilator associated pneumonia, pulmonary hypertension, acute renal failure on dialysis, and septic shock. On study day 6 the patient developed questionable seizure activity described as irregular, rhythmic jaw movements/mouth twitching, which occurred intermittently throughout the day. She remained responsive during these episodes. A brain CT scan and EEG were non-diagnostic, a neurology consultant questioned whether this event was a seizure. The event occurred at 18 hrs after the last dose of anidulafungin.
The patient was started on imipenem/cilastatin for pseudomonas pneumonia on 6th of February (day3). Concurrent to this event, the patient had a respiratory acidosis (arterial blood gas pH 7.13, pO_2 48, HCO_3 25) and eventually required intubation. One month later, the patient experienced a grand-mal seizure that was considered unlikely related to study drug.
Note: This case is also described in the serious adverse events section.

Medical officer's comment
The diagnosis of seizure in this case was questioned by the neurologist who saw the patient. The neurological symptoms (rhythmic jaw movements/mouth twitching while the patient remained responsive), described (on day 6) for this patient is unlikely to be related to study drug. The case is confounded by other possible etiologies for neurological dysfunction or seizures that include hypoxia, acidemia, and imipenem/cilastatin therapy. Imipenem /cilastatin can be associated with CNS side effects including encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, and psychic disturbances including hallucinations.

Infusion Reactions

A total of 13.7% of anidulafungin-treated patients and 7.2% of fluconazole-treated patients had infusion reactions. Dyspnea was the most common infusion-associated adverse event, it was reported in 10.8% of anidulafungin treated patients, and 3.2% of fluconazole treated patients.
Two of the 22 patients in the anidulafungin group who experienced dyspnea had events classified as severe. Approximately, 2% of patients in each treatment group experienced flushing, with all events being mild or moderate. Rash was reported by 3.9% of anidulafungin-treated patients versus 8.8% of fluconazole-treated patients. Flushing occurred in three (approximately 2.3%) patients in both arms. Urticaria was experienced by 1.0% of patients in the anidulafungin group; Urticaria was not reported in the fluconazole group. No anaphylaxis was reported in this study.

TABLE 40. POSSIBLE INFUSION EVENTS DURING IV TREATMENT ONLY (ITT POPULATION)

Event	Anidulafungin N = 131 n (%)	Fluconazole N = 125 n (%)
Dyspnea*	9 (6.9)	4 (3.2)
Infusion related reaction	0	3 (2.4)
Flushing / Hot flushes	3 (2.3)	3 (2.4)

* includes dyspnea exacerbated
Data from Section 14.3, Table 3.7, and Appendix 16.2.7, Listing 5.3

TABLE 41. POSSIBLE HYPERSENSITIVITY EVENTS DURING IV TREATMENT ONLY (ITT POPULATION)

Event	Anidulafungin N = 131 n (%)	Fluconazole N = 125 N (%)
Pruritus[a]	4 (3.1)	0
Rash[a]	2 (1.5)	9 (7.2)
Dermatitis	0	1 (0.8)
Face edema/swelling	1 (0.8)	1 (0.8)

a: includes all forms
Data from Section 14.3, Table 3.7 and Appendix 16.2.7, Listing 5.3

Medical officer's comment
Dyspnea related to infusion: There was a difference between the two arms with regard to dyspnea during infusion (10.8% and 3.2%). The ITT database was searched for any adverse event related to respiratory symptoms such as dyspnea, shortness of breath, wheeze. Twenty-three patients were identified. The case reports for each patient was reviewed. The majority of patients had respiratory co-morbid conditions such as congestive cardiac failure, and pneumonia. Dyspnea did not lead to discontinuation of

study drug. The respiratory adverse events described were unlikely to be related to anidulafungin or fluconazole.

Conclusions Regarding Safety Data In Study VER002-9

Anidulafungin was well tolerated in this group of critically ill patients with invasive candidiasis, mostly candidemia. Adverse events were reported by 130 (99.2%) patients in the anidulafungin arm and 122 (97.6%) patients in the fluconazole arm.
SAEs were considered related to treatment for only 2 patients in each study arm.
The proportion of patients with related adverse events was similar in the two treatment arms (approximately 25%). Fewer anidulafungin-treated patients (15, 11.5%) than fluconazole-treated patients (27, 21.6%) experienced an AE that led to discontinuation of study drug. Fewer anidulafungin-treated patients (30, 22.9%) than fluconazole-treated patients (39, 31.2%) died during and shortly after the study. None of the deaths were attributed to study drugs by the investigator. This review did not identify any deaths related to study drug. There were no cases of anaphylaxis. Infusion reactions were mild and rare. Seizure activity appears unrelated to study drug.
The additional hepatic safety data provided in this study demonstrates that there were more hepatic adverse events in the fluconazole group. Six patients in the fluconazole arm and one patient in the anidulafungin arm fulfilled the criteria for Hy's rule (ALT rise to > 2 X ULN, and concomitant or up to one month delayed rise in bilirubin > 1.5 X ULN). The Hy's rule patient in the anidulafungin arm was unrelated to study drug, and the patient continued on anidulafungin. The bilirubin returned to normal despite continued treatment with anidulafungin, which is not consistent with severe drug induced liver injury. Two patients who fulfilled the criteria for Hy's rule in the fluconazole arm were possibly related to study drug. Serious adverse events related to hepatic enzyme elevations were reported for one fluconazole patient and none of the anidulafungin treated patient.
No cases of hepatic failure, anaphylaxis, or QT prolongation occurred in either arm. Few systemic infusion reactions were reported. There was no major difference in adverse events. The safety data show that anidulafungin at a dose of 100 mg IV daily (for approximately two weeks) has a safety profile similar to and, in some instances, more favorable than that of fluconazole 400 mg IV daily in this critically- ill population.

HEPATIC SAFETY ACROSS STUDIES

Background
The FDA expressed concerns about potential liver toxicity at the time of the original review of NDA 21-362, following recognition of case #13-008. This was a confounded case of severe hepatic injury in a patient who died after three days of anidulafungin therapy. Therefore, additional safety was requested by the FDA on anidulafungin.
The applicant was advised to collate and analyze hepatic chemistry data from the clinical development program. Two hepatic safety documents were submitted by the applicant as

part of the complete response, a hepatologist's expert report and a hepatic safety summary for the clinical program.
Preclinical studies were reviewed in NDA21-632. In the preclinical studies in animals, mild to moderate liver toxicity was observed. In four- and thirteen week studies in rats and monkeys, increased liver weights, hepatocellular hypertrophy, increased AST and ALT and single cell hepatic necrosis were reported. Most of the hepatic adverse events in animals occurred at dosages 8 to 11-fold greater than those for the proposed dosage for esophageal candidiasis. (See Dr. Mc Master's and Dr. Ibia's original review of NDA 21-632). In healthy volunteer studies receiving multiple doses of anidulafungin, ALT elevations (< x 4 ULN) were asymptomatic and reversible upon cessation of treatment. These elevations tended to occur toward the end of the treatment period. Concomitant elevations in bilirubin were not observed. (See Dr Ibia's original review of NDA 21-632)

Medical officer's comment
A review of preclinical studies and healthy volunteer studies is contained in the original review of the NDA 21-632. The animal hepatotoxicity data presented is similar to that observed with other echinocandins. The ALT elevations observed in the healthy volunteer studies are not by themselves a significant liver safety signal. Results from all these studies indicate that close monitoring of liver function tests should be performed in patients receiving anidulafungin.

Methodology for Integrated Analysis of Hepatic Safety Across Studies
The applicant followed the strategy suggested by the FDA for collating hepatic chemistry data from the clinical program, i.e. hepatic chemistry data was collated from all clinical subjects who at any time experienced elevations ≥ 2 fold in any of the standard liver chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or bilirubin. These data were represented by graphing the serial value (expressed as log ULN on the y axis) versus time in study on the x-axis.
An expert hepatologist, Dr [ ], reviewed each subject graph and selected for further study, hepatic chemistry that fit the following conservative Hy's Rule definition:
*ALT rise to > 2 X ULN, **and** concomitant or up to one month delayed rise in bilirubin > 1.5 X ULN.* If the patient's baseline ALT or bilirubin was elevated, this baseline value replaced ULN in the search criteria. Following this analysis, narratives, and where indicated, original case report forms were reviewed for each of the cases identified by the above criteria.

Medical officer's comment
This methodology captures all significant hepatic chemistry abnormalities from the studies. The criteria used, ALT rise to > 2 X ULN, <u>and</u> concomitant or up to one month delayed rise in bilirubin > 1.5 X ULN is conservative. Concomitant elevations in serum bilirubin are recognized to indicate significant liver dysfunction. Low level elevations in ALT levels alone would not indicate significant hepatic injury.

Results

In the entire clinical development program, 1060 patients were exposed to anidulafungin. This included subjects who received oral doses, single-dose IV therapy, and sub-therapeutic doses. These types of exposures were not considered to reflect the safety of the proposed dosage regimen, and were excluded.

Table 42. Exposure To Anidulafungin During The Clinical Program

Route of Administration Dose Range	**Clinical Phase**	**No. of Subjects**
Oral		
Single dose: 25 – 1000 mg	1	35
Multiple dose: 100 – 600 mg	1 - 2	99[a]
Single-Dose Intravenous		
0.1 – 100 mg	1 - 2	113
Multiple-Dose Intravenous	1 - 3	
100 mg/day		337
< 100 mg/day		479
	Total	**1060**

Note;
a Includes three subjects in Study XBAW who received both single- and multiple-dose regimens.
Source: Submission 2005-05-27, Integrated Review of Safety, section 4.1

The remaining patients included a total of 690 anidulafungin-treated patients and 426 fluconazole-treated patients who were evaluated for hepatic safety assessment across studies. Among the 690 patients, 292 were new patients who were not reported in the original NDA 21-632.
These patients received multiple therapeutic doses ranging from 50mg and 100mg IV daily. Of the 690 anidulafungin-treated and 426 fluconazole-treated patients who had repeated IV doses, 294 (42.6%) and 152 (35.7%) patients respectively had elevations ≥ 2 x ULN in AST, ALT, ALKP, or total bilirubin. Patients who had baseline hepatic chemistry abnormalities were included.
Following a review of each subject graph, case narratives for 10/294 (3.4%) anidulafungin-treated patients and 8/152 (5.3%) fluconazole-treated patients were further reviewed, Table 43. A case by case assessment was done on whether each of these patients fulfilled the predefined criteria for Hy's rule.

Table 43: Number of Patients with Hepatic Figures and Narratives by Study

Study	No. of anidulafungin/ fluconazole-treated patients	No. of hepatic figures for anidulafungin produced (patients with 2-fold increase in transaminases)	No. of narratives for anidulafungin requested by Dr. [redacted]	No. of hepatic figures for fluconazole produced	No. of narratives for fluconazole requested by Dr. [redacted]
VER002-4	300/301	102	2	103	2
VER002-5	30	4	0	NA	NA
VER002-6	120	70	4	NA	NA
VER002-7	30	23	3	NA	NA
VER002-9	131/125	78	1	49	6
VER002-11	19	7	0	NA	NA
VER002-12	25	8	0	NA	NA
VER002-15	35	2	0	NA	NA
Total	690/426	294	10	152	8

Source: Adapted from Hepatology Experts Report, in submission 2005-05-27

Table 44 summarizes the cases that fulfilled the predefined criteria of ALT > x2ULN and total bilirubin >1.5 X ULN as well as the opinions of the hepatology expert, the investigator and the FDA clinical reviewer with regard to causation assessments. Cholestasis was not considered by the consultant and the clinical reviewer to reflect true hepatocellular injury. Patients who had predominant cholestasis and clear cases of shock liver were not regarded as cases of hepatocellular drug toxicity.

There were four Hy's rule cases in the anidulafungin group, and seven in the fluconazole group. Two of 294 (0.68%) cases among the anidulafungin-treated patients were considered by the clinical reviewer to be possibly related to anidulafungin and confounding factors that might account for the findings were present in both. One of 152 (0.66%) fluconazole-treated cases was considered by clinical reviewer to be possibly drug-related. The clinical reviewer and the hepatology expert came to a different conclusion with regard to causation assessment of one Hy's rule case, ID # 67-001. The hepatologist attributed the hepatic chemistry abnormalities in this case to be due to anidulafungin. The clinical reviewer and an FDA hepatologist concluded that tuberculosis drugs could have caused the hepatic chemistry abnormalities observed in this case, and therefore the case was confounded. A more detailed review of case #67-001 and all the cases in the hepatic safety analysis are included in Appendix A. Dr. Senior, hepatology expert at the FDA consulted on case #67-001, and his report is included in Appendix B.

Table 44: Summary of Cases and Causation Assessments

Patient ID # Study No.	age	sex	Study Drug Exposure	Prior and concomitant meds with potential for liver toxicity	Co morbid Disease	Causation Assessments and Comments Hepatologist	Investigator	FDA
Anidulafungin Cases								
13-008 VER002-4	53	M	100/50mg x 3 days	yes	AIDS TB Cor pulmonale	Unrelated Probable shock liver Hy's rule case	possibly related	[redacted]
16-003 VER002-4	35	M	100/50mg x 14days	yes	Disseminated TB Esophageal candidiasis	Unrelated Not Hy's rule	unrelated	Unrelated
001-002 VER002-6	37	M	150/75mg X 10 days	yes	Staph endocarditis candidemia	Unrelated Not Hy's rule	Unrelated	Unrelated
030-009 VER002-6	62	F	200/100mg X14 days	yes	Candidemia Respiratory arrest colon cancer	Multifactorial Not Hy's rule	Not stated	Multifactorial Unlikely related
033-002 VER002-6	75	M	150/75mg x 17 d	yes	Staph pneumonia, intestinal perforation Resp failure candidemia	Multifactorial Not Hy's rule	Not stated	Multifactorial Unlikely related
035-003 VER002-6	42	M	200/100mg x 11 d	yes	Surgery for colonic perforation Staph bacteremia Candidemia Alcoholic hepatitis	Unlikely related Not Hy's rule case	Unlikely related	Multifactorial Unlikely related
007-001 VER002-7	29	M	200/100mg X 38 days plus L-AmB	yes	Aspergillus endocarditis	Unlikely related Hy's rule case	Not stated	Multifactorial Unrelated
033-001 VER002-7	56	M	200/100mg X 28 days plus L-AmB	yes	Invasive Aspergillosis Acute leukemia	Related Not Hy's rule	Unrelated	Multifactorial Possibly related

67-001* ER002-7	33	F	200/100mg X 30 d	yes	Pulmonary aspergillosis Tuberculosis	Related Hy's rule case	Unrelated	possibly related but more likely to be due to TB drugs
-006 ER002-9	46	M	200/100mg X 30 d	yes	Pulmonary aspergillosis	Unrelated Hy's rule case		Unlikely related
Fluconazole cases								
-002 ER002-4	41	M	200mg/100mg x 14 days	yes	AIDS Esophageal candidiasis Disseminated TB	Unrelated Hy's rule case	unrelated	unrelated
-003 ER002-4	39	M	200mg/100mg x14 days	yes	AIDS Disseminated TB Esophageal candidiasis	Unrelated Hy's rule	Not stated	unrelated
-002 ER002-9	62	F	800/400mg X 2 d	yes	Pancreatic cancer Cardiac arrest	Unrelated Hy's rule case Probable shock liver	Not stated	unrelated
-009 ER002-9	26	F	800/400mg x 26 d	yes	Crohn's disease Small bowel resection Cardiac arrest	Unrelated Hy's rule case Probable shock liver	Not stated	Unrelated
07-003 VER002-9	49	M	800/400mg x 21 d	yes	Colonic perforation	Not Hy's rule	Not stated	unrelated
-004 ER002-9	24	F	800/400mg x 15 d	yes	Nasopharyngeal cancer Esophageal candidiasis	Not stated Hy's rule case	Possibly related	Inconclusive
-010 ER002-9	74	M	800/400mg x 15 d	yes	Bladder cancer	Not stated Hy's rule case	Possibly related	Possibly related
-010 ER002-9	62	M	800/400mg x 6 d		Bacterial sepsis Retroperitoneal bleed	Not stated Possible Hy's rule	unrelated	unrelated

*See Appendix A and B. Note: L-AmB = Liposomal Amphotericin B, AmBisome®

Conclusion
There were more Hy's rule cases in the fluconazole arm, seven versus four cases. Of the 690 patients with representative exposure to anidulafungin, the reviewer identified two cases of significant hepatic injury possibly related to anidulafungin. Both cases were confounded by concomitant intercurrent illness and drugs with potential for hepatotoxicity. The hepatic chemistry abnormalities resolved after drug discontinuation. Of the 426 fluconazole-treated patients, one cases of significant hepatic injury were considered possibly related to study drug by the clinical reviewer. The frequency of liver injury was slightly less with anidulafungin- than fluconazole-treated patients, and cases could not be definitively attributed to anidulafungin.

Analysis of the hepatobiliary parameters for the two comparative studies

A second analysis of the hepatobiliary parameters for the two comparative studies was performed by the clinical reviewer. In the esophageal candidiasis study (VER002-4), of the 431 anidulafungin-treated patients and 426 fluconazole-treated patients, 283 patients and 281 patients, respectively were evaluable for all hepatic chemistry on-therapy. Of the131 anidulafungin-treated patients in the invasive candidiasis study (VER002-9), between 90 to 93 patients were evaluable for hepatic chemistry on-therapy depending on the parameter being measured. In the fluconazole arm, there were 82 to 84 of 125 patients who were evaluable for hepatic chemistry on therapy depending on the parameter being measured. Repeat hepatic chemistry testing was not available on all subjects for a variety of reasons including withdrawal from the study due to death or lost to follow up. Two dosing levels were pooled i.e. 50mg IV daily and 100mg IV daily. The study populations consisted of patients with AIDS and critically ill hospitalized patients, all of whom had multiple co-morbid diseases. Table 45 integrates hepatobiliary parameters on therapy from the two comparative phase 3 studies.

Table 45: Integrated Summary of Hepatobiliary Parameters from Comparative Phase 3 Data on Therapy (Study VER002=4 and study VER002-9)

Hepatic parameter	Anidulafungin	Fluconazole
ALT> X3 ULN	18/376 (4.8%)	27/364 (7.4%)
ALT > X5 ULN	6/376 (1.6%)	9/364 (2.5%)
ALT > 10 ULN	0/376 (0.0%)	1/364 (0.27%)
AST > X3 ULN	43/374 (11.5%)	39/364 (10.7%)
AST > X5 ULN	17/374 (4.5%)	14/364 (3.8%)
ALT > X3 ULN and bilirubin > X1.5 ULN	4/283 (1.06%)	2/277 (0.72%)

The numbers of patients with abnormal hepatic chemistry abnormalities in the anidulafungin- and fluconazole-treated patients were similar. There were more patients with abnormal hepatobiliary parameters in the esophageal candidiasis study at the lower dose (50mg IV daily) than in the invasive candidiasis study at the higher dose (100mg iv daily). For example, 2 of 18 patients in the anidulafungin arm who had ALT > x 3 ULN, were in the invasive candidiasis study; 1of 6 patients in the anidulafungin group with

ALT > x 5 ULN, was in the invasive candidiasis study. The four anidulafungin-treated cases with ALT>3 XULN and total bilirubin > 1.5 x ULN are summarized in Table 45a.

Table 45a. **Anidulafungin cases with ALT>3 XULN and total bilirubin > 1.5 x ULN**

Patient ID # Study No.	Diagnosis	Comment on hepatic chemistry	Relationship to study drug by clinical reviewer
13-008 * VER002-4	Esophageal Candidiasis	Elevations in hepatic chemistry are most likely secondary to shock liver due to right heart failure	Unrelated
16-003* VER002-4	Esophageal candidiasis	Elevations in hepatic chemistry are most likely secondary to disseminated TB and TB drugs	Unrelated
41-006* VER002-9	Candidemia	Liver enzymes returned to normal despite continued treatment with anidulafungin	Unrelated
42-001 VER002-9	Candidemia	Hepatic transaminases and bilirubin were elevated at baseline and improved on anidulafungin	Unrelated

*See Appendix A for detailed discussion of these cases.

Conclusion

The percentage of biochemical hepatic abnormalities is similar for anidulafungin- and fluconazole- treated patients, see Table 45. The four anidulafungin patients with concurrent elevations of transaminases and bilirubin were considered to be unrelated to study drug upon detailed review as summarized above (Table 45a.)

Summary

In the preclinical studies, the majority of the hepatic adverse events in animals occurred at dosages 8 to 11-fold greater than those for the proposed dosage for esophageal candidiasis. Hepatic adverse events in preclinical studies were also found to be reversible upon cessation of drug administration. It is unlikely that any of these hepatic chemistry abnormalities were due to drug interactions because elimination of anidulafungin in preclinical studies was by chemical degradation indicating that the drug was not likely to interact with the metabolism of other drugs that might be used concomitantly with anidulafungin.

In Phase 1 studies in healthy volunteers, elevations in ALT levels tended to occur toward the end of the treatment period, were less than four times the upper limit of normal, were asymptomatic, and reversible off-therapy.

Phase 1 – 2 studies provided additional evidence of the hepatic safety of intravenous anidulafungin. Results from clinical studies in patients with renal insufficiency (study VER002-3) and hepatic insufficiency (study VER002-2) found that no dosage adjustments were required to compensate for hepatic or renal dysfunction.

In a pharmacokinetic study of anidulafungin in neutropenic children (age 2 to 17y), there was no dose-limiting toxicity at the doses tested and that there were no dose- or age-dependent differences in clinical chemistry values, changes from baseline for hepatobiliary parameters, or hepatobiliary parameters of potential clinical significance.

Five major studies were included in the phase 2-3 program. There was a range of doses from 50mg to 100mg daily in these studies. Two studies had a dose of 50mg IV daily for 14 to 21 days, i.e. the esophageal candidiasis study VER002-4 and the refractory mucosal candidiasis study, (VER002-11). One phase 2 study, (VER002-6) in patients with invasive candidiasis had maintenance doses of 50, 75, or 100 mg/day for 15 to 42 days. Two studies, an invasive candidiasis study (VER002-9) and an invasive aspergillosis study (VER002-7) had a maintenance dose of 100mg IV daily for $\geq$ 14 days. There were no serious hepatobiliary events in the follow-up open-label study to study 9, i.e. VER002-9b.
One case in the invasive candidiasis study (VER002-9) experienced a 5-fold increase in serum ALT and a 1.6-fold increase in serum bilirubin seven days into treatment with anidulafungin. The bilirubin level returned to normal despite continuation of anidulafungin. No case from the invasive candidiasis study was found to be related to anidulafungin therapy. One patient in the invasive aspergillosis study experienced a 20-fold increase in hepatic transaminases that was attributed to anidulafungin. Following a review of this case, the clinical reviewer and FDA hepatologist concluded that anti-tuberculosis medications could have caused the hepatic chemistry abnormalities observed in this case, and therefore the case was confounded. A second case in the invasive aspergillosis study had abnormal liver transaminases at baseline, the elevations in transaminases were reversible following discontinuation of study drug;this was not a Hy's rule case. Many of the cases in these studies were confounded by severe underlying disease and concomitant medications with potential to cause hepatotoxicity.
Other than case #13-008, already reviewed in the original NDA 21-632, no similar cases of fulminant liver injury were observed in any other patient during the clinical development program of anidulafungin. This patient most likely died from shock liver due to right heart failure and did not represent a case of anidulafungin toxicity. Two cases with similar hepatic profiles were found in the fluconazole arm of the invasive candidiasis study; the liver injury in these cases was reported to be due to shock liver and unrelated to study drug.

In summary, a few cases of significant hepatic dysfunction and hepatitis, were reported in patients receiving anidulafungin in studies completed since the original NDA submission. However, a causal relationship to anidulafungin was not established. In the two comparative studies with fluconazole, both sets of data were confounded by co-morbid conditions and concomitant medications with potential for hepatotoxicity. No hepatic safety concerns emerged when compared to fluconazole. As with other FDA approved echinocandins, monitoring of hepatic function should be done at baseline and during anidulafungin therapy. Significant elevations in hepatic chemistry should prompt an assessment of the risks and benefits of continuing therapy.

RISK/BENEFIT ANALYSIS

Anidulafungin is a useful addition to the current antifungal armentarium for esophageal candidiasis. There is a need for new fungicidal agents with fewer drug interactions. *Candida albicans* accounts for greater than 90% of *Candida* isolates in esophageal candidiasis. Fluconazole is the commonly prescribed antifungal agent for esophageal candidiasis, however fluconazole resistance has been described in *Candida albicans.* Infection with non-albicans *Candida* species are increasing in hospitalized patients, and some of these species are less susceptible to fluconazole.

Echinocandins, including anidulafungin are fungicidal *in vitro* against *Candida* species including species that are less susceptible or resistant to azoles, such as *C. glabrata and C. krusei*, respectively. Anidulafungin is active against fluconazole- resistant, and fluconazole- susceptible strains of *Candida* species, (Pfaller 1997, Vazquez 2005).

It must also be stated that a correlation between antifungal *in vitro* susceptibility testing and clinical outcome has not been adequately demonstrated. No cross resistance between anidulafungin and azoles or polyenes have been demonstrated *in vitro*, and therefore anidulafungin could be used for treatment of azole-resistant and polyene-resistant *Candida* species (Pfaller 1997, Steinbach 2004, Vazquez 2005).

Severe disease and azole- refractory esophageal candidiasis, seen in patients with advanced AIDS, can be difficult to treat and an intravenous agent is sometimes required as initial therapy. Amphotericin B formulations have excellent fungicidal activity against *Candida* species but are associated with renal toxicity. Anidulafungin has a clear advantage over amphotericin B in these types of cases.

Anidulafungin is not metabolized by the kidney and has not been associated with renal toxicity. A dose adjustment is not required for renal insufficiency. This agent would be of benefit in a patient with renal insufficiency who is potentially at risk for developing renal toxicity from amphotericin B. A dose adjustment is required for azole drugs in patients with renal insufficiency. Intravenous voriconazole is contraindicated in patients with moderate or severe renal impairment.

Uniquely among the echinocandins, anidulafungin is eliminated almost exclusively by slow chemical degradation, and not by hepatic metabolism. Dose adjustments are not required in mild, moderate or severe hepatic insufficiency. The currently approved echinocandins have not been studied in severe hepatic insufficiency. A dose adjustment for moderate hepatic insufficiency is recommended for other approved echinocandins, caspofungin, and micafungin. As with echinocandin drugs, isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to anidulafungin has not been established.

It is recommended for echinocandins that patients who develop abnormal liver function tests during therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing therapy.

Anidulafungin has an advantage over some other echinocandins in that it does not interact with some of the immuosuppressive drugs commonly used in clinical practice. In drug interaction studies, there were no interactions between anidulafungin and, tacrolimus and cyclosporine. Concomitant use of caspofungin and cyclosporine is not recommended. Monitoring of tacrolimus levels and appropriate tacrolimus dose

adjustments are required for patients receiving caspofungin and tacrolimus. No drug interactions have been demonstrated between anidulafungin, and voriconazole.
Anidulafungin was efficacious in the treatment of esophageal candidiasis, as demonstrated in VER002-4, the pivotal, phase 3, randomized, controlled, double-blind, double-dummy trial. In this population, most of which had AIDS, the primary analysis of efficacy demonstrated that anidulafungin is at least as efficacious as fluconazole, as assessed by endoscopic success at the end of therapy (97.2% in the anidulafungin; 98.8% in the fluconazole group, treatment difference -1.6%; (95% CI -4.1, 0.8). A high relapse rate off- therapy was demonstrated in this study. Anidulafungin was as effective as the comparator agent during the 14-21 day treatment period but was associated with a significantly higher rate of relapse at two weeks post therapy. Consideration of the relapse rates off-therapy should be taken into account when considering anidulafungin as initial therapy.
Anidulafungin has shown efficacy in other forms of invasive candidiasis. In a randomized controlled clinical trial of anidulafungin in patients with invasive candidiasis, anidulafungin had statistically superior anti-*Candida* activity over fluconazole at all time points. In the anidulafungin arm, 96 patients (75.6%) had a global success versus 71 patients (60.2%) in the fluconazole arm. The between group difference in global success rate (anidulafungin minus fluconazole) was 15.42% (95% CI 3.85, 26.99). The majority of study subjects were critically ill patients (~90%) with candidemia. Patients were treated with a 200mg IV loading dose followed by 100mg IV daily i.e. double the proposed dose for treatment of esophageal candidiasis study.
There were no major safety concerns for this dose of anidulafungin compared to fluconazole. Most patients did not experience adverse events related to study medication. The two most common related adverse events for anidulafungin were hypokalemia (3.1%) and diarrhea (3.1%). For fluconazole, the two most common related adverse events were increased hepatic enzyme (7.2%) and increased blood alkaline phosphatase (4.0%). In this study the hepatic toxicity profile of anidulafungin was comparable with that of fluconazole.
Anidulafungin is intravenous product only (same as all other approved echinocandins), which potentially limits its use to hospitalized patients.
In summary, anidulafungin has a favorable risk/benefit ratio in the treatment of esophageal candidiasis. It has shown efficacy in esophageal candidiasis, and in candidemia. Safety concerns are mainly related to hepatic effects. A review of the data submitted in the complete response shows that the hepatic toxicity profile of anidulafungin was comparable with that of fluconazole. Anidulafungin appears to be similar to other echinocandins in its hepatic and overall safety profile. As with other approved echinocandin drugs, isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to anidulafungin has not been established. Monitoring of hepatic function is recommended for patients receiving anidulafungin.

APPENDIX A

Predefined Hepatobiliary Parameters by the Applicant
The applicant's predefined abnormalities in hepatobiliary parameters in the clinical studies are as follows, ALT or AST: >3, 5, 10, or 20 x ULN, Alkaline phosphatase >1.5x ULN, and ALT or AST >3 x ULN + total bilirubin >1.5 x ULN. These criteria are used in the following studies to define abnormal hepatic chemistry.

Study VER002-7

Study VER002-7 is an open-label, phase 3, non-comparative study of the safety and efficacy of intravenous anidulafungin plus liposomal amphotericin B (AmBisome®) as treatment for invasive Aspergillosis. A total of 32 patients were enrolled; 30 patients received at least one dose of study medication. Eighteen patients reported 43 AEs that were considered related to one or both study drugs; 20 of these events were related to AmBisome.

Hepatic Adverse Events

Related Non-Serious Hepatic Adverse Events
Five patients had non-serious hepatobiliary AEs that were possibly related to anidulafungin by investigator attribution. Of these, 4 had elevated GGT or ALKP at baseline.

Related Serious Adverse Events
Sixteen patients reported a total of 21 hepatic AEs. Four patients had abnormal liver function tests reported as severe AEs (two patients) or as serious AEs (two patients) as summarized in Table 46. Two of these AEs were considered possibly/probably related to anidulafungin (ID # 67-001 and 33-001). One of the four patients (patient #ID 67-001) required discontinuation of study medications i.e. anidulafungin and AmBisome after stopping four medications for tuberculosis. Brief summaries of the four patients follow.

Table 46: Patients with Abnormal Hepatobiliary Parameters Recorded as Severe or Serious Adverse Events in patients with invasive aspergillosis

Patient Number	Hepatic Parameter	Unit	Normal Range	Baseline Value	Study Day	Abnormal Value	Categorization-Attribution	Expected Event for AmBisome?	Co-morbid Condition
007-001	ALKP	U/L	35-125	118	28	236	AE-unrelated	N/A	*Aspergillus* endocarditis
	GGT	U/L	8-78	N/A		507			
	AST	U/L	17-59	39		8736			
	ALT	U/L	21-72	51		5230			
	Total Bilirubin	mg/dL	0-1.2	0.2		2.7			
033-001	ALKP	U/L	24-110	149	30	449	AE-possibly	No	Sepsis syndrome
	GGT	U/L	0-54	85		388			
	ALT	U/L	0-40	82		197			
	Total Bilirubin	Umol/l	0-17	15		22			
065-001	ALKP	U/L	40-120	379	7	1457	SAE-unlikely	N/A	Hepatic aspergillosis
	GGT	U/L	5-43	207		1169			
	AST	U/L	10-32	36		61			
	ALT	U/L	10-32	40		123			
	Total Bilirubin	Umol/l	2-20	10		14			
067-001	ALKP	U/L	26-92	64	28	111	SAE-probably	No	Active tuberculosis
	GGT	U/L	7-30	13		110			
	AST	U/L	7-41	86		415			
	ALT	U/L	7-31	59		359			

AE = Adverse Event; ALKP = Alkaline phosphatase; ALT = Alanine transaminase; AST = Aspartate transaminase/serum glutamic pyruvic transaminase; GGT = Gamma-Glutamyl Transferase; N/A= No data available; SAE = Serious Adverse Event

Study Day pertains to study day on serum chemistry listing (18.9), and not to study day on AE and SAE listings, 18.1 and 18.3, respectively.

Reference: adapted from Section 14.3, Table 15.6; Appendix 16.2, Listings 18.1, 18.3, and 18.9

Patient ID # 67-001,
Serious Adverse Event: Abnormal LFTs (Elevated LFTs)
Relationship to Study Drug: Probably Related (Not an Expected Event with AmBisome)
This is a 33 year old woman, with pulmonary aspergillosis and on recent therapy for tuberculosis, who experienced a gradual 20-fold elevation in serum ALT and a 2.5-fold increase in serum bilirubin during the second half of a 28 day course of anidulafungin. There were only minor elevations in serum alkaline phosphatase. There was a positive dechallenge after a lag of several days, and the investigator considered the event to be probably related to anidulafungin. The patient had a history of asthma, dyspnea, hemoptysis, pulmonary tuberculosis, TB of the spine, pulmonary aspergillosis, acquired immunodeficiency due to chronic steroid use for chronic obstructive pulmonary disease, recurrent urinary tract infections, and painful legs. The patient was admitted with ongoing hemoptysis and was commenced on rifampin, isoniazid, pyrazinamide and ethambutol combination, (RIFAFOUR e-200®) on day -4. Concomitant medications included paracetamol. Bronchial aspirates obtained on the day of screening were positive for *Aspergillus* species, and anidulafungin and AmBisome was started on day 1.
The patient was on the four drug regimen for suspected tuberculosis from Day -4 to Day 20. The patient was receiving AmBisome concomitantly with anidulafungin from Day1 through Day 28, and both drugs were stopped at the same time on Day 28. Screening LFTs were abnormal; the patient was on anti-tuberculous medications for 3 days at the time of screening. AST and ALT on day 21 began to increase one day after TB meds were stopped. AST and ALT continued to increase to ~ X20ULN after anidulafungin and AmBisome were stopped. AST and ALT levels gradually returned to screening levels within one month following the discontinuation of anidulafungin and AmBisome.

The following table* shows the patients liver enzyme results

Date	***Total Bilirubin*** *(Normal Range 1-17 umol/L)*	***Alkaline Phosphatase*** *(Normal Range 26-92 U/L)*	***SGPT (ALT)*** *(Normal Range 7-31 U/L)*	***SGOT (AST)*** *(Normal Range 7-41 U/L)*
(Screening)	10	65	57	93
(Day 1)	7	64	59	86
(Day 3)	7	67	67	94
(Day 7)	9	68	66	52
(Day 14)	12	73	37	36
TB meds stopped on *(day20)*				
(Day 21)	11	82	72	104
(Week 4)	9	111	359	415
Anidulafungin &AmBisome stopped on *(day28)*				
	18	145	651	613
	21	129	576	562
	45	72	280	240
	23	137	102	143
(Follow-up)	21	110	71	84

*Table is modified from study report VER-002-7, section 12.7.2

Liver function tests between day 21 and day 28 were not done (communication from the sponsor). The consultant hepatologist for the sponsor concluded that "a delayed onset of toxicity due to the TB medications was possible, but unlikely. He attributed this injury to anidulafungin.

The case was reviewed by Dr. John Senior, hepatologist at the FDA, and he concluded that the increase in hepatic transaminases in this patient was more likely due to the recently discontinued antituberculous regimen, particularly, isoniazid. He noted that a delayed increase in hepatic transaminases due to INH can occur several months after TB therapy and thus this case has probably a weak association with anidulafungin. See appendix B. for Dr Senior's review of this case.

Medical officer's comment
Tuberculosis medications (rifampin, isoniazid, pyrazinamide) could have caused the increased in transaminases that were observed. The patient's screening LFTs were abnormal (on TB medications x 3 days) before anidulafungin and Ambisome was started. Concomitant medications included paracetamol and ampicillin. Liver transaminases were already trending up one day after TB meds were stopped. INH, pyrazinamide, and rifampin are well known to cause hepatitis. The fact that there was a delay in the rise of transaminases after the TB drugs were discontinued would not out rule TB medications as a cause of hepatitis (FDA hepatology consult). Concomitant use of INH can increase the risk of hepatoxicity from paracetamol. Hepatitis is more frequently associated with INH; for individuals in the 20 to 34yr age group the case rates for hepatitis are 3 per 1000, and for those in the 35 to 49 yr age group the case rate is 12 per 100 (Physicians Desk Reference, 2005). In this case, the increase in liver transaminases was gradual and the levels gradually returned to screening levels after anidulafungin and Ambisome were discontinued.
See Table 44 for causation assessment in this case, and Dr. J. Senior's (FDA hepatologist) review of this case in Appendix B.

Follow-up information from applicant regarding patient, ID #67-001

Updated November 14, 2005 per information received from investigator, _____
No LFTs prior to screening are available. LFTs were only done on DAY 21 and DAY 28, not in between. The patient had no documentation of prior underlying liver disease. She did not have a liver sonar anytime before enrollment as there was no suggestion of liver disease. The report of the CAT scan of the chest at enrollment did not comment on the available cuts of the liver. The patient did survive her hospitalization for pulmonary aspergillosis, but the investigator did not respond to queries for additional follow-up information.
Updated November 14, 2005 per information received from investigator, _____
The patient had follow-up visit to the pulmonary clinic this year (2005) and was well.

Patient ID #33-001
Adverse Event: Abnormal LFTs (Deranged LFTs)
Relationship to Study Drug: Possibly Related (Not an Expected Event with AmBisome)
This is a 56 year old man with acute myeloid leukemia and pulmonary aspergillosis who experienced a ~ 8-fold elevation in serum ALT and a 2.5-fold elevation in serum bilirubin throughout the second half of a 28 day treatment with anidulafungin. The baseline hepatic chemistries were elevated. This patient's serum alkaline phosphatase also rose almost 5-fold during this period, indicating a large cholestatic component to the liver injury. This was not a

Hy's Rule case. There was a prompt dechallenge when anidulafungin and Ambisome were stopped.

Following a diagnosis of myeloid leukemia in [illegible] he remained in remission until [illegible], at which time he relapsed and was again treated with chemotherapy. The patient subsequently developed neutropenia and was diagnosed with invasive aspergillosis. The patient was treated with anidulafungin and AmBisome (200 mg to 350 mg daily) from 30-Aug-2002 through 27-Sep-2002(study day 29). The patient was reasonably well until [illegible] when he started to deteriorate. On [illegible] the patient was diagnosed with overwhelming sepsis. During this period the patient started spiking fevers and became dyspnoeic. The assumption was that this was a breakthrough of the underlying fungal disease and the patient was withdrawn from the trial and blood and urine cultures were done.

At screening on [illegible] LFTs were elevated, AST=100 U/L, ALT=82 U/L, and ALKP 149 U/L. Total bilirubin= 17mmol/l. On [illegible], the ALT=107 U/L, ALKP=208 U/L, and total bilirubin=16 U/L, (AST not done). The patient had elevated levels for ALT (303 U/L) and total bilirubin (44 umol/L) on [illegible] and again on [illegible] [ALT (286 U/L); total bilirubin (38 umol/L)]. Further increases in alkaline phosphatase (449 U/L), GGT (388U/L), AST (197 U/L), and total bilirubin (22 umol/L) were noted on [illegible] ALT = 74U/L on [illegible] There was a positive dechallenge. This patient's blood and urine culture results were positive for CMV antigens - the patient began ganciclovir therapy on [illegible] The patient died on [illegible] due to sepsis, acute myelogenous leukemia, and pulmonary aspergillosis. Concomitant antibiotic therapy included, ceftazidime, meropenem, piperacillin/tazobactan, metronidazole. Meropenem was received from (Sept 20 to 30th), is known to cause increased SGPT (ALT), SGOT (AST), alkaline phosphatase, LDH, and bilirubin levels.

The patient further deteriorated and was hypotensive and began to desaturate on the [illegible] The decision was made not to ventilate because of the underlying disease. There was no evidence of renal failure and although patients liver function was abnormal this was not indicative of multiorgan failure. The patient continued to deteriorate and died on [illegible] of overwhelming sepsis manifested by respiratory collapse. Ganciclovir was administered for CMV pneumonitis. The death certificate states the cause of the death was AML. The event is not considered related to treatment except as a possible failure of treatment.

Hepatic Chemistry

	Study Day											
Hepatic Parameter	**1**	**3**	**7**	**14**	**18**	**19**	**20**	**21**	**28**	**30**	**32**	**Upper Limit of Normal Range**
Alk Phos	149	128	208	164	213	310	554	468	518	449	336	110 U/L
ALT	82	79	107	76	303	242	277	199	286	197	74	40 U/L
AST	100	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	42 U/L
Total Bilirubin	15	18	16	21	44	29	33	30	38	22	15	17 µmol/L

Note: Anidulafungin was stopped on study day 29.

Medical officer's comment

This case is possibly related to study drug. However, baseline transaminases were elevated. The patient was on several concomitant antibiotic therapy included, ceftazidime, meropenem, clarithromycin, trimethroprim/sulfamethoxazole, piperacillin/tazobactan, and metronidazole. Meropenem can cause an increase in ALT, AST, alkaline phosphatase, LDH, and bilirubin levels. CMV disease could also cause abnormal hepatic chemistry. Therefore, there are a

number of possible etiologies for the observed increase in transaminases. The investigator attribution was that this patient's death was related to sepsis, pulmonary aspergillosis and the patient's pre existing acute myeloid leukemia. An autopsy was not performed.

Patient ID #007-001

Adverse Event: Abnormal Liver Function Tests (Worsening Transaminitis)
Relationship to Study Drug: Unrelated

Patient 007-001 was a 29-year old Hispanic/Latino male with a medical history that included congenital bicuspid aortic valve, endocarditis (due to *Streptococcus viridans*) (resulting in bioprosthetic aortic valve replacement), mycotic aneurysm of the right middle cerebral artery (resulting in left-sided hemiparesis, headache, and vision loss to right eye), and cerebral hemorrhage lesions consistent with septic emboli. The patient was diagnosed with severe *Aspergillus* endocarditis with emboli to the right eye, brain, and leg, and a history of heroin and alcohol abuse.

Following the diagnosis of invasive aspergillosis, the patient was treated with anidulafungin from 19-Jun-2002 through 26-Jul-2002 and AmBisome (305 mg daily) from 20-Jun-2002 through 26-Jul-2002. On [redacted] the patient underwent a repeat sternotomy and aortic root replacement. Cultures of the aortic root showed *A. fumigatus* and rare *Propionibacterium acnes*. Post-operatively, the patient developed anemia, leukocytosis, acute renal failure, arterial thrombus (cultures of the thrombus showed *A. fumigatus* and coagulase-negative *Staphylococcus*), complete heart block, and intracerebral hemorrhage.

During the period following surgery, the patient also had transaminitis, which began [redacted] and resolved on [redacted] Elevated values that were associated with abnormal hepatobiliary parameters included alkaline phosphatase (236 IU/L), GGT (507 IU/L), ALT (5230 IU/L), AST (8736 IU/L), and total bilirubin (2.7 mg/dL).

Patient ID # 065-001

Serious Adverse Event: Abnormal Liver Function Tests (Raised Liver Functions)
Relationship to Study Drug: Unlikely

This was a 61-year old Caucasian female with a medical history that included hepatic aspergillosis, chronic myeloproliferative syndrome (that progressed to acute myeloid leukemia), immunosuppression, splenectomy, thrombocytopenia, hematuria, anemia, nausea, edematous feet, petechiae, and purpura. This patient's social history included smoking and alcohol use.

The patient underwent a splenectomy on [redacted] and was subsequently diagnosed with hepatic aspergillosis. The patient was treated with anidulafungin and AmBisome(250 mg daily) from 14-May-2002 through [redacted] 2002.The patient's liver enzymes were increased on [redacted] with the highest values noted on [redacted] (alkaline phosphatase, 10457 IU/L; GGT, 1169 IU/L; ALT,61 IU/L; AST, 123 IU/L). The Investigator considered these increases to be related to the invasive aspergillosis, the patient was continued on study drug. The patient was diagnosed with severe pneumonia on [redacted] and study drug was subsequently discontinued on [redacted] 2002. The patient did not recover from the pneumonia and died on [redacted] The liver sample obtained from the patient's autopsy revealed the presence of necrotizing granulomata with fungal elements resembling *Aspergillus* species.

Medical Officer's Comment

Two of these patients had investigator attribution of possibly or probably related to study drug, one cholestatic and one hepatocellular profile. The medical officer disagrees with the investigators attribution in one of these cases (#67-001), Table 44. The hepatic chemistry abnormalities were more likely due to anti-tuberculous medications. All of these cases are confounded by severe underlying disease such as hematological malignancies, and complications such as septic emboli from an infected bioprosthetic aortic valve, overwhelming sepsis, hepatic aspergillosis, and active tuberculosis on TB therapy. All of the patients received multiple concomitant medications of which several have the potential to cause hepatotoxicity. The elevations in hepatic chemistry observed with the antifungal combination study of anidulafungin plus AmBisome is multifactorial in these patients.

Study VER002-11

VER002-11 is a phase 2, open-label study of the safety and efficacy of intravenous anidulafungin as a treatment for azole-refractory mucosal candidiasis. In this non-comparative study, 19 patients with azole-refractory mucosal (oropharyngeal and/or esophageal) candidiasis (ARMC) received 50 mg anidulafungin IV for 14 to 21 days.
A total of 17 patients (89%) had AIDS with a median CD4 cell count of 9 cells/mm3, and had multiple prior episodes (median=5.5) of oropharyngeal candidiasis (OPC) and/or esophageal candidiasis (EC). The numbers of patients with mild, moderate and severe AEs were 13, 14, and 7, respectively. Four patients reported 23 AEs that were considered related to study drug by Investigator attribution. There was one death during the study due to AIDS and was unrelated to study drug.

Hepatic Adverse Events

Thirteen patients had an abnormality in a hepatobiliary parameter at any time, on or post-therapy, regardless of baseline value. Most of these patients had abnormal results at baseline and 7 patients had AE onset dates following completion of anidulafungin (range +1 to +26 days).

Table 46. Abnormality in a hepatobiliary parameter at any time on or post-therapy Study VER002-11

Patient	Sex	Age	Abnormal Parameter	Test Result[a] (U/L)	Baseline Result (Lab Normal Range) (U/L)	Day of Onset[b]	Day of Resolution
2-002	M	47	ALKP>1.5xULN	513	117 (46-139)	14/+1	Ongoing
			GGT>1.5xULN	132	62 (11-51)	14/+1	Ongoing
2-003	F	34	GGT>1.5xULN	50	22 (7-33)	33/+12	Ongoing
2-004	M	39	GGT>1.5xULN	152	68 (11-51)	35/+14	Ongoing
2-005	M	39	GGT>1.5xULN	181	138 (11-51)	7	Ongoing
5-001	M	37	ALKP>1.5xULN	266	251 (39-117)	14	Ongoing
			GGT>1.5xULN	149	149 (5-75)	1	Ongoing
5-002	F	45	ALKP>1.5xULN	185	85 (39-117)	33/+13	Ongoing
			GGT>1.5xULN	318	217 (5-75)	33/+13	Ongoing
8-001	F	31	GGT>1.5xULN	212	ND (8-78)	6	Ongoing
8-002	F	45	GGT>1.5xULN	250	250 (8-78)	1	Ongoing
8-003	M	44	AST>3xULN	197	104 (0-60)	20	Ongoing
			ALKP>1.5xULN	1027	299 (50-185)	39/+19	Ongoing
			GGT>1.5xULN	1598	411 (8-78)	39/+19	Ongoing
8-005	M	32	GGT>1.5xULN	124	105 (8-78)	7	Ongoing
8-006	M	40	ALKP>1.5xULN	518	511 (50-185)	4	Ongoing
8-009	M	37	ALKP>1.5xULN	2145	1490(50-185)	47/+26	Ongoing
			GGT>1.5xULN	4639	4100(8-78)	14	Ongoing
9-001	M	53	ALT>3xULN	200	51 (0-40)	22/+8	Ongoing
			AST>3xULN	198	43 (0-40)	14	Ongoing
			ALKP>1.5xULN	268	65 (25-150)	22/+8	Ongoing

ALKP=alkaline phosphatase; ALT=alanine transferase; AST=aspartate transferase; GGT=gamma glutamyl transferase; ND=Not done

[a] Highest recorded test result

[b] Number of days since the first dose of study drug/+number of days after the last dose of study drug

Reference: Study report, Section 14.3, Table 3.11; Appendix 16.2.4,Listing 1.2;Appendix 16.2.8, Listing 1.22.

There were four patients (patient ID #5-002, 8-001, 8-003, and 9-001) who reported a total of six laboratory AEs that was associated with the liver. All of the AEs were mild or moderate in intensity and none was serious. Of these four patients, three (Patients 5-002, 8-001, and 8-003) had a total of four AEs that were considered possibly related to study drug. A brief summary of these three patients follows.

Patient ID # 005-002

Adverse Event: AST increased, alkaline phosphatase (ALKP) increased
Relationship to Anidulafungin: Possibly related (by investigator)

Patient 005-002 was a 45 year-old Hispanic and African-American female with a past medical history of HIV, oral hairy leukoplakia, disseminated MAC (*Mycobacterium avium Complex*) infection, pancytopenia secondary to MAC infection, encephalitis (CMV/herpes), recurrent HIV related esophageal aphthous ulcers, recurrent oral thrush, and hepatitis B*(see section 12.7 of study report)*. Anidulafungin was received for 21 days, from 8-May-2003 to 28-May-2003. Prior antifungal therapy consisted of oral fluconazole at dosages ranging from 100-300 mg daily from 23-Apr-1998 through 8-Jul-1999; oral fluconazole 200 mg daily from 9-Dec-2002 through 2-Jan-2003 and 29-Apr-2003 through 1-May-2003; IV fluconazole 200 mg daily 28-Apr-2003through 29-Apr-2003; and IV fluconazole daily 400 mg on 27-Apr-2003, 2-May-2003through 8-May-2003. Concomitant medications included azithromycin, ethambutol, levofloxacin, metoprolol, bactrim, morphine, cefoxitin, oxycocet?(*as in study report*), tenofovir, efavirenz, and lamivudine.

An AE of increased AST (59 U/L) (baseline 35 U/L; normal range 13-58 U/L) was noted on Day 4. Increased AST was of mild intensity and was considered as ongoing. AST values at later time points were 48 U/L on Day 7, 40 U/L on Day 14, 58 U/L on Day 21,and 48 U/L on Day 33. ALT values remained within the normal range. Increased ALKP (baseline 85 U/L; normal range 39-117 U/L) was also noted as an AE on Day 21 (170U/L). Increased ALKP was of mild intensity and considered as ongoing, presumably due to MAC infection. Other ALKP values outside the normal range were recorded on Day14 (130 U/L) and Day 33 (185 U/L).

Medical officer's comment

This case is confounded by concomitant infection with Mycobacterium avium complex and HAART; both are known to cause hepatic injury. Therefore, an assessment of the relation to anidulafungin is inconclusive. The hepatic abnormalities observed are more likely due to HAART and disseminated MAC infection.

Patient ID #008-001

Adverse Event: GGT increased
Relationship to Anidulafungin: Possibly related (by investigator)

Patient 008-001 was a 31 year-old African-American female with a past medical history of HIV, toxoplasmosis, PCP, recurrent OPC and EC, elevated ALT, elevated AST, thrombocytopenia, and anemia. Study drug was received for 13 days, from 28-Aug-2002 to 9-Sep-2002. Prior antifungal therapy consisted of itraconazole in June-2001 (unknown length of time, dose and frequency) and oral fluconazole: 200 mg daily from 25-Sep-2001 through 26-Sep-2001 and 4-Dec-2001 through 13-Dec-2001, 100 mg daily from 26-Sep-2001 through 26-Oct-2001, and 800 mg daily 23-Apr-2002 through 30-Apr-2002. Concomitant medications included trimethobenzamide?, hydromorphone,pyrimethamine, sulfadiazine, kaletra, zidovudine, and lamivudine. An AE of increased GGT (baseline not done; normal range 8-78 U/L) was noted on Day 6 (212 U/L). Increased GGT was of mild intensity and considered ongoing and improved (GGT was 121 U/L on Day 14).

Medical Officer's Comment
On day 10 of anidulafungin therapy, this patient developed pruritis and a maculopapular rash with wheals during an infusion of anidulafungin which required the infusion to be stopped and led to discontinuation of study drug. No further antifungal therapy was required to treat her mucosal candidiasis. The patient recovered. This was the only serious adverse event considered possibly related to study drug in study VER002-11.

Patient ID #008-003
Adverse Event: Liver function tests abnormal
Relationship to Anidulafungin: Possibly related (by investigator)
This was a 44 year-old Caucasian male with a past medical history of HIV, *Mycobacterium avium* infection (MAC), CMV retinitis, diarrhea, anemia, recurrent OPC and EC, elevated ALT, elevated AST, elevated ALKP (probably due to MAC infection), and elevated GGT.
He enrolled into this study for fluconazole-refractory OPC and EC. Study drug was received for 20 days, from 10-Jan-2003 to 29-Jan-2003. Prior antifungal therapy consisted of fluconazole(exact dates are unknown). Concomitant medications included clarithromycin, ethambutol, ciprofloxacin, valganciclovir, vicodin, ritonavir, and indinavir. An AE of abnormal liver function tests of moderate intensity was noted on Day 14, and was considered to be ongoing. The table below shows the abnormal values. On Day 39 (17-Feb- 2003), the patient was commenced on voriconazole at 200 mg bid.

	ALKP (U/L)	GGT(U/L)	ALT (U/L)	AST (U/L)
Normal range	50-185	8-78	0-65	0-60
Screening	299	Not done	68	104
Day 1	322	411	68	104
Day 3	450	540	82	130
Day 7	347	487	66	109
Day 14	483	635	89	153
Day 20(EOT)	631	958	98	197
Day 39	1027	1598	63	158

Medical officer's comment
Several factors contributed to the abnormal hepatic chemistry. This patient had abnormal baseline hepatic chemistry, concomitant hepatotoxic medications i.e. protease inhibitors, and co-morbid disease affecting the liver. The elevation in ALKP levels is likely to be due to disseminated MAC infection.

Conclusion
These cases are confounded by underlying co-morbid diseases and concomitant therapy with protease inhibitors that are known to cause hepatotoxicity. A causal attribution to anidulafungin is inconclusive in these cases.
(Dr. Sack's review of efficacy for study VER002-11 is included in Appendix C).

Study VER002-12

This is a phase 1/2 study of the safety, tolerance, and pharmacokinetics of anidulafungin in children with neutropenia, ages 2 to 17 years. Twenty-five patients were enrolled in the ITT population. All patients had received chemotherapy therapy, other immunosuppressive treatments and/or bone marrow transplant. Ten patients had relapsed AML, ALL, and aplastic anemia. Several of the patients had on going opportunistic infections. All study patients received multiple concomitant medications. Adverse events attributed to study drug were increased BUN, erythema, feeling abnormal, hypotension, pyrexia, and rash; each was experienced by one patient each. There were no serious drug-related events. Two patients were withdrawn from study due to persistent fever which was unrelated to study drug by investigator assessment.

Hepatobiliary adverse events

Five patients experienced hepatobiliary adverse events, all of which were elevations of enzymes: 2 patients were in the 0.75-mg/kg/day dosage group and 3 patients were in the 1.5-mg/kg/day dosage group, Table 48. All patients had hematological malignancies at baseline; all except one had a stem cell transplant. No patient experienced an elevation in serum transaminase exceeding x3 ULN with a concurrent increase in total bilirubin exceeding 1.5 ULN.

Four patients in each treatment group had abnormal hepatobiliary tests at any time point and regardless of baseline value. Table 49. In the 0.75-mg/kg group, 2 patients had a cholestatic picture with isolated elevated ALKP (Patient 2-04; Day +13, Patient 5-01; Day +10), 3 patients had isolated elevated bilirubin (Patient 2-05; Day 3, Patient 2-07; Days 5, 7 and 9, Patient 3-01; Day 7 and Day +15) and 1 patient had an abnormal hepatocellular pattern associated with an isolated elevated ALT (Patient 2-06; Day +11). All patients had hematological malignancies at baseline; all except one (Patient 3-01; AML in relapse) had a stem cell transplant.

Table 48. Number (%) of Patients with Transitions in Hepatobiliary Parameters (Intent-to-Treat Population)

	Anidulafungin 0.75 mg/kg N=13				**Anidulafungin 1.5 mg/kg** N=12			
Parameter[a]	Age 2 to 11 (n=6)		Age 12 to 17 (n=7)		Age 2 to 11 (n=6)		Age 12 to 17 (n=6)	
	n/N	(%)	n/N	(%)	n/N	%	n/N	(%)
ALT								
>3 to 5 ULN	0/6		1/7	(14.3)	3/6	(50.0)	0/6	
>5 to 10 ULN	0/6		0/7		0/6		0/6	
>10 ULN	0/6		0/7		0/6		0/6	
>3 ULN with total bilirubin >1.5 ULN	0/6		0/7		0/6		0/6	
AST								
>3 to 5 ULN	0/6		0/7		0/6		0/6	
>5 to 10 ULN	0/6		0/7		1/6	(16.7)	0/6	
>10 ULN	0/6		0/7		0/6		0/6	

>3 ULN with total bilirubin >1.5 ULN	0/6		0/7		0/6		0/6	
Total Bilirubin >1.5 ULN	1/6	(16.7)	1/7	(14.3)	2/6	(33.3)	1/6	(16.7)
ALKP >1.5 ULN	0/6		1/7	(14.3)	1/6	(16.7)	0/6	

a Abnormal hepatobiliary test results of special interest are summarized from baseline through the follow-up visit
ALKP Alkaline phosphatase; ALT Alanine aminotransferase;
AST Aspartate aminotransferase; ULN Upper limit of normal
Laboratory values of liver enzymes above 5 to 20 ULN are CTC Grade 3; values above 20 ULN are CTC Grade 4.
Source: Study report Section 14, Table 14.3.23 and Appendix 16.2, Listings 2.1, 6.1.1, 6.1.2, 7.2, and 7.4

Table 49: Patients Who Experienced Abnormal Transitions of Hepatobiliary Parameters (Intent-to-Treat Population)

Anid dosage (mg/kg/day)	Patient number	Sex (M/F)	Age (yr)	Abnormal Parameter	Test Result of Special Interest	Baseline Result (Laboratory Normal Range)[a]	Day of Onset[b]	Day of Resolution
Age Cohort								
0.75 mg/kg/day								
2 to 11 y	2-05	M	5	Total bilirubin >1.5 ULN	1.7 mg/dL	1.5 mg/dL (0.1 to 1)	3	5
12 to 17 y	2-04[d]	M	16	ALKP >1.5 ULN	281 IU/L	53 U/L (52 to 171[c])	23/+13	Ongoing
	2-06	M	16	ALT >3 ULN	147 IU/L	20 IU/L (6 to 41)	21/+11	Ongoing
	3-01	M	13	Total bilirubin >1.5 ULN	3.1 mg/dL	0.4 mg/dL (0.6 to 1)	7	Ongoing
				Total bilirubin >1.5 ULN	1.2 mg/dL	0.4 mg/dL (0.6 to 1)	21/+15	Ongoing
	5-01	F	14	ALKP> 1.5 ULN	216 IU/L	107 IU/L (39-117)	30 (10)	Ongoing
1.5 mg/kg/day								
2 to 11 y	1-06	M	11	ALT >3 ULN	148 IU/L	27 IU/L (10 to 45)	19/+15	Ongoing
	2-11	F	11	Total bilirubin >1.5 ULN	1.9 mg/dL	0.9 mg/dL (0.1 to 1)	7	Ongoing
				ALT >3 ULN	137 IU/L	11 IU/L (6 to 41)	20	Ongoing
	5-02	M	9	ALT >3 ULN	153 IU/L	21 (10 to 40 IU/L)	8	Ongoing
				AST >3 ULN	142 IU/L	24 (10 to 37 IU/L)	8	Ongoing
				AST >3 ULN	186 IU/L	24 (10 to 37 IU/L)	53/+42	Ongoing
				Total bilirubin >1.5 ULN	1.7 mg/dL	1.3 mg/dL (0.1 to 1)	20/+9	49
				ALKP >1.5 ULN	209 IU/L	129 IU/L (39 to 117)	20/+9	Ongoing
12 to 17 y 2-07		M	15	Total bilirubin >1.5 ULN	1.7 mg/dL	1.1 mg/dL (0.1 to 1)	5	90
				Total bilirubin >1.5 ULN	1.8 mg/dL	1.1 mg/dL (0.1 to 1)	7	90
				Total bilirubin >1.5 ULN	1.8 mg/dL	1.1 mg/dL (0.1 to 1)	9	90

Reference: Section 14, Table 14.3.23 and Appendix 16.2, Listings 2.1, 6.1.1, 6.1.2, 7.2, and 7.4

A Laboratory normal range supplied by investigational site.

B Number of days since the first dose of study drug/+ number of days after last dose of study drug. Negative number indicates number of days before the first administration of study drug.

C The local laboratory did not report the normal range for alkaline phosphatase prior to database lock. See footnote 'd' of Table 20.

D This patient (2-04) is not represented in any summary tables for alkaline phosphatase because normal ranges were not available prior to database lock. This patient appears in Table 29 (not Table 28) following a manual review of listings.

ALKP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; Anid Anidulafungin

Medical officer's Comment

The changes observed in hepatic chemistry were not severe, and attribution to anidulafungin was inconclusive because of the all of the patients had concomitant medications with potential for hepatoxicity including chemotherapy and for example, isoniazid prophylaxis in one case. No patient experienced an elevation in serum transaminase exceeding x3 ULN with a concurrent increase in total bilirubin exceeding 1.5 ULN. No patient had an ALT, AST, or ALKP test result that was both potentially a clinically significant chemistry value and a potentially clinically significant change from baseline. No patient had a hepatobiliary adverse event that was thought to be related to study drug.

Study VER002-9b

This was an open-label continuation of the invasive candidiasis study, VER002-9. The same entry criteria applied. There were 33 patients enrolled in the study. As part of the complete response these patients were evaluated for hepatic safety.

No significant hepatic injury was noted in this study. No patient, at any time during the study, had ALT > 5x ULN or had AST > 10 x ULN. No patient developed ALT >3 x ULN + Total Bilirubin >1.5 xULN during the study. Two patients had cholecystitis and one had a biloma, none of these events were related to study drug.

Two patients in the study had a serious adverse event and both recovered. Both cases were critically ill and had confounding factors that made attribution to anidulafungin therapy inconclusive. One patient developed increased creatinine on day 2 of anidulafungin therapy. This was thought to be related to anidulafungin by the investigator. However, on review of this case, the clinical reviewer found that this case had abnormal renal function prior to anidulafungin therapy and the increased creatinine was more likely to be secondary to muscle injury due to a lower limb degloving injury and fracture and subsequent surgeries.

The second patient, with liver disease and acute bowel obstruction, was admitted with an Apache score of 27. During hospitalization he experienced hypotension and renal failure with subsequent transfer to the intensive care unit for intubation and hemodialysis. He was commenced on anidulafungin therapy for *C. albicans* candidemia. He had a seizure following anidulafungin infusion on study day 11. On the same day, the patient developed respiratory acidosis, pulmonary edema and sepsis related to candidemia due to *C. parapsilosis*. All of these concomitant events could have contributed to seizure activity in this patient.

Study VER002-13

This is a double-blind, multiple-dose, randomized, crossover, pharmacokinetic interaction study between voriconazole, VFEND® and anidulafungin. The primary objective of this study was to assess the possible pharmacokinetic interaction of co-administration of VFEND® (voriconazole) and anidulafungin at steady state conditions in healthy male subjects. Eighteen patients were enrolled. Seven patients receiving anidulafungin alone had AEs. There were no deaths or serious adverse events (SAEs) in this study. There were no documented hepatobiliary adverse events and no clinically significant elevations in hepatic chemistry per investigator attribution. There were no drug interactions between anidulafungin and voriconazole in this study.

Study VER002-15

This is a phase 1, open-label, single-sequence, pharmacokinetic interaction study between oral tacrolimus and intravenous anidulafungin in healthy male subjects. Thirty-six patents were enrolled. All treatment-related AEs were mild in intensity.

Hepatic Adverse Events

ALT elevations were reported as AEs in five subjects, three of whom also experienced concomitant AST elevations that were also reported as AEs. All AEs related to increased ALT and AST were mild in severity and all subjects were asymptomatic. None of these subjects experienced a change in bilirubin or alkaline phosphatase that exceeded the reference range. Five subjects exhibited the AE of increased ALT, with four of the five subjects exhibiting the AE on treatment day 16. One subject exhibited an ALT value >3 x ULN. This subject also had markedly elevated CPK. All AEs of increased ALT were mild in severity. The investigator considered all increased ALT AEs to be possibly related to the study drug.

Hepatic Chemistry

Parameter [a]	ID #103	#110	#128	#131[b]	#134
	DAY 20	DAY 16	DAY 16	DAY 16	DAY 16
AST U/L	297 (>5 x ULN)	normal	50 (< 2 x ULN)	76 U/L (<2 x ULN)	normal
ALT U/L	174 (> 3 x ULN)	79 (< 2 x ULN)	98 (< 2 x ULN)	157 (< 3 x ULN)	71 U/L (< 2 x ULN)
ALKP	Normal	normal	normal	normal	normal
T BILI	Normal	normal	normal	normal	normal
CPK [c]	16446	normal	normal	normal	normal

a. Maximum AST, ALT levels recorded during study

b. Subject #131 exhibited elevated ALT (72 U/L) on Day 12 and elevated AST (61 U/L) on Day 13 (baseline 22 U/L and 25 U/L, respectively). Day 16 values for ALT and AST were 157 U/L and 76 U/L, respectively.

c. Maximum CPK levels recorded during study. Subject #103 indicated that strenuous exercise had been undertaken on Day 16 at 1400 consisting of treadmill work and use of weights over a 2-hour period, and on Day 17 at 1800

consisting of football and swimming over a 2-hour period. All values were found to have returned to within normal reference ranges on Day 48. The CPK levels returned to normal within days.

Study VER002-4

Study VER002-4 was the pivotal esophageal candidiasis study previously reviewed in the original NDA. The following is a brief summary of patient ID #13-008 who died during the study.

Patient ID #13-008 had hepatic failure with multisystem failure that was considered by the investigator to be possibly related to anidulafungin. The patient's liver function tests were normal at screening, although test done 14 days prior to screening revealed ALT 100 U/L. This patient was an alcohol abuser with a history of pulmonary tuberculosis (completed treatment a few months earlier), bronchiectasis, and right-sided heart failure on several medications. He died on the day 3 of anidulafungin therapy. The patient was on the following concomitant or recently discontinued medications: furosemide, spironolactone, theophylline, Gaviscon, Lentogesic, prednisone, Atrovent, Beclate, Fenotenol HBR, ciprofloxacin (2 courses), budesonide, omeprasole, prochlorperazine.
The investigator initially considered the death due to underlying pulmonary and cardiac conditions. Three months later, the investigator revised the cause of death and considered that the jaundice and respiratory failure resulted from hepatic necrosis with multisystem failure, which could possibly be related to anidulafungin.

Chemistry results for Patient, ID #13-008

Chemistry	Normal Range	(Screening 1)	(Screening 2)	(Study Day 3)
T. Bilirubin	3-21 µmol/L	20	20	100
CK	18-198 U/L	53	39	216
Alk Phos	35-131 U/L	72	76	81
ALT	6-43 U/L	100	16	4168
AST	11-36 U/L	30	16	7058
GGT	10-61 U/L	40	52	72
Urea	1.4-8.6 mmol/L	8.8	Invalid	19
Creatinine	40-119 µmol/L	91	Invalid	192
Uric acid	149-494 µmol/L	1050	Invalid	1430
Calcium	2.1-2.57 mmol/L	2.48	Invalid	2.79
Phosphorus	0.71-1.65 mmol/L	1.29	1.69	2.78
Albumin	33-49 g/L	40	43	44
LDH	53-234 U/L	265	248	6957

Source :Dr [illegible] hepatology expert's report

The primary clinical reviewer and the expert hepatologist's report in this submission concluded that the patient most likely died from shock liver due to right sided heart failure, congestion of hepatic veins, and that the immediate cause of death was most likely due to a cardiac arrhythmia.

Medical officer's comment
The case is confounded by the patient's many co morbid conditions of cor pulmonale, AIDS, and history of tuberculosis, alcohol abuse, and concomitant medications- all of which can contribute

to liver injury. Without a post mortem, the precise liver histopathology is unknown. However, a review of the case report strongly suggest that the most likely cause of death was due to shock liver secondary to heart failure, and was not related to anidulafungin.

Overall Conclusion

Elevation of hepatic chemistry occurred during anidulafungin therapy in these studies. Elevation in liver transaminases tended to be gradual and to resolve off therapy. These abnormalities were observed at twice the dose proposed for the treatment of esophageal candidiasis. Many of the patients in the clinical studies were critically-ill. The majority of these patients had co-morbid conditions and concomitant medications that could affect hepatic function. Therefore, a causal attribution to anidulafungin has not been established. Based on results from animal, healthy volunteer studies, and clinical trials, it is important to monitor hepatic function during anidulafungin therapy.

Addendum to Hepatic Expert's report

Brief case summaries prepared by Dr. [ ](consultant hepatologist for Vicuron) for the anidulafungin-treated patients who fulfilled the criteria for Hy's rule are included in this addendum.
One case in study VER002-9 was previously reviewed in this document on page 79. There were two patients from study VER002-7 (invasive aspergillosis study), and one patient from VER002-4 (the esophageal candidiasis study) who fulfilled criteria. These three cases are also reviewed on pages 103, and 116.

Study VER002-9 (Invasive Candidiasis)

Patient ID # 41-006: "*This is a 46 year old man who experienced a 5-fold increase in serum ALT and a 1.6-fold increase in serum bilirubin 7 days into treatment with anidulafungin. Serum alkaline phosphatase was elevated throughout treatment, but did not show much rise during treatment. Hence, this is a* ***Hy's Rule*** *case by the conservative criteria. However, the bilirubin returned to normal despite continued treatment with anidulafungin, which is* ***not consistent with severe drug induced liver injury****. I therefore do not feel this case represents a concern.*"

Study VER002-7 (Invasive Aspergillosis)

Patient ID # 007-001: "*This is a 29 year old man with severe aspergillus endocarditis with septic emboli who received anidulafungin treatment for ~38 days. He experienced a transient 5-fold rise in serum ALT at one week on therapy, and a secondary rise to ~ 80 X ULN on day 28 of therapy. At this time, there was a ~2 fold increase in serum bilirubin. The liver chemistries returned to ~baseline 5 days later and while still receiving anidulafungin. This is a* ***Hy's Rule*** *case that might have been attributed to anidulafungin had the patient not continued on treatment with resolution of the injury. Although drug induced ALT elevations commonly resolve despite continuation of therapy, resolution of a* ***Hy's Rule*** *case with continued therapy is very unlikely. This patient experienced numerous complications during therapy, including open heart surgery that may well have caused transient liver ischemia. This event was* ***probably not related*** *to anidulafungin treatment.*"

Patient ID #067-001: *This is a 33 year old woman who experienced gradual 20-fold elevation in serum ALT and a 2.5-fold increase in serum bilirubin during the second half of a 28 day course of anidulafungin. There was only a minor elevation in serum alkaline phosphatase, so this* ***is a Hy's Rule case.*** *There was a positive dechallenge after a lag of several days, and the investigator considered the event to be probably related to anidulafungin. The patient had been started on rifampin, isoniazid, pyrazinamide and ethambutol one month earlier (from Day -4 to Day 20). Anidulafungin was received for 28 days. However, according to the case report form, this potentially hepatotoxic treatment was stopped one day before a near normal serum ALT measurement (~2X ULN) was obtained. Dr [ ] stated that a delayed onset of toxicity due to the TB medications is possible, but unlikely. The patient was receiving AmBisome concomitantly with anidulafungin, and both drugs were stopped at the same time on Day 28. Hepatocellular toxicity has been rarely associated with amphotericin therapy, including one* report of a positive

rechallenge (Can Med Assoc J. 1984 Nov 15;131(10):1245-7). Nonetheless, it would seem most appropriate to ***attribute this injury to anidulafungin.***"

Study VER002-4 (Esophageal Candidiasis)

Patient ID # 13-008
This patient would qualify as a ***Hy's Rule case****. I am confident the diagnosis is* ***"shock liver".***

"Patient (13-008) in Study VER002-4 developed a fulminant liver injury and died after just 3 days of therapy with anidulafungin. This patient was the subject of a teleconference with the agency on July 27, 2004, in which I participated. Drs. John Senior and Mark Avigan, both hepatologists and FDA employees, participated in this call. It was agreed that the patient's presentation was entirely compatible with hepatic ischemia (also known as "shock liver "). This is because the very rapid rise and height of the serum ALT and AST observed (~ 40 fold and ~ 200 fold, respectively) are characteristic of ischemic hepatitis. Such aminotransferase elevations are not characteristic of idiosyncratic drug induced liver injury and are rarely observed in other types of liver injury. Moreover, the patient had severe right heart failure, respiratory failure, and a documented episode of hypotension, conditions that in aggregate classically produce "shock liver". During the teleconference with the FDA, Drs. Senior, Avigan and I agreed that the clinical presentation would be unusual for idiosyncratic hepatotoxicity. Dr. Senior raised the theoretical possibility that hepatic hypoperfusion or hypoxia could predispose the liver to a drug-induced injury. However, none of the participants, including Dr. Senior, knew of examples where this had been demonstrated."

APPENDIX B

Dr. J. Senior's consultation on patient ID# 67-001, Study VER002-7

DATE: 1 November 2005
SUBJECT: ODS consultation #D050601 regarding hepatotoxicity possibly induced by use of anidulafungin for treatment of invasive bronchopulmonary *Aspergillus* infection

Documents reviewed:

1) Consultation request from HFD-590 dated 27 October 2005, assigned #D050601 31 October
2) E-mail request dated 27 October 2005 from Dr. Elizabeth O'Shaughnessy, and clinical study report VER002-7 from the sponsor concerning patient V2-7-67-001
3) Medical literature (PubMed) on antifungal toxicity
4) DFS listings for reviews submitted up to 31 October 2005 for anidulafungin, N 021632 and N 021-948
6) My consultation report of 24 March 2004 to HFD-590 on anidulafungin hepatotoxicity

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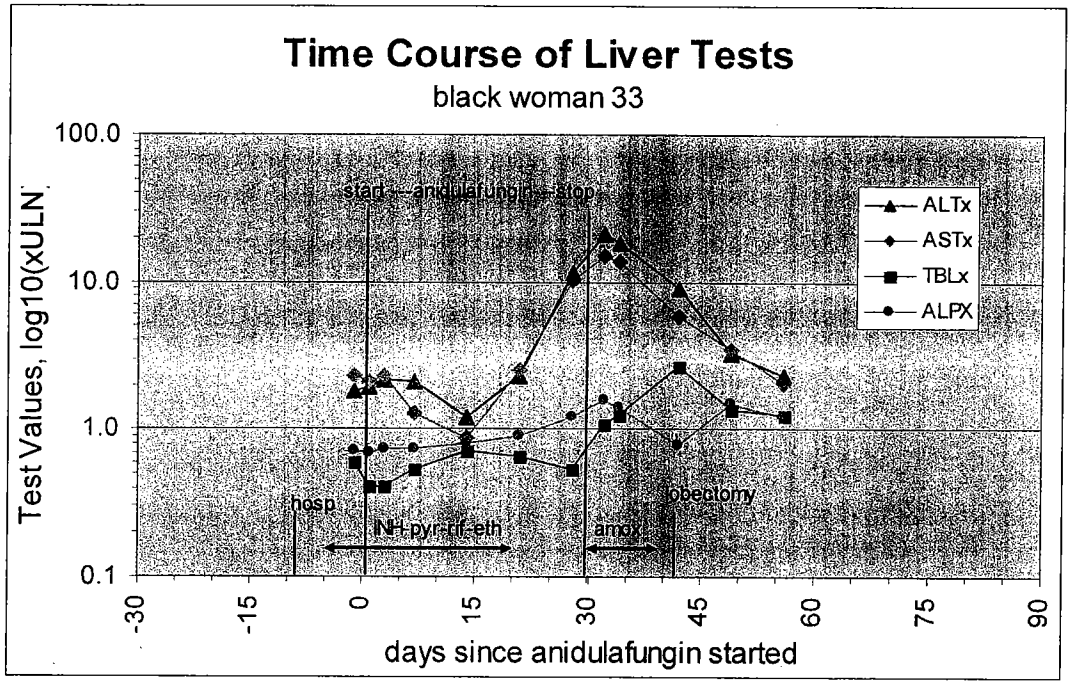
Dr. O'Shaughnessy asked on 27 October 2005 that we review and evaluate a case of non-fatal but serious liver injury occurring in a patient who had received 30 days of intravenous anidulafungin and AmBisome for treating an invasive Aspergillus infection. The patient was a 33-year-old black woman who was admitted to a hospital in South Africa on [ ] for treatment of hemoptysis thought to be due to reactivation of tuberculosis based on a radiology report. She was treated on a regimen of ethambutol, isoniazid, pyrazinamide, and rifampicin from [ ] but her smears for acid-fast bacilli and tuberculosis were negative. Bronchoscopy [ ] disclosed that aspirates showed Aspergillus fumigatus and she was treated with IV anidulafungin and liposomal amphotericin B from [ ]

The patient had a history of chronic obstructive airway disease for which she had been treated with steroids and was said to have consequent acquired immunodeficiency, pulmonary tuberculosis of the left lung (1990), with asthma, dyspnea, hemoptysis, as well as recurrent urinary tract infections, painful legs , all before the diagnosis of pulmonary aspergillosis was made. She was not overweight (height 158 cm, weight 53 kg); date of birth [ ]

Monitoring of serum alanine and aspartate aminotransferase (ALT and AST) activities and alkaline phosphatase (ALP) activity and total bilirubin (TBL) concentration was started [ ] the day of bronchoscopy . She showed slight elevations of AST and ALT, in the range of 2 times the upper limit of the normal range (x ULN) until mid-August but sharp increases in late August peaking on [ ] The anti-tuberculosis regimen was stopped on [ ] and the anidulafungin-AmBisome treatment was stopped on [ ] The abnormal serum enzyme

values continued to increase after the medications were stopped, and the ALP became slightly elevated. Peak values for ALT, AST, and ALP were noted on [ ] and the TBL peaked at 2.65 x ULN on [ ] after which all the abnormalities began to subside, and fell toward near-normal by [ ], the last reported follow-up information. Symptoms of generalized body pain were reported from [ ] a transient skin rash of the forearm on [ ] only, laboratory values indicating hypokalemia, hypomagnesemia, and neutropenia (no numbers provided) from [ ] The investigator expressed uncertainty as to which drugs may have caused the liver test abnormalities, but a consulting hepatologist attributed the liver injury to anidulafungin (and said the investigator considered the event probably related to anidulafungin).

Comment: This case description as provided by the sponsor ;eaves several questions unanswered, including why her AST and ALT were modestly elevated in late July and early August. There is no mention of whether or not she may have been an alcohol user, which could have explained the findings seen. There is no report of attempts to exclude disease causes for the sharp rise in serum ALT, and AST in late August, including hepatitis A, B, and other viral infections, autoimmune or ischemic liver injury, etc. There may be more information available that was not provided with this report, which presumes the acute liver injury was drug-induced hepatocellular injury. It may have been, but it would be useful to know more. Let us look carefully at a graphic display of the course:



If what was observed was indeed drug-induced, then which drug or drugs caused it? The most likely culprits were the isoniazid-pyrazinamide regimen that are well known to cause liver injury. It seems considerably less likely to me that the anidulafungin treatment caused the injury,

although it is still possible. The delay of a week or 10 days since the antituberculosis regimen was stopped is well within the range of latency for those drugs, and the delay cannot be taken to rule them out as a cause. The worsening of the hepatocellular injury after all drugs were stopped is also a well known phenomenon, and improvement often takes some weeks after offending drugs are stopped. It may be noted that the bilirubin peaked at 2.65 xULN two weeks after the anidulafungin was stopped, and over three weeks after isoniazid was stopped, again not unusual for drug-induced liver injury. I agree that this is a "Hy's Law" case, which means it was potentially serious, but hospitalization was for work-up of her hemoptysis and not because she was sick with acute liver failure. Alternative causes include trimethoprim-sulfamethoxazole (which usually causes cholestatic injury, not seen here), fluconazole (only three days) and acetaminophen, but amounts are not given. She also was treated with amoxicillin for 9 days starting in late August after the hepatic injury had occurred.

The case for anidulafungin-induced acute hepatocellular injury is weak, and it is somewhat more likely an isoniazid-pyrazinamide-induced injury, although not for certain. Like so many of the cases of drug-induced liver injury, there were too many possible causes, and none can be implicated with any high degree of likelihood. Why has it taken over three years for this case to be reported? The literature reports no anidulafungin-induced hepatotoxicity. There is no absolute or "gold" standard for determining causality of drug-induced liver injury; we are stuck with opinions, and in this case mine differs from that of their consultant (Dr. [redacted] whom I know very well.

Recommendations:

1. This case does not provide convincing evidence for anidulafungin-induced hepatocellular injury, which remains a distant possibility but appears somewhat less likely than isoniazid-pyrazinamide-induced liver injury, a well known phenomenon. A combination drug effect cannot be excluded.

2. The trail is old and cold, with over 3 years since the acute events occurred, but perhaps the sponsor could provide additional information as to her current status, past use of alcohol, and whether she has had further treatment for her pulmonary aspergillosis, and if so, what. Your note said you have requested more clinical information; let me know if you get it.

John R. Senior, M.D.

cc: ODS PID#D050601

M. Avigan, ODS/DDRE
P. Seligman, OPSS
S. Birdsong, DDRE
R. Albrecht, HFD-590
E. O'Shaughnessy HFD-590
L Sacks, HFD-590

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12 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

APPENDIX D

Proposed Labeling

Proposed labeling (draft) is attached with changes provided by clinical, microbiology, chemistry, clinical pharmacology, animal toxicology and statistics reviewers. The division concluded that the efficacy results reported for study VER002-4 should not include results from study site 19. See original review of NDA 21-632 regarding this site by Dr. E. Ibia. The numbers for clinical and endoscopic outcomes in the label exclude site 19.

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

APPENDIX E

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MEDICAL OFFICER

Clinical Review Cover Sheet

NDA 21-632

DRUG NAME
Anidulafungin

REVIEWER
Ekopimo Ibia, M.D., M.P.H.
Division of Special Pathogen and Immunologic Drug Products

DOCUMENTS REVIEWED

- Clinical Studies in NDA 21-632
  - Phase 3 Study in Esophageal Candidiasis (Protocol VER002-4)
  - Phase 2 Study in Esophageal Candidiasis (Protocol H4A-MC-XBAF)
  - Phase 2 Study in Invasive Candidiasis (Protocol VER002-6)
  - Phase 2/3 Study in Fluconazole-Refractory Mucosal Candidiasis (Protocol VER002-11)
- Sporanox® (Itraconazole) product labeling
- Diflucan® (Fluconazole) product labeling
- Cancidas® (Caspofungin) medical officer review and product labeling
- Vfend® (voriconazole) medical officer review and product labeling
- Post-marketing safety review for Cancidas® performed by Office of Drug Safety
- Extensive review of literature on esophageal candidiasis

CLINICAL REVIEW

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CLINICAL REVIEW

Clinical Review for NDA 21-632

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Despite the decline in the prevalence of esophageal candidiasis in the advent of highly active antiretroviral therapy (HAART), HIV-infected and other immune compromised patients continue to present with esophageal candidiasis necessitating therapy.

While several approved drug products are available to treat esophageal candidiasis, the need remains for additional therapeutic options, given the limitations inherent in the use of the available drug products.

Anidulafungin potentially offers such option. Anidulafungin is a new molecular entity belonging to the echinocandin class of antifungal agents. Caspofungin is currently the only.approved member of that class. One potential niche for anidulafungin is in a patient with esophageal candidiasis as the presenting diagnosis of AIDS and HIV infection. Initiating both HAART and antifungal therapy in such a patient could be a huge challenge, given the problems of drug-drug interactions, particularly if caspofungin or amphotericin were also contraindicated.

Anidulafungin has activity against *Candida* species both in vitro and in vivo. Its activity in esophageal candidiasis is superior to published treatment outcomes for placebo or inferior therapies. However, in the predominantly AIDS population with limited anti-HIV therapy studied in the large Phase 3 esophageal candidiasis trial, it is expected that once treatment is stopped, patients will relapse as was seen on both arms although the relapse was significantly worse on the anidulafungin arm relative to the fluconazole arm.

The most common treatment-emergent adverse events considered at least possibly related to study drug included phlebitis, superficial thrombophlebitis, nausea, headache, thrombocytopenia, and cough, occurring in two patients each. Overall, adverse events profiles were similar on the two arms. Nevertheless, animal studies identified the liver as a potential target organ of toxicity for anidulafungin, as shown by mild to moderate hepatopathy with related elevations in serum alanine transominase (ALT) and aspartate transaminase (AST). In the Phase 1 study evaluating the maximum tolerated dose up to 260 mg loading dose and 130 mg maintenance dose for a total of 10 days, there was a dose-related and temporal

trend towards mild increases in ALT, AST (< 3 x upper limit of normal [ULN]), and alkaline phosphatase (<1.5 x ULN). A single case of fatal hepatic necrosis was seen in the large Phase 3 esophageal candidiasis trial (VER002-4). The event was considered possibly related to anidulafungin. This case was greatly confounded by multiple underlying medical conditions and concomitant medications. No similar event occurred on the fluconazole arm; however, a full analysis of hepatobiliary parameters found no relevant differences between the two arms. In addition, evaluation of anidulafungin in patients with varying degrees of hepatic impairment (N=20) revealed no relevant trends compared with unimpaired controls (N=7).

From a clinical perspective, anidulafungin could be approved and appropriately labeled to reflect the inferior durability of response against the lowest approved dose of the comparator (given over a duration shorter than minimum of 21 days in labeling) for a non-inferiority design. Given the animal findings of hepatopathy, the finding of mild elevations in ALT, AST, and alkaline phosphates, the single case of possibly related hepatic necrosis, and the small size of the safety database, labeling should draw appropriate attention to the importance of monitoring liver function.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The applicant should commit to collect additional data in the post-approval period to fully characterize the safety and efficacy of intravenous anidulafungin by age, gender, geographic locale, and ethnicity.

Conduct surveillance study to collect additional safety information to further characterize the impact of anidulafungin on liver function.

Explore higher doses of anidulafungin for a longer duration in the treatment of esophageal candidiasis.

Risk Management steps for intravenous anidulafungin should include insertion of its potential for hepatotoxicity and the need to monitor for this in the WARNING section. The lack of sustained durability of treatment should be captured in the PRECAUTION section of labeling.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Drug Established Name: Anidulafungin
Drug Proposed Trade Name: [ ]
Drug Class: Echinocandin antifungal agent

CLINICAL REVIEW

Executive Summary Section

Proposed Indication:	Treatment of esophageal candidiasis
Dose Regimen:	100 mg loading dose on Day 1 followed by 50 mg daily maintenance for a total of 14 to 21 days.
Route of Administration:	Intravenous
Age Group:	Adults (patients older than 18 years)

In support of the proposed indication, the applicant presents data from a large, adequate and well-controlled study in patients with esophageal candidiasis with underlying AIDS in the majority of the patients. The proposed dose and duration is 100 mg intravenously of anidulafungin on the first day of therapy followed by 50 mg intravenously daily for 14 to 21 days (this dosage regimen is abbreviated as "100/50"). In addition to the single large adequate and well-controlled study in patients with esophageal candidiasis, the applicant presents supportive data from three smaller phase 2 studies as follows:

- a dose–ranging study of 36 patients with esophageal candidiasis randomized to receive one of two doses of anidulafungin smaller than the dose used in the pivotal study (the dose for which the applicant is seeking approval) proposed indication for a duration of 14 to 21 days. (either a dose of 50/25 mg or a dose of 70/35 mg IV daily was used in this phase 2 study.)
- an on-going, open-label, non-randomized study of anidulafungin 100/50 mg IV daily for 14 to 21 days for the treatment of fluconazole-refractory mucosal candidiasis (data from 5 patients are included in the NDA (2 of these 5 patients had esophageal candidiasis) of a planned total enrollment of 20 patients).
- an open label, randomized, dose-ranging study that enrolled 120 patients (40 on each of the three arms) with invasive candidiasis (nearly 90% with candidemia alone) treated with anidulafungin doses of 100/50 mg, 150/75 mg, or 200/100 mg intravenously daily for a minimum duration of 14 days and up to 42 days. (The median duration of therapy was 14 days.) Most of these patients were immunocompromised

Five months prior to NDA submission, the applicant identified a problem with mislabeling of the study drug randomization kit for the single pivotal esophageal candidiasis study before the study results were unblinded and notified the Division. This issue came to the company's attention in the following way: During the study, patients at selected centers had serum samples obtained for population pharmacokinetic analysis. These serum samples were sent to an independent contract laboratory for analysis and the laboratory – having the randomization schedule – assayed the samples from patients randomized to anidulafungin; these assays showed no detectable anidulafungin, prompting an investigation. The investigations revealed that at the vendor responsible for packaging and distributing products to study sites, a systematic error occurred, that affected 70% of the study patients. Packages containing anidulafungin (VER002) and placebo for fluconazole OR placebo for anidulafungin and active for fluconazole were switched because the wrong "drug" was circled in the header.

Because the information on the systematic error in randomization was known at the time of the NDA submission, the Division of Scientific Investigations was promptly consulted

and undertook inspection of the parties involved in drug distribution and assay of serum samples.

The laboratory analyzed serum samples for 274/601 (46%) of the patients in the study and found agreement with the sponsor's proposed corrected treatment assignment for the subgroup of patients in the sites that received the mislabeled drug. Once all the data were collected, it was observed that there were also 30 patients identified who had detectable drug levels for both anidulafungin and fluconazole present. Fifteen of these patients were in site 19 (total enrolled at site 19 was 47 patients), the other 15 patients were from 7 additional study sites. (Efficacy analyses that excluded data from Center 19 were conducted and the overall results of the analyses were consistent with the analyses that included Center 19.) For these 30 patients, samples were available from days 3, 7 and 14 of study, and the presence of both anidulafungin and fluconazole was generally detected in one of the three samples. Several patients in site 19 had both drugs present on 2 or 3 of the sampled days. The Agency's statistical review team modeled the data in several ways and concluded that the randomization incident could not have made the outcome any worse for anidulafungin.

Similarly, the biopharmaceutical review team commented that "for [the] few patients who had their randomization codes corrected from anidulafungin to fluconazole, at study sites other than Site 19, there were low concentrations of anidulafungin detected on varying days, with no consistent pattern. But, it appeared that there was only one detectable anidulafungin concentration per patient on only one given day, with the other days being BLQ (below limit of assay quantitation)." The team noted that "... the ***times*** when these PK samples were drawn for anidulafungin is unknown, rendering interpretation of these concentrations impossible." Finally, the team noted that "the assay itself - i.e., LC/MS/MS - is typically very specific and the analytical report shows very good precision (as measured by percentage coefficient of variation) and accuracy (as percentage difference from Theoretical Quality Control concentration) ." The team then concluded that "(1) no therapeutic concentrations/therapeutic concentration ranges have been established for anidulafungin or even fluconazole [therefore, there is need for caution in interpreting dual drug levels found in some of the subjects]; (2) the low anidulafungin concentrations (especially for those patients correctly randomized to fluconazole) are not consistent with the anidulafungin concentrations achieved when giving the proposed clinical dosage regimen of 100mg loading dose/50mg maintenance dose."

The overall number of patients exposed in the Phase 2/3 trials in the NDA database is 461. Additional safety data is included on 17 patients in the ongoing Phase 2/3 study of intravenous anidulafungin in the treatment of invasive aspergillosis in protocol VER002-7 titled "An open-label non-comparative study of the safety and efficacy of intravenous anidulafungin plus Ambisome® as a treatment for invasive aspergillosis."

In the entire program, a total of 412 subjects received ≥ 100/50 mg (proposed dose) for at least 10 days and 332 subjects for at least 14 days.

B. Efficacy

Findings from the single large adequate and well-controlled study of esophageal candidiasis show that at the end of therapy, anidulafungin met the protocol-specified primary endpoint with 97.4% endoscopic success in evaluable patients at end of therapy compared to 98.7 % for fluconazole, a difference of -1.3% with a 95% confidence interval (95% CI) of -4.2% to 1.6%. The success rate in the anidulafungin arm is much higher than would be expected for placebo at the end of therapy timepoint. At the two week post-therapy follow-up visit anidulafungin was found to be statistically significantly inferior to fluconazole for the endpoint of sustained endoscopic success, i.e., those who did not relapse following cure or improvement at EOT (39.0% [anidulafungin] vs. 69.1% [fluconazole]), a difference (95% CI) of -30.1 (-39.1,-21.1). While the protocol-specified primary endpoint was endoscopic response at end of therapy, for antimicrobial drugs we typically utilize a primary endpoint that is assessed at a time point removed from the time at which antimicrobial drug therapy is completed (e.g., 5 half-lives post completion of therapy).

The clinical course of disease for patients with esophageal candidiasis can be a course of relapsing or recurrent disease over the weeks to months following successful treatment. However, HAART therapy has contributed greatly to the treatment and control of opportunistic infections such as esophageal candidiasis in patients with AIDS and has lead to a reduction in the frequency of esophageal candidiasis. It is pertinent to note that subjects enrolled in the single large adequate and well-controlled study of esophageal candidiasis were predominantly from AIDS patients from South Africa. The bulk of subjects enrolled in that study received no HAART before or during study participation. In the US, majority of AIDS patients would be on HAART. However, patients presenting with esophageal candidiasis as the clue to their underlying HIV infection would be somewhat similar to patients enrolled in the single large adequate and well-controlled study of esophageal candidiasis this application. Even so, such patients would be very few and would immediately be started on HAART.

It is pertinent to briefly mention two products recently approved for the treatment of esophageal candidiasis are caspofungin and voriconazole. It is also relevant to note that in NDA 21-632 for anidulafungin injection, the sponsor performed the single largest trial submitted to the Agency for evaluation of products for this indication. For caspofungin, approved in January 2001, the product was already marketed at the time the company sought indication for esophageal candidiasis. Voriconazole was approved on November 14, 2003 for the treatment of esophageal candidiasis.

The response rates in the clinical studies used for the approval of caspofungin and voriconazole cannot be directly compared with those in the current anidulafungin NDA given the differences in study populations, study designs, definitions of outcomes, endpoints, use of prophylaxis antifungal therapy, and use of antiretroviral therapy among others. Moreover, associated oropharyngeal candidiasis was systematically documented in the caspofungin and voriconazole studies, but not in the anidulafungin studies.

For caspofungin, the primary efficacy endpoint was the proportion of patients with a favorable combined response (symptoms and endoscopy) at the 5-7 days post-therapy visit. The overall combined response included the assessment of symptoms and endoscopic lesions. A "favorable" response was defined as both complete symptomatic resolution and complete resolution of lesions or a 2-grade reduction from baseline scores. The relapse assessment at the 14 and 28 day post-therapy time points compared the proportion of patients with recurrent symptoms of esophageal candidiasis in patients with previous successful outcomes. (Please recall that the anidulafungin follow-up evaluation discussed above is based on endoscopic assessment.) Like anidulafungin, caspofungin performed numerically poorer than fluconazole at the 14- and 28-day post-therapy follow-up time points, although the difference was statistically significant only at the 28-day time point.

For voriconazole, on the other hand, a successful response was defined as a normal endoscopy at EOT (primary endpoint) or at least a 1 grade improvement over baseline endoscopic score while follow-up visit 4 weeks post EOT was based on symptomatic assessment. Response rates at EOT therapy observed in the voriconazole trial is similar to that in the aniduloafungin trial even though a lower dose of fluconazole was used as comparator in the latter trial.

The Clinical Studies Sections from the Labeling of caspofungin and voriconazole for the indication of esophageal candidiasis are provided in the Appendix.

Exactly why the efficacy of anidulafungin is not sustained is unclear. The applicant attributes it to a possible class effect, as capsofungin also performed somewhat poorer than fluconazole at follow-up. Fluconazole is known to achieve high concentrations in the saliva[1], which could play a role in the treatment of oropharyngeal candidiasis. Persistence of oropharyngeal candidiasis may contribute to the relapse of esophageal candidiasis in a severely compromised population such as was studied in the current application.

In the Phase 1 single-and multiple-dose oral formulation Study in healthy and HIV-infected subjects, 65 saliva samples were obtained from 9 subjects in the multiple dose phase of the study. In the single-dose phase of the study, anidulafungin levels were below limits of quantitation (< 20 ng/mL) in most cases. Anidulafungin levels in saliva were highly variable with a mean peak to plasma concentration ratio of ~20% (range 2-81%). It is noteworthy that clinical development of oral formulation of anidulafunfin was discontinued due to poor oral bioavailability. Information is unavailable for the salivary excretion of the intravenous formulation. In immune compromised rabbit model of esophageal and oropharyngeal candidiasis, the saliva concentration of anidulafungin was only ~1% of the plasma drug concentration. The clinical relevance of these findings is unclear. Poor salivary concentration was also observed with caspofungin.

It is also possible that suboptimal dose and duration of therapy were selected for the large Phase 3 trial. Indeed, results of the phase 2 invasive candidiasis/candidemia trial seems to suggest this view.

Anidulafungin as a Treatment Option for Esophageal Candidiasis
For a patient in whom amphotericin and the azoles are contraindicated, the only available therapeutic option is intravenous (IV) caspofungin. Intravenous anidulafungin provides an alternative to IV caspofungin.

Another possible role for anidulafungin is in patients presenting with esophageal candidiasis as first diagnosis of AIDS who require the initiation of HAART. Such a patient requires very skilled drug management to minimize potential drug-drug interactions. Treatment of the esophageal candidiasis with an azole may not be ideal, given the increased risk for such interactions.

C. Safety

The human safety database for anidulafungin comprises data from 461 subjects from the Phase 2 and 3 studies in the clinical development program, including 300 patients from the pivotal Phase 3 study (see discussion of site 19 below). Additional safety data is included on 17 patients in the ongoing Phase 2/3 study of intravenous anidulafungin in the treatment of invasive aspergillosis in protocol VER002-7 titled "An open-label non-comparative study of the safety and efficacy of intravenous anidulafungin plus Ambisome® as a treatment for invasive aspergillosis." In the entire program, a total of 412 subjects received ≥ 100/50 mg (proposed dose) for at least 10 days and 332 subjects for a t least 14 days. Although relatively small, the size of the safety database is sufficient to conclude that a true rate of a significant adverse event is not more than one in 100. Given the substantial differences in the socioeconomic conditions between the US and the sites from where most of patients in the single large adequate and well-controlled study were enrolled and the fact that a large number of the patients in that study received no HAART before or during study participation, the population studied is expected to be sicker than the population of patients likely to have esophageal candidiasis in the United States.

The most common treatment-emergent adverse events considered at least possibly related to anidulafungin included phlebitis, superficial thrombophlebitis, nausea, headache, thrombocytopenia, and cough, occurring in two patients each. Overall, the safety profile for anidulafungin in the single large Phase 3 study was similar to the control drug, fluconazole, in terms of overall adverse events, drug related adverse events, and discontinuations. Preclinical and clinical data did not reveal a signal or evidence of QT prolongation. Additionally, there are no signals for drug-drug interactions, which seems to support the findings that anidulafungin is not a substrate, an inducer or an inhibitor of the cytochrome P450 enzyme system.

Several acute and/or repeated-dose animal studies identified the liver as a potential target organ of toxicity as shown by slight to moderate hepatopathy with related elevations in

ALT and AST levels. In Phase 1 studies dose-dependent elevations in AST, ALT (< 3 x ULN) and a dose-dependent elevation of alkaline phosphatase was observed. In the single large phase 3 clinical trial, abnormal liver function tests reported as adverse events occurred in 10 (3.3%) anidulafungin vs. 4 (1.3%) fluconazole patients. However, overall elevation of AST reported as adverse events was seen in 4 (1.3%) anidulafungin vs. 10 (3.3%) fluconazole patients and judged to be severe/life-threatening in 1 vs. 3 patients and drug-related in 1 vs. 2 patients, respectively.

In the Phase 3 trial there were 23 deaths (7.7%) on anidulafungin and 20 deaths (6.6%) on fluconazole. One death (anidulafungin arm) was considered by the investigator to be possibly drug-related. This patient was an alcohol abuser with pulmonary tuberculosis, bronchiectasis, and right-sided heart failure on several concomitant medications. His ALT was 100 U/L 14 days prior to screening but ALT, AST, and total bilirubin were normal at screening. At screening, work up for viral hepatitis was negative for hepatitis B surface antigen, anti-hepatitis B surface antibody and hepatitis C antibody. He died on the 3rd day of anidulafungin therapy. The investigator initially considered the death due to underlying pulmonary and cardiac conditions. No autopsy was performed. About 3 months later, the investigator revised the cause of death and considered that the jaundice and respiratory failure resulted from hepatic necrosis with multisystem failure, which could possibly be related to anidulafungin.

A review of line listing of chemistry clinical laboratory data in the single large Phase 3 esophageal candidiasis study was conducted to capture patients with elevated Serum ALT and/or AST (≥ 3 x ULN) who also had elevated total bilirubin (≥ 1.5 x ULN) but with normal alkaline phosphatase ("Hy's law"). With the single patient with hepatic necrosis included, 2 patients on each arm met the criteria. When the data was examined without regard to elevation of total bilirubin, an additional 16 patients on anidulafungin arm and 15 on fluconazole arm were found. In most of these patients, ALT or AST was marginally greater than 3x ULN.

Given the animal findings of hepatopathy, the finding of mild elevations in ALT, AST, and alkaline phosphates, the single case of possibly related hepatic necrosis, and the small size of the safety database, labeling should draw appropriate attention to the liver. The WARNING SECTION of labeling should read:

[

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The PRECAUTIONS SECTION should read:

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D. Dosing

Data from the large single Phase 3 and the smaller Phase 2 esophageal candidiasis trials as well as the supportive Phase 2 trial of anidulafungin in patients with invasive candidiasis (predominantly candidemia) suggests a suboptimal dose might have been selected for the Phase 3 trial. In the Phase 2 esophageal candidiasis trial that used doses lower than used in the large Phase 3 study, successful outcomes were generally lower that those in the Phase 3 trial. The Phase 2 dose-ranging trial in invasive candidiasis evaluated three doses, two of which were higher than the currently proposed dose 100/50 mg, 150/75 mg, and 200/100 mg). Outcomes obtained with the 150/75 mg dose were consistently higher than with the currently proposed dose but similar to those obtained with the 200/100 mg dose. No dose-dependent trends were observed in the study. This suggests the optimal dose could be about 150/75 mg. The sponsor should consider further exploration of the optimal dose and duration of treatment for the indication of esophageal candidiasis.

E. Special Populations

Pharmacology

None of the covariates gender, race, age affect the pharmacokinetics (PK) of anidulafungin. Based on PK studies conducted in patients with renal impairment and hepatic impairment, no dosage adjustment is needed for these conditions.

Efficacy

There were no interactions by age, gender, race, or study site at EOT. However at follow-up, race and age appeared to have impacted outcomes. Endoscopic response rates showed a significant trend of being higher the older the subjects. Similarly, endoscopic response rates were higher in Hispanics and Asians compared to Whites and Blacks. These findings are not explained by known pharmacology of anidulafungin in humans. The significance of the findings are unclear as the trial was not powered to detect differences in special populations. However, the sponsor should gather data in the post-approval period to provide a better understanding of the efficacy of anidulafungin in these subgroups.

Safety

Given the small size of the database, the variables age, ethnicity, disease status, and geographic location are not sufficiently independent to draw definitive conclusions regarding safety of anidulafungin across these subgroups. Nevertheless, available data suggest there are no discernable safety issues based on these variables.

Clinical Review

I. Introduction and Background

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

Drug Established Name:	Anidulafungin
Drug Proposed Trade Name:	[ ]
Drug Class:	Echinocandin antifungal agent
Proposed Indication:	Treatment of esophageal candidiasis
Dose Regimen:	100 mg loading dose on Day 1 followed by 50 mg daily maintenance for a total of 14 to 21 days.
Route of Administration:	Intravenous
Age Group:	Adults (patients older than 18 years)

B. Esophageal Candidiasis

Epidemiology and Risk Factors

Candida species are normal commensals of the oropharyngeal mucosa and on rare occasions may cause oropharyngeal candidiasis without any known predisposing factors. Esophageal candidiasis, on the other hand, is typically an opportunistic infection that usually occurs in the context of an underlying impairment of host immunity. By far the most common cause of such immune impairment is human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). Indeed, esophageal candidiasis is an AIDS-defining illness. Esophageal candidiasis was common among the HIV infected population in the US but incidence has significantly declined since the advent of highly active antiretroviral therapy (HAART), which was introduced into the US market in late 1995. Nevertheless, occasional HIV-infected patients still present with esophageal candidiasis, either as a clue to their HIV status or in advanced AIDS stages.[ii] Esophageal candidiasis was the third most common AIDS-defining infection (after *Pneumocystis jiroveci* pneumonia and recurrent bacterial infections), occurring in 16% of children < 13 years reported through 2001.[iii]

Other predisposing factors to esophageal candidiasis include immunosuppressive therapy (recipients of transplant anti-rejection drugs, cancer chemotherapy or radiation therapy, systemic or inhaled corticosteroids), in patients with diabetes mellitus, rheumatologic disorders, gastric acid suppressive therapy, esophageal motility disorders, following gastric or esophageal surgery, esophageal injury, and following prolonged antibiotic use.

Etiologic Agents

Several species of *Candida* have been implicated in esophageal candidiasis; however, an overwhelming majority is caused by *Candida albicans*, up to 90% of isolates in some series. The non-*albicans Candida* species include *C. glabrata* and *C. tropicalis* (each isolated in 5-8% of infections), and very rarely *C.*

lusitaniae, C. krusei, C. parapsilosis, C. guliermondi, and the more recently recognized *C. dubliniensis*. The cellular arm of immunity plays a vital role in host defense against *Candida* infection. Exactly how T-cells and other elements of the host cell mediated immunity protect against mucosal *Candida* infection is not fully understood.

Clinical Features

Clinical features of esophageal candidiasis vary from asymptomatic or mildly symptomatic to severe and rarely life-threatening. Typically, patients present with dysphagia, odynophagia, and/or retrosternal chest pain. Constitutional symptoms are rather unusual. Occasional patients with long standing symptoms could present with malnutrition with or without fluid and electrolyte derangements. Sometimes features of esophageal candidiasis are masked by the manifestations of the underlying predisposing conditions. In severe cases, patients may also be asymptomatic due to denervation. Untreated in the face of sustained immune compromise, esophageal candidiasis could result in uncommon but life-threatening conditions such as esophageal perforation, extensive destruction of the entire esophageal mucosa, hemorrhage, bezoar formation, and candidal dissemination. Death can occur from these complications.

Diagnosis

Diagnosis of esophageal candidiasis relies on clinical history. A recent study from Uganda shows sensitivity, specificity, and the positive and negative predictive values of esophageal symptoms as markers of esophageal infection to be 83.3% (confidence interval [CI] 69.2 to 92.0), 100% (CI 88.3 to 100), 100% (CI 89.1 to 100), and 82.2% (CI 67.4 to 91.5), respectively.[iv] A known predisposing condition in a patient with typical symptoms should lead to a diagnostic consideration of esophageal candidiasis, particularly if the patient also presents with current or past history of oral thrush. It should be added that in many patients esophageal candidiasis occurs without such a history of oral thrush and in some patients esophageal candidiasis may be the marker for underlying immune deficiency state. However the patient presents, the diagnostic gold standard is esophagoscopy (usually with a fiberoptic endoscope) with mucosal brushing or biopsy to identify hyphal invasion. Esophagoscopy not only allows visualization of the lesions but enables evaluation of possible differential diagnosis. The typical esophagoscopic findings in esophageal candidiasis are pale creamy white plaques. Grading of these esophagoscopic findings as proposed by Kodsi et al.[v] correlates with disease severity and is widely used in clinical trials.

Esophageal Candidiasis: Historical Treatment Experience

In a patient with underlying severe immune compromise such as AIDS, esophageal candidiasis is unlikely to resolve spontaneously. Moreover even with adequate treatment, esophageal candidiasis is very likely to recur following discontinuation of therapy in the face of persistently severe immune compromise.

Literature dating back to the early 1950s reveals that with therapies available at that time (such as 1% gentian violate and nystatin suspension), some patients showed symptomatic improvement. It should, however, be pointed out that many of such seeming recoveries followed overall improvements in underlying predisposing conditions. In addition, esophageal and other forms of candidiasis were common autopsy findings in patients dying of cancer during that era.[vi]

In a 1992 an open-label, comparative efficacy study, 141 Zairian AIDS patients with oropharyngeal candidiasis (with endoscopically diagnosed esophageal candidiasis in 136) were randomized to one of three arms: gentian violet mouth washes (1.5 ml of 0.5% aqueous solution b.i.d.), oral ketoconazole (200 mg/day, after a meal), or nystatin mouth washes (200,000 U oral suspension q.i.d.). After 14 days of therapy, 72 patients were evaluable. Esophageal lesions had disappeared in 5 (24%) of the 21 patients on ketoconazole, compared to less than 10% of patients on both other treatments.[vii]

Two other studies provide further perspective on the historical experience with treatment of esophageal candidiasis in patients with AIDS. First is the double blind study by Ravera et al[2] in which 77 Ugandan AIDS patients with endoscopically diagnosed esophageal candidiasis were randomized to receive oral miconazole 250 mg 6-hourly or oral nystatin 1,000,000 international units 8-hourly for 7 days. Follow-up assessment and endoscopy was performed at a mean of 7.6 (± 0.9) days. Patients treated with nystatin who still had esophageal candidiasis were then treated with oral miconazole for another 7 days and reassessed with endoscopy. At the initial post-therapy assessment, clinical success (absence of symptoms) and endoscopic cure (clearance of lesions) in the nystatin arm were 10/37 (27%) and 8/37 (22%), respectively. These responses were significantly inferior to those on the miconazole arm (38/40 [95%] and 37/40 [92.5%] for clinical and endoscopic responses, respectively, $p < 0.001$). In the second phase of the study, of 29 patients on nystatin arm who failed initial therapy and got switched to miconazole, 27 (93%) were endoscopically cured after 7 days of therapy.

The second study is the double-blind, multicenter, placebo-controlled study of fluconazole versus itraconazole-flucytosine in the treatment of esophageal candidiasis. In this study conducted from several centers in Italy, 85 AIDS patients with endoscopically confirmed first episode of esophageal candidiasis were randomized to receive fluconazole (3 mg/kg/day orally, n=30), itraconazole ([3 mg/kg/day orally] plus flucytosine [100 mg/kg/day orally], n=30), or placebo (n=25). After two weeks of treatment, patients originally randomized to placebo where doubly-blindly randomized to fluconazole or itraconaolze plus flucytosine as above also for two weeks. Patients were evaluated clinically and endoscopically at weeks 2 and 4 and at end of follow-up (3 months). Endoscopic evaluation was based on the modified Kodsi score. At week two assessment, clinical cure (complete resolution of symptoms) and endoscopic cure (grade 0)

were 75.8% and 68.9%, 72.4% and 72.4%, and 0.0% and 0.0% in the fluconazole, itraconazole plus fluctyosine, and placebo groups, respectively. Among the placebo group, partial clinical and endoscopic responses were observed in 27.3% and 22.7%, respectively[viii]

These studies from the pre-HAART era consistently show that confirmed esophageal candidiasis lesions are unlikely to resolve spontaneously in the persistently immunocompromised patient, although partial improvement may be seen in some patients. Furthermore, response at end of therapy is likely to be poor with the less potent therapies such as gentian violet or nystatin suspension.

I should add that other literature sources show that overtime, the majority of AIDS patient with esophageal candidiasis will relapse following withdrawal of therapy, in the absence of effective antiretroviral therapy, although in the current NDA follow up was only 2 weeks post therapy.

Please note that these studies from the pre-HAART era are germane to this discussion, as patients in the current NDA were largely treatment naïve for esophageal candidiasis and did not receive HAART. Furthermore, the socioeconomic background of patients enrolled in the current NDA could be considered similar to that of patients in the studies by Ravera et al[iv] and Nyst et al.[vii]

It is well documented that without suppressive antifungal therapy and/or effective antiretroviral therapy, majority of AIDS patient with esophageal candidiasis will relapse within weeks to months of withdrawal of the antifugal therapy, irrespective of the therapy.[ix] The time to relapse varies with the agent used and the level of immune suppression. This has led to the recommendation by some experts in the pre-HAART era that "...both short- and long-term antifiungal treatment of esophageal candidiasis should aim mainly at symptom relief, rather than at obtaining complete eradication of *Candida*, which constitutes and unrealistic goal in these patients."[x]

C. State of Armamentarium for Indication(s)

Treatment of esophageal candidiasis has significantly evolved over the past decades. As noted earlier, in the past, gentian violet, nystatin, miconazole, and clotrimazole had been used with varying degrees of outcome, but none of these is currently FDA approved for esophageal candidiasis, although these products predate Drug Efficacy Study Implementation (DESI).

Currently approved treatment options in the US could be broadly classified into: Out-of-Class and In-class Treatment Options.

Out-of-Class Treatment Options include:

- Fungizone® (amphotericin B [IV])

- Nizoral® (ketoconazole [oral])
- Diflucan® (fluconazole [oral and IV])
- Sporanox® (itraconazole [oral solution])
- Vfend® (voriconazole [oral and IV])

Voriconazole, the latest product on the market for the indication of esophageal candidasis, was approved for this indication in November 2003.

In-Class Treatment Options:

- Candcidas® (caspofungin [IV])

Caspofungin, the only in-Class Treatment Option was first approved in January 2001 and received approval for esophageal candidiasis in September 2002.

These agents are effective but each has limitations to their use. Amphotericin B frequently causes nephrotoxicity and infusion reactions, which could limit its therapeutic utility. Ketoconazole has a potential for hepatotoxicity and oral bioavailability is unreliable, especially in patients on H2-receptor blockers. Moreover, there is no IV formulation of ketoconazole.

The triazoles (fluconazole, itraconazole, and voriconazole) are excellent drugs for esophageal candidiasis but potential hepatotoxicity and drug-drug interactions (particularly at higher doses) may limit their use. In addition, emerging azole resistant isolates present another potential limitation to their use.

D. Clinical Studies and Indications and Usage Sections of Labeling for Products Approved for the Treatment of Esophageal Candidiasis

Fungizone® (amphotericin B)
No clinical information in labeling

Nizolral® (ketoconazole)
No specific clinical information in labeling

Sporanox® (itraconazole)
Clinical Studies Section states:
"**Esophageal Candidiasis:** A double-blind randomized study (n=119, 111 of whom were HIV seropositive) compared itraconazole oral solution (100 mg/day) to fluconazole tablets (100 mg/day). The dose of each was increased to 200 mg/day for patients not responding initially. Treatment continued for 2 weeks following resolution of symptoms, for a total duration of treatment of 3-8 weeks. Clinical response (a global assessment of cured or improved) was not significantly different between the two study arms, and averaged approximately 86% with 8% lost to follow-up. Six of 53 (11%) itraconazole-treated patients and 12/57 (21%) fluconazole-treated patients were escalated to the 200 mg dose in

this trial. Of the subgroup of patients who responded and entered a follow-up phase (n=88), approximately 23% relapsed across both arms within 4 weeks."

Indication and Usage Section states:
"SPORANOX® (itraconazole) Oral Solution is also indicated for the treatment of oropharyngeal and esophageal candidiasis."

Diflucan® (fluconazole)
Clinical Studies Section
No clinical information in labeling
Indications and Usage Section states:
"DIFLUCAN (fluconazole) is indicated for the treatment of: Oropharyngeal and esophageal candidiasis."

Cancidas® (caspofungin)
Clinical Studies Section states:

"The safety and efficacy of CANCIDAS® in the treatment of esophageal candidiasis was evaluated in one large, controlled, noninferiority, clinical trial and two smaller dose-response studies.

In all 3 studies, patients were required to have symptoms and microbiological documentation of esophageal candidiasis; most patients had advanced AIDS (with CD4 counts $<50/mm^3$).

Of the 166 patients in the large study who had culture-confirmed esophageal candidiasis at baseline, 120 had *Candida albicans* and 2 had *Candida tropicalis* as the sole baseline pathogen whereas 44 had mixed baseline cultures containing *C. albicans* and one or more additional *Candida* species.

In the large, randomized, double-blind study comparing CANCIDAS® 50 mg/day versus intravenous fluconazole 200 mg/day for the treatment of esophageal candidiasis, patients were treated for an average of 9 days (range 7-21 days). The primary endpoint was favorable overall response at 5 to 7 days following discontinuation of study therapy, which required both complete resolution of symptoms and significant endoscopic improvement. The definition of endoscopic response was based on severity of disease at baseline using a 4-grade scale and required at least a two-grade reduction from baseline endoscopic score or reduction to grade 0 for patients with a baseline score of 2 or less.

The proportion of patients with a favorable overall response for the primary endpoint was comparable for CANCIDAS® and fluconazole as shown in Table 1.

Table 1: Favorable Response Rates for Patients with Esophageal Candidiasis

	CANCIDAS®	Fluconazole	% Difference * (95% CI)
Day 5-7 post-treatment	66/81 (81.5%)	80/94 (85.1%)	-3.6 (-14.7, 7.5)
*calculated as CANCIDAS® - fluconazole			

Adapted from CANCIDAS® labeling

The proportion of patients with a favorable symptom response was also comparable (90.1% and 89.4% for CANCIDAS® and fluconazole, respectively). In addition, the proportion of patients with a favorable endoscopic response was comparable (85.2% and 86.2% for CANCIDAS® and fluconazole, respectively).

As shown in Table 2, the esophageal candidiasis relapse rates at the Day 14 post-treatment visit were similar for the two groups. At the Day 28 post-treatment visit, the group treated with CANCIDAS® had a numerically higher incidence of relapse, however, the difference was not statistically significant.

Table 2: Relapse Rates at 14 and 28 Days Post-Therapy in Patients with Esophageal Candidiasis at Baseline

	CANCIDAS®	Fluconazole	% Difference *(95% CI)
Day 14 post-treatment	7/66 (10.6%)	6/76 (7.9%)	2.7 (-6.9, 12.3)
Day 28 post-treatment	18/64 (28.1%)	12/72 (16.7%)	11.5 (-2.5, 25.4)
*calculated as CANCIDAS® - fluconazole			

Adapted from CANCIDAS® labeling

In this trial, which was designed to establish noninferiority of CANCIDAS® to fluconazole for the treatment of esophageal candidiasis, 122 (70%) patients also had oropharyngeal candidiasis. A favorable response was defined as complete resolution of all symptoms of oropharyngeal disease and all visible oropharyngeal lesions. The proportion of patients with a favorable oropharyngeal response at the 5- to 7-day post-treatment visit was numerically lower for CANCIDAS®, however, the difference was not statistically significant. The results are shown in Table 3.

Table 3: Oropharyngeal Candidiasis Response Rates at 5 to 7 Days Post-Therapy in Patients with Oropharyngeal and Esophageal Candidiasis at Baseline

	CANCIDAS®	Fluconazole	% Difference * (95% CI)
Day 5-7 post-treatment	40/56 (71.4%)	55/66 (83.3%)	-11.9 (-26.8, 3.0)
*calculated as CANCIDAS® - fluconazole			

Adapted from CANCIDAS® labeling

As shown in Table 4, the oropharyngeal candidiasis relapse rates at the Day 14 and the Day 28 post-treatment visits were statistically significantly higher for CANCIDAS® than for fluconazole.

TABLE 4: Oropharyngeal Candidiasis Relapse Rates at 14 and 28 Days Post-Therapy in Patients with Oropharyngeal and Esophageal Candidiasis at Baseline

	CANCIDAS®	Fluconazole	% Difference * (95% CI)
Day 14 post-treatment	17/40 (42.5%)	7/53 (13.2%)	29.3 (11.5, 47.1)
Day 28 post-treatment	23/39 (59.0%)	18/51 (35.3%)	23.7 (3.4, 43.9)
*calculated as CANCIDAS® - fluconazole			

Adapted from CANCIDAS® labeling

The results from the two smaller dose-ranging studies corroborate the efficacy of CANCIDAS® for esophageal candidiasis that was demonstrated in the larger study.

Indication and Usage Section states:
"CANCIDAS® is indicated for the treatment of: Esophageal Candidiasis."

Vfend® Voriconazole
Clinical Studies Section states:
Esophageal Candidiasis
The efficacy of oral voriconazole 200 mg bid compared to oral fluconazole 200 mg od in the primary treatment of esophageal candidiasis was demonstrated in Study 150-305, a double-blind, double-dummy, study in immunocompromised patients with endoscopically-proven esophageal candidiasis. Patients were treated for a median of 15 days (range 1 to 49 days). Outcome was assessed by repeat endoscopy at end of treatment (EOT). A successful response was defined as a normal endoscopy at EOT or at least a 1 grade improvement over baseline endoscopic score. For patients in the Intent To Treat (ITT) population with only a baseline endoscopy, a successful response was defined as symptomatic cure or improvement at EOT compared to baseline.Voriconazole and fluconazole (200 mg od) showed comparable efficacy rates against esophageal candidiasis, as presented in Table 5.

Table 5: Success Rates In Patients Treated for Esophageal Candidiasis

Population	Voriconazole	Fluconazole	Difference % (95% CI)[a]
PP[b]	113/115 (98.2%)	134/141 (95.0%)	3.2 (-1.1, 7.5)
ITT[c]	175/200 (87.5%)	171/191 (89.5%)	-2.0 (-8.3, 4.3)

Adapted from Vfend® labeling

[a] Confidence Interval for the difference (Voriconazole minus Fluconazole) in success rates.
[b] PP (Per Protocol) patients had confirmation of *Candida* esophagitis by endoscopy, received at least 12 days of treatment, and had a repeat endoscopy at EOT (end of treatment).
[c] ITT (Intent to Treat) patients without endoscopy or clinical assessment at EOT were treated as failures.

Microbiologic success rates by *Candida* species are presented in Table 6.

Table 6: Clinical and mycological outcome by baseline pathogen in patients with esophageal candidiasis (Study 150-305).

Pathogen[a]	Voriconazole		Fluconazole	
	Favorable endoscopic response[b]	**Mycological eradication[b]**	**Favorable endoscopic response[b]**	**Mycological eradication[b]**
	Success/Total (%)	Eradication/Total (%)	Success/Total (%)	Eradication/Total (%)
C. albicans	134/140 (96%)	90/107 (84%)	147/156 (94%)	91/115 (79%)
C. glabrata	8/8 (100%)	4/7 (57%)	4/4 (100%)	1/4 (25%)
C. krusei	1/1	1/1	2/2 (100%)	0/0

[a] Some patients had more than one species isolated at baseline
[b] Patients with endoscopic and/or mycological assessment at end of therapy

E. Potential of Anidulafungin as a Treatment Option for Esophageal Candidiasis

For a patient in whom amphotericin (conventional and lipid-based products) and the azoles are contraindicated, the only available therapeutic option is intravenous (IV) caspofungin. Intravenous anidulafungin provides an alternative to IV caspofungin.

Another possible role for anidulafungin is in patients presenting with esophageal candidiasis as the first diagnosis of AIDS requiring ignition of highly active antiretroviral therapy. Such a patient requires very skilled drug management to minimize potential drug-drug interactions. Treatment of the esophageal candidiasis with an azole may not be ideal, given the potential for such interactions associated with this class of drugs.

F. Important Milestones in Product Development

Anidulafungin was previously called V-echinocandin and LY303366. The original IND filed by Eli Lilly and Company on July 15, 1996 was for oral formulation of the product. Original IND 54,597 for this product (injectable formulation) was subsequently filed by Eli Lilly and Company on November 20, 1997. Poor oral bioavailability and marked variability lead to the selection of the intravenous formulation for further clinical development. Sponsorship of IND 54,597 was transferred to Versicor, Inc. on June 18, 1999. In a submission to the IND dated March 31, 2003, Serial Number 167, Versicor, Inc. informed the Agency of its merger with another company to form Vicuron Pharmaceuticals, the applicant for the current NDA.

The Agency held a clinical development meeting with the applicant on January 31, 2002. At that meeting, the applicant indicated its plan to pursue an indication of use of anidulafungin for primary treatment of esophageal candidiasis. The

Agency commented on the planned size for the NDA, reliance on one adequate and well-controlled study, use of lowest approved dose of comparator for 14 days (shorter than minimum of 21 days in labeling) for a non-inferiority design. Please note that the 2000 IDSA guideline recommends a 14-21 day course of either fluconazole (100 mg/day orally) or itraconazole solution (200 mg/day orally).

The Agency further suggested to the applicant that, given these concerns, the data may be presented before the Agency's Advisory Committee and that should the proposed indication be approved, labeling would reflect the dose of the comparator. The applicant agreed to use a one-sided alpha of 0.025 for the primary outcome analysis. The Agency agreed to consider one pivotal study with supportive data from phase 2 but that the pivotal study must be robust. Other areas of concern the Agency raised during the meeting included: potential effect on cytochrome P450 (CYP450) enzyme, interaction with cyclosporin, potential immunotoxicity and potential interaction with glucocorticoids. Other agreements reached with the applicant were as follows:

- Applicant to provide data on the activity of anidulafungin on CYP450 enzyme system
- Applicant to submit mass balance study protocol
- Agency accepted available toxicology data as adequate to cover 14-21 days of human dosing but noted that longer duration of therapy would require a 6 months toxicology studies
- Applicant agreed to consider the Agency's input in design of protocols to study the concerns raised about the immunotoxicity and interaction with glucocorticoids
- Agency accepted the NDA would be fileable as proposed by the applicant

On July 29, 2002, the Agency held the Pre-NDA meeting with the applicant. Key agreements reached at the meeting included

- the submission of the NDA as a hybrid electronic NDA and Common Technical Document (CTD) format and not as an electronic CTD, guidance for which had not been finalized
- use of population pharmacokinetic (PK) analyses of pooled data from phases 2 and 3 studies to address the possibility of drug interactions with anidulafungin. Depending on the population PK results, additional studies may be required to quantify the extent of any changes in PK parameters.
- submit data in the NDA to document the cidality of anidulafngin against *Candida*.
- provide individual study results rather than integration across studies
- provide narratives on all SAEs
- provide case report forms for death and discontinuations due to adverse events from all phases 1 (including studies using the oral formulation and 2/3 intravenous studies)

- the Agency requested the applicant to share sham datasets

At the Pre-NDA meeting, the Agency reiterated the overall leanness of the database, bringing attention again to the use of the lowest approved dose of comparator in a non-inferiority trial, and the fact that the indication is relatively less serious. The Agency informed the applicant that as a result of these issues, there was limited room for unanticipated problems with the NDA.

In a subsequent teleconference with the applicant on August 22, 2002, the applicant noted that the CIOMS form which they proposed to use for SAE reporting did not provide a clear way to specify cause of death. The applicant proposed to still use the form but give more detail about any deaths in the narrative. The Agency agreed with the applicant's proposal, notwithstanding the observed limitations, provided that the narratives were clear as to the relationship of the SAE and death. The Agency also agreed with the applicant's proposals to gather, analyze, and interpret electrocardiogram (ECG) results from the trials. However, the Agency also informed the applicant that additional analyses may be needed if animal or other studies showed ECG signals. The applicant agreed to provide in the NDA a more detailed ECG analysis plan to address issues such as blinding to treatment assignment and digitized ECG reading among others.

The Chemistry review team of the Agency held additional teleconferences with the applicant on October 11, 2002 and April 30, 2003. Key agreements reached at these meetings revolved around stability protocols, designation of C_ J as the starting material for the synthesis of anidulafungin drug substance, and approach to setting impurity specifications for the drug substance. The meetings also discussed stability plans, format/content of manufacturing description and validation strategy, fermentation by-products, and format of the CMC section of the NDA. These issues are appropriately addressed by CMC reviewers.

G. Other Relevant Information

NDA 21-632 is the first marketing application submitted to any regulatory agency for anidulafungin.

H. Important Issues with Pharmacologically Related Agents

Anidulafungin belongs to a class of antinfungals known as echinocandins. Other members of this class of compounds are caspofungin and micafungin. Echinocandins are semisynthetic lipopeptides with potent and broad-spectrum antifungal activity. This activity is mediated by non-competitive inhibition of (1,3)-β-D-glucan synthase, which synthesizes (1,3)-β-D-glucan, a major component of fungal cell wall, a mechanism different from other class of antifungal agents. Many pathogenic fungi possess (1,3)-β-D-glucan, an essential

cell wall homopolysaccharide. This essential glucose polymer provides rigidity and osmotic/structural integrity to the cell wall of susceptible fungi. Inhibition of cell wall synthesis results in cell wall damage by osmotic lysis and eventual fungal death. (1,3)-β-D-glucan target is not a known component mammalian hosts. Thus, a mechanism-based toxicity is potentially unlikely, which could be a major attraction of the echinocandins.

In the 1980s, poor spectrum of activity and nephrotoxicity led to discontinuation of development of the first member of the class, cilofungin. In 2001, caspofungin (Cancidas®) was approved for marketing in the United States. A third member of the class, micafungin, is in advanced stages of development but had been approved in Japan for treatment. One characteristic of this class of drugs is their uniformly poor oral bioavailability, which precludes development of oral formulations. The drugs can only be administered intravenously. This could be considered a disadvantage among this class of drugs compared to the azoles. Nonetheless, intravenous administration ensures compliance in a setting of sick patients that these products are to be used.

There have been no major unexpected safety concerns since marketing approval of caspofungin. A common safety issue shared by members of the echinocandin class is histamine release effect following infusion. Such infusion reaction includes rash, facial swelling, pruritus, and a sensation of warmth. This adverse event is easily controlled with reduction in rate of infusion. In early clinical studies of anidulafungin, infusion-associated AEs were also observed. Symptoms typically included facial flushing, shortness of breath, nausea or wheezing, and generally occurred within minutes of starting an infusion. Symptoms typically resolved without treatment upon halting the infusion, and the infusion has been resumed without recurrence of symptoms in some cases. Injection site reactions appear also to be common with the echinocandins.

In vitro, hemolysis seems to be a safety concern with all echinocandins. The exact mechanism remains unknown. Fortunately, so far hemolysis has not been a major safety problem with clinical use of caspofungin.

The liver is the primary target for toxicity in animal studies. Such hepatic toxicity include changes in liver function tests (alanaine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase) and histopathological changes (single cell necrosis, acidophilic bodies, nuclear hypertrophy, and hepatocellular hypertrophy).

There have been concerns that concomitant use of echinocandins with corticosteroids in rats could result in increased toxicity. An animal study by Clemmons et al,[xi] suggested co-administration of anidulafungin with corticosteroids results in excess mortality. This study is yet to be replicated in any other laboratory. At the Agency's request, the applicant conducted a study in mice

to fully address this issue. The study was entitled "acute toxicity study of cortisone acetate, anidulafungin, and cortisone acetate in combination with anidulafungin administered to DBA/2 and BALB/c mice. The study concluded that a single administration of 125 mg/kg (adjusted to 89 mg/kg) cortisone acetate, 10 daily administrations of 25 mg/kg anidulafungin alone, or the single administration of 125 mg/kg (adjusted to 89 mg/kg) cortisone acetate in combination with 25 mg/kg anidulafungin followed by an additional nine days of anidulafungin administration produced no adverse toxicological findings.

Echinocandins have low minimum inhibitory concentrations (MIC) against *Candida* species, including strains resistant to azoles and amphotericin B; however, the clinical significance of this is uncertain. Partial growth inhibition is seen with *Aspergillus* species, which presents as short, stubby, and highly branched hyphae on microscopy. The drug concentration at which this growth inhibition occurs is called the minimum effective concentration (MEC). As noted above for *Candida*, the clinical and microbiologic relevance of MEC is unknown as there are no established interpretative breakpoints for the echinocandins.

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

Animal Pharmacology and Toxicology

Toxicology studies of anidulafungin have mostly been conducted in rats and monkeys and include intravenous studies of up to 13 weeks. These are supported by additional studies in mice and dogs. The longest human exposure has been reported to be 90 days but the typical treatment in humans for the proposed indication is expected to be on the order of 14-21 days.

In repeat dose studies, the principal clinical finding was a transient infusion reaction consisting of swollen snout, red ears and hypoactivity. These signs were only observed for the first few days of dosing.

Rats treated with anidulafungin exhibited a regenerative anemia which the sponsor ascribes to excessive blood sampling. No hemolysis was observed in monkeys. *In vitro* exposure of rat or human blood cells to anidulafungin showed that rat erythrocytes were more sensitive than human erythroctes to the hemolytic effects of anidulafungin (0.7 % hemolysis in humans versus 17 % in rat cells at 8.78 mg/ml anidulafungin).

In four- and thirteen week studies in rats and monkeys, mild to moderate liver toxicity was observed , including increased liver weights, hepatocellular hypertrophy, increased activity of AST and ALT and liver necrosis. Animals allowed a one month recovery period after the end of dosing still showed

microscopic changes in the liver. Increased liver enzymes have been observed in patients that received high doses of anidulafungin. Other signs observed in high dose animals included kidney tubular vacuolation, skeletal muscle atrophy and increased spleen kidney and lung weight.

In reproductive toxicology studies, high doses of anidulafungin (four times the exposure produced by the proposed maintenance dose of 50mg) produced incomplete ossification of the metacarpals and supression of fetal weight. Anidulafungin crossed the placental barrier in rats and was detected in fetal plasma. Anidulafungin was also found in the milk of lactating rats.

The minimum lethal dose of anidulafugin in Fischer rats was 100 mg/kg. This dose is equivalent to a human dose of 15.9 mg/kg or about 3.7 times the highest single dose given to patients (10 times the loading dose in proposed indication). The minimum lethal intravenous dose of anidulafungin in CD-1 mice was greater than 100 mg/kg (8.1 mg/kg human dose or about 1.9 times the highest single dose given to patients [5 times the loading dose in proposed indication]).

For more details on Animal Pharmacology and Toxicology, reader should please refer to the review by Owen McMaster, Ph.D.

III. Human Pharmacokinetics and Pharmacodynamics

This section is excerpted from Human Pharmacokinetic and Bioavailability subsection in the Summary section (Item number 3 of the NDA Table of Contents) of the applicant's submission.

A. Pharmacokinetics

Absorption

Anidulafungin has low oral bioavailability (2% to 7% in the clinic) and high intersubject variability (> 40% at steady state in multiple dose study) when administered orally. Development of oral formulation is currently stalled.

Distribution

The applicant performed multiple-dose, dose-ascending studies of intravenous anidulafungin in healthy subjects using doses ranging from 30/15 mg regimen for 7 days to 260/130 mg regimen for 10 days. In these studies, steady state was reached following the second dose when the loading dose was twice the maintenance dose. Intersubject variability is low (coefficient of variation <25%) for Cmax and AUCss. The highest tested dose in the Phase 1 dose-escalation studies was a 260/130 mg regimen through 10 days. No maximum tolerated dose (MTD) was established in these studies.

Both plasma concentrations and exposures are dose-proportional. Steady state volume of distribution (V_{ss}) of approximately 30 to 50 L is in the range of total body water volume indicating rapid and wide distribution to tissues.

Plasma clearance (CL) and half-life ($t_{1/2}$) are dose-independent. CL is approximately 1 L/h. A $t_{1/2}$ of about 1 day characterizes the majority of the anidulafungin concentration-time curve and supports once daily dosing in the clinic. PK parameters of anidulafungin in patients being treated for fungal infections were similar to those observed in healthy subjects.

Nonclinical studies have shown that anidulafungin is not highly protein bound in human plasma (~ 84% bound), does not accumulate in the cellular components of blood, does not accumulate in any one organ or tissue, has similar tissue and plasma $t_{1/2}$ values, and that the highest drug concentrations are found in the liver, kidney, lung, and spleen.

Medical Officer's Comment: *In the Phase 1 single- and multiple-dose oral formulation Study in healthy and HIV-infected subjects, 65 saliva samples were obtained from 9 subjects in the multiple dose phase of the study. In the single-dose phase of the study, anidulafungin levels were below limits of quantitation (< 20 ng/mL) in most cases. Anidulafungin levels in saliva were highly variable with a mean peak to plasma concentration ratio of ~20% (range 2-81%).Information is unavailable for the salivary excretion of the intravenous formulation. In immune compromised rabbit model of esophageal and oropharyngeal candidiasis, the saliva concentration of anidulafungin was only ~1% of the plasma drug concentration. The clinical relevance of these findings is unclear. Poor salivary concentration was also observed with caspofungin.*

Metabolisim

Anidulafungin is eliminated predominantly by chemical degradation to inactive ring-opened product at physiological temperature and pH, presumably in all tissues and organs of the body. The ring-opened product, a linear peptide, is subsequently degraded further by ubiquitous nonspecific peptidases.

Excretion

About 10% of intact anidulafungin is eliminated in feces together with the degraded products. In a human mass balance study that accounted for all of the radioactivity administered (single dose of ^{14}C-anidulafungin) to healthy subjects, samples of whole blood, plasma, feces, and urine were collected over 8 weeks. Plasma concentrations of anidulafungin and drug-derived radioactivity were similar through the first 48 hours post-dose. Thereafter, drug-derived radioactivity had a longer observed elimination half-life than anidulafungin. Plasma concentrations of anidulafungin fell below the lower limit of quantitation ~ 6 days after the dose. Radioactivity recovered in blood, urine, and feces were negligible at 8 weeks after the dose. Both intact drug (< 10% of the dose) and

biotransformation products (> 90% of the dose) were excreted in human feces (interpolation to > 99% of administered radioactivity after ~ 42 days after the dose) along with negligible amounts of ring-opened product. Results from a rat mass balance study show that fecal excretion of intact drug proceeds by both biliary and non-biliary routes while fecal excretion of tertiary degradants proceeds mainly via the bile. In the human mass balance study, negligible amounts (< 1% of administered dose) of drug and/or degradation products were found in the urine, indicating no renal clearance of the drug.

Drug Interactions

Anidulafungin is not metabolized by the liver, and there is no evidence of drug-drug interactions involving the cytochrome P450 system. *In vitro*, it is not metabolized by human hepatocytes. It was also determined in nonclinical studies that anidulafungin is not a substrate, inhibitor, or inducer of human cytochrome P450 enzymes. Furthermore, anidulafungin PK parameters were not affected by co-administration of cytochrome P450 substrates, inducers (including rifampin, a potent inducer), or inhibitors. When assessed through concentrations well above maximum concentrations expected in clinical use, anidulafungin had no effect on the *in vitro* metabolism of cyclosporine by human hepatic microsomal proteins. Furthermore, in a clinical study, concomitant use of cyclosporine (a drug metabolized by CYP3A enzymes) did not result in any clinically relevant changes in anidulafungin PK in healthy subjects. Subjects were given a loading dose of 200 mg of anidulafungin followed by 100 mg/day for a total of 8 doses. On Days 5 through 8, subjects were also given 1.25 mg/kg of cyclosporine twice a day. Anidulafungin maximum concentration (Cmax) was unchanged and the area under the concentration-time curve at steady state (AUCss) increased by 22% with concomitant dosing of cyclosporine. This difference was within the range of anidulafungin intersubject variability. Anidulafungin was well tolerated when coadministered with cyclosporine. No dosage adjustments are required on the basis of concomitant medications.

B. Pharmacodynamics

Two nonclinical studies in animals provide an understanding of the pharmacodynamics (PD) of anidulafungin. In a PD study using an immunocompromised rabbit model of fluconazole-resistant oropharyngeal and esophageal candidiasis (Petraitis *et al.* 2001), anidulafungin at 2.5 or 5 mg/kg/day resulted in statistically and clinically significant reductions/clearances of fungal burden in a dose-dependent manner. The plasma anidulafungin levels in rabbits receiving 2.5 mg/kg/day were 3.6 mg/L, 2 h following the dose, and were in the range of what has been observed in clinical trials for patients on the proposed 100/50 mg regimen (~ 0.7 mg/kg/day). The AUCss predicted in this animal model at the 2.5 and 5 mg/kg doses were 26 and 52 mg •h/L, respectively, and are similar to or below the exposures observed in patients receiving the proposed 100/50 mg regimen (Groll *et al.* 2001b).

The appropriateness of the anidulafungin dosage for esophageal candidiasis was assessed following the completion of the therapeutic studies. Data from oral and IV studies were combined and exploratory PK-PD analyses were conducted. A PK-PD relationship between AUCss, Css, and Ctrough was established as depicted by a sigmoidal maximum effect (Emax) model. Although no single PK parameter can best describe the relationship due to the inter-dependence of these parameters, general observations between drug concentrations and response can be summarized. Clinical response is associated with drug exposures of greater than 35 mg •h/L within each dosing interval, average steady state concentrations of 1.5 mg/L, and trough concentrations of greater than 1 mg/L.

No dosage adjustments are required for geriatric status, gender, ethnicity, disease status, hepatic impairment, or renal impairment.

Medical Officer's Comments: *Anidulafungin, like other echinoncandins, has low MICs against most species of Candida and low MECs against Aspergillus species. In addition, anidulafungin displays a post antifungal effect greater than 12 hours against Candida species when tested at higher than the MIC for the organism. In broth-based assays of echinocandins against Aspergillus species, a dose-dependent formation of microcolonies occurs followed by progressively truncated, swollen, hyphal elements deficient in cell wall. These cell-wall deficient elements regain their cell walls when subcultured in the absence of drug. Given the lack of an established method to measure inhibitory concentrations or defined breakpoints, the correlation between the PK, MICs of the isolates, and clinical response remains difficult to interpret.*

IV. Description of Clinical Data and Sources

A. Overall Data

Sources of Clinical Data

The clinical data in this NDA are derived primarily from clinical trials sponsored by the applicant. The applicant also includes copies of extensive literature cited to support the nonclinical contents of the application.

B. Tables Listing the Clinical Trials

Tables 7 summarizes all the clinical trials conducted to support this NDA for the indication of the treatment of esophageal cadidiasis.

Tables 7: Summary of Clinical Trials Supporting Proposed Indication in the Current Application

Protocol # (Phase)	Objective	Design	Treatment	Primary Endpoint	Population	# Enrolled
VER002-4 (3)	Safety and efficacy in esophageal candidiasis compared to fluconazole	randomized, controlled, double-blind, double-dummy, non-inferiority	IV Anidulafungin 100/50 mg for 14-21 days Vs PO Fluconazole 200/100 mg for 14-21 days	Endoscopic response at EOT	Clinically evaluable	Anidulafungin 300 Fluconazole 301
VER002-6 (2)	Safety and efficacy in patients with invasive candidiasis	Open label, randomized, dose-ranging	IV Anidulafungin 100/50 mg, 150/75 mg, and 200/100 mg for 15-42 days	Global response (clinical and mycologic) 2 weeks post EOT	Evaluable at follow up	120 (40 per dose cohort)
XBAF (2)	Safety and efficacy in esophageal candidiasis	Open label, randomized dose-ranging	Anidulafungin 70/35 mg or 50/25 mg for 14-21 days	Clinical response at EOT. A post hoc analysis was done using endoscopic response at EOT	Clinically evaluable	36 (19 on 50/25 mg arm and 17 on 70/35 mg arm)
VER002-11 (2/3)	Safety and efficacy in patients with fluconazole-refractory mucosal candidiasis	On-going open-label, non-randomized study	Anidulafungin 100/50 mg for 14-21 days	OPC: Clinical Response at EOT EC: Endoscopic response at EOT	Clinically evaluable	5 of planned 20 (3 OPC and 2 EC)

Source: Adapted from Applicant's Submission (NDA 21-632, Study VER002-4 Table 1 Integrated Summary of Efficacy)

For a perspective to the Division's approval decisions on esophageal candidiasis, Table 8 summarizes characteristics of databases submitted in current NDA compared with those in NDAs for caspofungin and voriconazole that were recently approved for the indication of esophageal candidiasis.

Table 8: Comparative Summary of Study Database from NDAs Submitted for Anidulafungin, Caspofungin, and Voriconazole in the Treatment of Esophageal Candidiasis.

Parameter	Anidulafungin	Voriconazole	Caspofungin
# of EC studies	2	1	5*
Pivotal	1	1	1*
Supportive	1	0	4*
Total # of patients enrolled (All Studies)	637	391	467
# that received study drug	336	200	284
# that received comparator	301 (Fluconazole 301)	191	183 (Fluconazole 94, Amphotericin 89)
% *C. albicans* in Mycological ITT Set (Pivotal Study)	425/466 (91.2%)	354/391 (90.5%)	115/155 (74.2%)
% HIV infected (Pivotal Study)	237/279 (84.9%)**	368/391 (94.1%)	154/177 (87.0%)
% with Concurrent OPC	Not available	325/391 (83.1%)	122/175 (69.7%)
Location of study sites (Pivotal Study)	South Africa 453/601 (75.4%) Thailand 91/601 (15.1%) Argentina 51/601 (8.5%) US 6/601 (1.0%)	Europe, Australia, Russia, Singapore, South Africa, Thailand (proportions not available)	Latin American 157/177 (88.7%) US 20/177 (11.3%)

Adapted from multiple sources including current NDA, medical officer reviews of caspofungin and voriconazole for esophageal candidiasis.

The current application constitutes the largest submitted to the Agency for the indication of esophageal candidiasis as summarized on Table 9. However, it should be noted that caspofungin and voriconazole were already marketed products at the time of their approval for esophageal candidiasis.

Table 9: Comparative Size of Current and Recent NDAs Submitted to Support the Indication of Esophageal Candidiasis.

	Anidulafungin*	Caspofungin	Voriconazole
Phase 3 Study			
Test Drug	276	83	200
Active Comparator	278	94	191
Phase 2 Supportive Studies			
Test Drug	161	284	32
Active Comparator	0	89	0
Total Database	**715**	**550**	**423**

*Data Exclude Site 019 (24 Anidulafungin, 23 Comparator)

*Excluding site 019 (24 Anidulafungin, 23 Comparator)

C. Postmarketing Experience

This is the first marketing application for anidulafungin. This drug product has not been marketed in any other country or region. Therefore, there is no post-marketing experience.

D. Literature Review

The applicant has conducted an extensive review of the literature spanning 1976 to 2002. Electronic copies of the cited literature are also provided with the submission. The bulk of the cited literature discusses diagnose and treatment of esophageal candidiasis. However, given the fact that the echinocadins are relatively new molecular entities, only few of the cited literature address safety and efficacy aspects of echinocandins in general. The applicant also cites from the package insert of approved antifungal drug products. On June 30, 2003 and January 31, 2004, additional literature searches were conducted using PubMed and Embase. The search covered the period starting from January 2002 through January 31, 2004. Two papers by Ostrosky-Zeichner et al[xii] from the US and Marco et al [xiii] from Spain confirm the in vitro activity of anidulafungin against blood stream isolates of *Candida* species, including those resistant to other agents; although same data suggests the drug is less active against *Candida parapsilosis* and *Candida guilliermondii*.

V. Clinical Review Methods

A. How the Review was Conducted

For efficacy, this review focuses on trials supporting the indication of treatment of esophageal candidiasis. Trials providing evidence for the efficacy of anidulafungin in this indication include the single large randomized Phase 3 trial of esophageal candidiasis (Protocol VER002-4) and three small Phase 2 or 2/3 supporting trials (Protocol numbers VER002-6, XBAF, and VER002-11). These studies are reviewed separately with a significant portion of the review devoted to Study VER002-4. For safety, the studies listed for efficacy are also reviewed as well as the integrated safety data across all studies. Finally, a review of post-marketing adverse event reports for caspofungin (Cancidas®) provides a perspective to the safety of yet another echinocandin, anidulafungin. Studies using oral formulation of anidulafungin or involving microorganisms other than *Candida* are considered in the assessment of safety but not efficacy.

B. Overview of Materials Consulted in Review

The archival copy of this NDA was submitted in an electronic format. The electronic submission provided the main source of material for this review. Supplementary sources of material for this review include medical officers' reviews of anidulafungin protocols and NDAs for the following approved products Cancidas® (caspofungin), V-fend® (voriconazole), Ambisome® (liposomal amphotericin B), Sporonox® (itraconazole), and Abelcet® (amphotericin B colloidal dispersion). Further, the detailed review of the post-marketing safety of Cancidas® conducted by Sarah Singer, R.Ph. Safety Evaluator, Office of Drug Safety (ODS) was consulted. In addition, more literature review was conducted to supplement the literature cited by the applicant. Finally, written evaluations from the Division of Scientific Investigation and Division of Drug Marketing, Advertising, and Communications were considered in the overall assessment of this NDA.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Five of 26 sites enrolled nearly 70% of 601 patients in the pivotal study. About 75% of 601 patients were enrolled in South Africa. Since outcome appeared to be uniform across all sites, the two largest sites (152 and 113 patients, respectively) were selected for auditing. The location of both sites in South Africa should facilitate auditing. Furthermore, given the systematic reversal of randomization in approximately 70% of enrolled subjects, the analytical data and processes of the population PK substudy were audited by the Division of Scientific Investigation (DSI). For additional details of DSI inspection, reader should please refer to Section VI (C) (Integrated Review of Efficacy: Detailed Review of Trials by Indication-Randomization Incident and Data Integrity).

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

For all trials reviewed in this NDA submission, the applicant affirms that the protocols were reviewed and approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of participating institutions. The applicant also affirms that the studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and that written informed consent was obtained from each patient or legal guardian prior to enrollment. Further, the NDA contains a copy each of debarment certification, field copy certification, current Good Manufacturing Practices (cGMP) certification, and certificate of quality assurance. Finally, the applicant has provided justification for categorical exclusion from the requirement to submit an environmental assessment for anidulafungin for injection as analysis indicates that environmental effects associated with the release of anidulafungin drug substance to the environment due to patient use are expected to be negligible.

E. Evaluation of Financial Disclosure

In accordance with 21 CFR Part 54, the applicant certifies that it has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR 54.2(a). The applicant also certifies that none of the listed clinical investigator required to disclose to the applicant whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) disclosed any such interests. The applicant finally certifies that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). However, the applicant disclosed that one of the principal investigators, [ ] participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

"Any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria."

Specifically, Dr.[ ] received grants from the applicant to support his laboratory research.

Medical Officer's Comment: *This involvement is unlikely to potentially influence the study outcome, particularly given Dr.[ ] stature and reputation within the international scientific community.*

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Anidulafungin is active in the treatment of esophageal candidiasis. Its activity in this indication is superior to published treatment outcomes for placebo or marginally effective therapies. However, in the population studied in the large Phase 3 esophageal candidiasis trial, a population that was made up predominantly of AIDS patients without adequate anti-HIV treatment, it is expected that once treatment is stopped, patients will relapse as was seen on both arms, although the relapse was significantly worse on the anidulafungin arm relative to the fluconazole arm.

B. General Approach to Review of the Efficacy of the Drug

Clinical Development Program (for the indication)

The efficacy database comprises one pivotal study and three supporting studies as summarized below.

Pivotal study

- **VER002-4:** Phase 3, randomized, controlled, double-blind, double-dummy, non-inferiority study to assess the safety and efficacy of anidulafungin compared to fluconazole, for the treatment of esophageal candidiasis.

Supportive studies

- **VER002-6:** Phase 2 randomized, dose-ranging trial of 3 different dosages of anidulafungin in patients with invasive candidiasis, including candidemia
- **XBAF:** Phase 2, randomized dose-ranging, proof of concept efficacy study of anidulafungin in esophageal candidiasis
- **VER002-11:** Ongoing Phase 2/3 open-label study of the safety and efficacy of intravenous anidulafungin as a treatment for fluconazole-refractory mucosal candidiasis

Additional details on these studies are summarized in Table 7. All the studies listed in Table 7 are reviewed in this document. Much of the review focuses on the large randomized controlled study (VER002-4). The small Phase 2 esophageal candidiasis study (that employed doses lower than the proposed dose) is also reviewed in some detail to provide corroborative evidence of efficacy at the proposed dose of anidulafungin in the treatment of esophageal candidiasis. The relatively large Phase 2 study on invasive candidiasis (Study VER002-6) is also reviewed. The remaining study (Phase 2/3 study of anidulafungin in fluconazole-refractory mucosal candidiasis VER002-11) is briefly summarized, [

C. Detailed Review of Trials by Indication

Sponsor's protocol # VER002-4. Title Phase 3, randomized, controlled, double blind, double-dummy, non-inferiority study to assess the safety and efficacy of anidulafungin compared to fluconazole, for the treatment of esophageal candidiasis. **[conducted (April 18, 2001) to (October 25, 2002)]**

Protocol
Objective/Rationale

Primary objective
The primary objective of Study VER002-4 was to determine whether anidulafungin is at least as effective as fluconazole in the treatment of esophageal candidiasis. The primary endpoint used to assess the non-inferiority of anidulafungin vs. fluconazole was endoscopic response at the end of therapy (EOT) in the clinically evaluable at EOT population.

Secondary objectives
Secondary objectives of Study VER002-4 were:
1) Evaluate the safety of anidulafungin in the study patient population. This was measured by the frequency of adverse events (AEs), serious adverse events (SAEs), changes in laboratory parameters and premature terminations.
2) Compare the efficacy of anidulafungin vs. fluconazole in the treatment of esophageal candidiasis as measured by endoscopic response at follow-up (FU).
3) Compare the efficacy of anidulafungin vs. fluconazole in the treatment of esophageal candidiasis as measured by clinical response at EOT and at FU.
4) Compare the efficacy of anidulafungin and fluconazole as measured by mycological response at end of therapy (EOT) and at follow-up (FU).

Overall Design
As noted previously, VER002-4 was a randomized, double-blind, double-dummy, non-inferiority, international, multi-center study to assess the efficacy of intravenous anidulafungin versus oral fluconazole in the treatment of esophageal candidiasis.

Medical Officer's Comment: *The design of this trial is an appropriate one to answer the trial question. However, a major challenge of the design is the need for consistent interpretation and application of the protocol across the many study sites in this international multi-center study.*

As noted earlier, another issue in the study is the choice of the lowest approved dose of the active comparator (and for less than labeled duration of therapy) for this non-inferiority trial. Nonetheless, literature shows that the selected dose of comparator is as effective as higher doses. Moreover, the 2000 IDSA guideline(current at the time of the trial) recommended a 14-21 day course of either fluconazole (100 mg/day orally) or itraconazole solution (200 mg/day orally).

Population and Procedures
Inclusion Criteria
Key inclusion criteria were:

- Predisposing risk factor for fungal infection including antibiotic, corticosteroid, or radiation therapy; myelosuppression; malnutrition; seropositivity for human immunodeficiency virus (HIV); or a diagnosis (according to CDC criteria) of acquired immunodeficiency syndrome (AIDS).
- Diagnosis of esophageal candidiasis.
- Biopsy of esophageal lesion that ruled out the presence of HSV and CMV using standard methodology.

Medical Officer's Comment: *Please note that testing for HIV was not mandatory and that history of HIV infection was common in those not tested.*

Exclusion Criteria
The following key exclusion criteria were applied to the selection of the study population:

- Patients who had evidence of systemic fungal infection (except for the study indication).
- Patients who had esophageal biopsy or viral culture consistent with HSV or CMV, using standard methodology for assessment.
- Patients whose expected survival (in the opinion of the investigator) was less than 2 months from time of study entry or whose underlying condition would not reasonably assure ability to complete the study.
- Patients who had received systemic anti-fungal therapy in the week prior to enrollment. This criterion did not exclude patients who had received oral topical or oral non absorbable therapies (i.e., clotrimazole troches, nystatin) prior to enrollment.

Medical Officer's Comment: *Allowing those on oral topical or oral non-absorbable antifungal medication to enroll in this could potentially confound the result and render interpretation difficult. The review will look to ensure a balance between the treatment groups in the use of such permissible medications.*

Most recent laboratory results (within 30 days of enrolment) indicating any of the following:

- ALT or AST > 3 times upper limit of normal
- Serum creatinine > 2.5 times upper limit of normal
- Total serum bilirubin > 3 times the upper limit of normal
- Absolute neutrophil count of < 500 polymorphonuclear cells/mm^3, or < 1000 polymorphonuclear cells/mm^3 and expected to fall below 500 polymorphonuclear cells/ mm^3 during the study.

- Most recent laboratory results prior to baseline endoscopy indicating a platelet count of < 60,000/mm 3 or prothrombin time of > 1.4 times upper limit of normal.

- Patients with ulcerative esophageal lesions by endoscopy.
- Use of drugs of abuse and/or positive findings for drugs of abuse on optional urinary drug screening (excluding prescribed medications taken as prescribed).
- Participation in a study involving administration of an investigational compound within the past 4 weeks or blood donation or more than 1000 mL for males or 500 mL for females, within the past 3 months.
- Regular alcohol intake (> 28 units per week for males, or > 21 units per week for females)[1], or subject unwilling to stop alcohol intake for the duration of the study.
- Known atopy (e.g., hay fever, allergic rhinitis, eczema) requiring regular use of antihistamine medication.

Adequate provisions were made to prevent exposure of pregnant or lactating females to anidulafungin. In addition, subjects who had previously enrolled in the study were ineligible for re-enrollment. Similarly, patients with known hypersensitivity to anidulafungin, echinocandins or pneumocandins and those with known hypersensitivity to any of the excipients or with the potential for such hypersensitivity were excluded.

Medical Officer's Comment: *This study was conducted primarily outside the US and a large majority of subjects were enrolled in South Africa. The population enrolled was made up predominantly of AIDS patients with limited or no anti-HIV treatment. In the US, most patients with AIDS would likely be receiving HAART. However, a small number of patients could present with esophageal candidiasis leading to the diagnosis of their underlying AIDS.*

The entry criteria were fairly non-restrictive. Table 10 summarizes data for screen failures. However, the reviewer could not find data on the demographic and other characteristics of screen failures to assess their comparability with those randomized and thus generalizability to the target population.

Table 10: Most Frequent Reasons for Screen Failure (Total Screen Failures = 597)

Parameter	Number
No presence of esophageal candidiasis	196
Patient not reliable	72
Patient older than 65 years	36
Ulcers on endoscopy	36
ALT/AST > 3 x ULN	34
Unable to give consent	33
Underlying condition precludes enrollment	29
Expected survival < 2 moths	26
No symptoms	16
Use of systemic antifungal in week prior	15
Creatinine > 2.5 x ULN	14

Source: Adapted from Applicants Submission (NDA 21-632 Study VER002-4 End-of-Text Table 1.1 of Study Report)

[1] 1 unit = 8g ethanol, e.g., ½ pint of beer, 1 glass of wine, 1 measure of spirits

Evaluations/Endpoints

Primary Efficacy Endpoint
The primary endpoint used to assess the non-inferiority of anidulafungin versus fluconazole was endoscopic response at the end of therapy (EOT) in the clinically evaluable at EOT population.

Secondary Efficacy Endpoints
- Endoscopic Response at Follow-up in Clinically Evaluable At Follow Up Population
- Endoscopic Response at End of Therapy and Follow-Up in Intent-to-Treat Population
- Clinical Response at End of Therapy and Follow-Up in Clinically Evaluable Populations
- Clinical Response at End of Therapy and Follow-Up in Intent-to-Treat Population
- Per-Patient Mycological Outcomes and Responses
- Per-Pathogen Mycological Outcome and Responses
- Time to Resolution of Symptoms
- Duration of Therapy

Medical Officer's Comment: *The endpoints defined in this study are clear, objective, and appropriate and have been used in identical trials. The original protocol (August 2000) defined the intent-to-treat (ITT) as its primary efficacy analysis population with a planned enrollment of 800 patients to provide evaluable data on 600 patients with esophageal candidiasis. In the final protocol dated June 3, 2002, the primary analysis population for efficacy was the clinically evaluable at EOT. However, in addition to the clinically evaluable at EOT population, the sponsor defined another evaluable population post hoc as the clinically evaluable at Follow-up population. The clinically evaluable at Follow-up population was defined in the course of data analysis as "patients who were clinically evaluable at EOT, had a follow-up assessment with clinical outcome other than indeterminate, had a follow-up endoscopy result and did not have any protocol violations between EOT and follow-up that impacted the assessment of efficacy."*

There were four amendments to the protocol, one prior to patient enrollment and three while study was ongoing. Highlights of the amendments are as follows:

Amendment 1 of December 19, 2000
Upper age limit for eligibility was lowered from 75 to 65 years and criteria involving dose-limiting toxicity were deleted.

Amendment 2 of February 2, 2001
This amendment clarified the duration of treatment from a "maximum treatment duration of 14 to 21 days" to a "minimum treatment duration of 14 days and a maximum treatment duration of 21 days." The amendment also changed the study design from equivalence to non-inferiority with appropriate redefinition of primary and secondary objectives as well as changes in sample size and statistical analysis to reflect change in study design.

Amendment 3 of June 15, 2001
There were no changes under this amendment that could significantly impact study efficacy outcome. Indeed, the amendment incorporated viral testing for herpes simplex virus (HSV) and cytomegalovirus (CMV) and daily symptom assessments, which were inadvertently omitted from previous versions of the protocol. In addition, the amendment allowed assessments and procedures in patients who had recurrences or received systemic antifungal agents between EOT and 14 day post EOT follow up visit.

On July 16, 2001, the applicant added a sub-protocol to allow collection of blood samples from a subgroup of patients within protocol VER002-4 for the purpose of determining the PK of anidulafungin in patients with esophageal candidiais.

Medical Officer's Comment: *The decision to add this population PK is significant in other ways. The primary purpose of this sub-study was to further characterize the PK of anidulafungin in the population of patients enrolled in Study VER002-4. To be eligible for the population PK sub-study, patients were required to give a second written consent and be willing and able to complete the sub-study procedures. In the course of PK analysis of samples from patients in the sub-study, a large number of patients supposedly randomized to anidulafungin were found to have levels of anidulafungin below limits of detection. This discordant finding led the sponsor to conduct an investigation that uncovered a systematic reversal in a 1:1 manner of randomized treatment administration to 70% of patients enrolled in study VER002-4. Additional details of this incident, the corrective steps taken by the sponsor to ensure data integrity and the outcome of investigation by the Bioequivalence Branch of the Division of Scientific Investigations (DSI) of the Agency is further discussed below:*

Randomization Incident and Data Integrity: ***Systematic reversal of treatment kit in 70% of subjects***

On December 15, 2002, the sponsor reported to the Division a randomization error affecting 70% of the enrolled patients in the pivotal esophageal candidiasis study (VER002-4). The sponsor was alerted to the error by the results obtained from pharmacokinetic (PK) analysis of plasma samples from anidulafungin patients. With amendment number 3 to Study VER002-4 protocol, a sub-protocol was initiated for population PK analysis for anidulafungin. This process required selective testing for anidulafungin in samples drawn from patients randomized to the anidulafungin arm. On testing of the initial set of samples obtained for the population PK analysis, there was no detectable amount of anidulafungin. With efforts made to maintain the blind, the laboratory informed the sponsor and a chain of investigative action was set off.

On further investigation, the sponsor found that the problem originated from the vendor who packaged and shipped clinical trial supplies to study sites. While the trial remained blinded, the sponsor found that the vendor systematically reversed in a 1:1 fashion the two treatment arms as compared to the randomization schedule provided to them by the

study statistician. The error began on September 27, 2001 (the implementation date of a revised procedure for labeling and distribution of drug treatment kits) and continued to the end of study on October 31, 2002.

The sponsor had to reconstruct a schedule of treatment assignments for the study prior to unblinding the database.

On December 16, 2002, the sponsor reported to the Agency that together with the vendor it planned to take the following actions to ensure the integrity of the study results:

1. Vendor performed a 100% paper audit of all work orders and for all kits assembled for the study.
2. Vendor traced the receipt and use of all lots of drug and labels used in the study.
3. Vendor constructed a corrected schedule of treatment assignments based upon the above actions.
4. Vendor examined samples of retained kits and returned kits (both used and unused) to verify corrected schedule of treatment assignments.
5. Versicor performed 100% paper audit of packaging vendor's findings.
6. All pharmacokinetic plasma samples, regardless of treatment assignment, were analyzed for anidulafungin.
7. Versicor initiated discussions with FDA of findings and actions to verify FDA agreement prior to unblinding of study.
8. After the above actions had been completed, the sponsor provided corrected schedule of treatment assignments to statistician for unblinding of study.
9. The sponsor reviewed findings and required corrective actions with vendor prior to any consideration of awarding future packaging of blinded study supplies to them.

At a teleconference on December 17, 2002, the Agency informed the sponsor that the proposed action plans were acceptable but that the issue would be revisited when the NDA is submitted. Following submission of the NDA, the Division consulted the Division of Scientific Investigation (DSI) and requested evaluation of the randomization incident and the sponsor's remedial actions.

DSI Investigation

DSI determined that Population PK plasma samples were obtained from 262/601 patients and although all were analyzed for anidulafungin, only 32% of patients had been analyzed for fluconazole. However, of the 32% analyzed for fluconazole, five patients in site 19 had both fluconazole and anidulafungin in their Population PK samples. In light of this finding, DSI recommended that fluconazole be determined for the remaining 68% of the Population PK samples to determine the extent of discrepancy between the Population PK results and the revised randomization code.

The company analyzed the remaining samples and provided a report that among 274 patients assayed (representing 46% of the 601 patients enrolled), the drug levels confirmed the corrected randomization scheme. In addition, the company reported that 30 patients from 8 study sites in the trial had at least one sample with both anidulafungin

and fluconazole detected; 15 of these patients were in site 19 (out of a total of 47 patients enrolled at this site), the other 15 patients were from 7 additional study sites For these 30 patients, samples were available from days 3, 7 and 14 of study, and the presence of both anidulafungin and fluconazole was generally detected in one of the three.

The Company's Jan 6, 2004 submission presents all sample drug levels. In attachment 4, they describe unexpected results - 30 patients (43 samples) from 8 different sites had unexpected results:

- 1 patient from site 4 (of 13 assayed)
- 7 from site 10 (of 85 assayed)
- 3 from site 12 (of 16 assayed)
- 1 from site 17 (of 20 assayed)
- 1 from site 18 (of 20 assayed
- 15 from site 19 (of 39 assayed)
- 1 from site 20 (of 3 assayed)
- 1 from site 22 (of 4 assayed – from Argentina, not involved in randomization mix-up)

Patients have sample from days 3, 7, and 14 of therapy. The most common pattern is that a patient has assigned drug on all three days and one sample with the unassigned drug. Usually, but not always, the assigned drug is present in clearly therapeutic amounts and the other drug usually in smaller amounts. In site 19, 2 patients had both drugs present in samples on all 3 days and another 4 patients had both drugs present on 2 of 3 days. The other 9 patients from site 19 had 1 of 3 samples with both drugs present. In site 12, 18 and 22, there was one patient each at each site that had 2 of 3 samples with both drugs present. The full report of DSI findings is archived in the Agency's Division Filing System.

Implication of the Systematic Error Incident from the Agency's Statistical and Biopharmaceutical Perspectives

The Agency's statistical review team modeled the data in several ways and concluded that the randomization incident could not have made the outcome any worse than it already is for anidulafungin.

Similarly, the biopharmaceutical review team commented that "for [the] few patients who had their randomization codes corrected from anidulafungin to fluconazole, at study sites other than Site 19, there were low concentrations of anidulafungin detected on varying days, with no consistent pattern. But, it appeared that there was only one detectable anidulafungin concentration per patient on only one given day, with the other days being BLQ (below limit of assay quantitation)." The team noted that "... the ***times*** when these PK samples were drawn for anidulafungin are unknown, rendering interpretation of these concentrations impossible."

Finally, the team noted that "the assay itself - i.e., LC/MS/MS - is typically very specific and the analytical report shows very good precision (as measured by percentage coefficient of variation) and accuracy (as percentage difference from Theoretical Quality Control concentration) ." The team then concluded that "(1) no therapeutic concentrations/therapeutic concentration ranges have been established for anidulafungin or even fluconazole [therefore, there is need for caution in interpreting dual drug levels found in some of the subjects]; (2) the low anidulafungin concentrations (especially for those patients correctly randomized to fluconazole) are not consistent with the anidulafungin concentrations achieved when giving the proposed clinical dosage regimen of 100mg loading dose (LD)/50mg maintenance dose."

Amendment 4 of June 3, 2002
In this amendment, the applicant updated and clarified the definitions of mycologic response. Further, the amendment added 10 days of therapy and EOT endoscopy to the criteria for clinically evaluable at EOT population. Finally, statistical analysis was changed from one-sided alpha of 0.05 to a two-sided alpha of 0.05 which resulted in an increase of sample size from 190 patients per arm to 222 patients per arm.

Medical Officer's Comments: *It is worth noting that no patients were enrolled using the original protocol dated August 22, 2000 or using the protocol amendment 1 version dated December 19, 2000. The number of patients enrolled into subsequent versions of the protocol were 81, 404, and 116 following amendments 2, 3, and 4, respectively. These amendments were reviewed and considered acceptable and, indeed, some of the amendments followed guidance obtained from the Division.*

Blinding
This was a double-blind study. All study procedures were the same regardless of assignment to anidulafungin or fluconazole treatment. Emergency codes identifying treatment assignment were available to the investigator. In the event of an emergency in which the patient's condition required the knowledge of the treatment assignment, the study blind was broken for that patient only. Randomization treatment codes were also available to the bioanalytical laboratory that performed the anidulafungin PK assays. Even under such circumstances, adequate provision was made to document in the CRF and to maintain integrity of the rest of the study. In all, treatment codes for six patients were broken during the study due to SAEs. None of these compromised the integrity of the study.

Protocol Violations and Prior/Concomitant Medications
From the random sample of patients reviewed, protocol violations were few and none significantly impacted the study outcome. Similarly, only very few patients received prior systemic or oral antifungal medications and during the study such medications were administered as salvage only to failing patients, who had already met an endpoint.

Statistical Plan
Study VER002-4 was designed to show that anidulafungin is no worse than fluconazole in the treatment of esophageal candidiasis. To attain this statistical goal with a power of 90% and a delta of 10%, approximately 592 were required to provide evaluable data on 444 patients with esophageal candidiasis (222 patients per treatment arm). Given the randomization incident, the non-inferior outcome at EOT but significantly inferior rate of sustained success to be discussed below, the Division's statistical review team conducted several sensitivity analyses and modeling in their assessment of the efficacy of anidulafungin. As noted earlier, the sponsor defined two clinically evaluable populations, one at EOT and the other at FU. However, the Division's statistical analyses were based on the pre-specified clinically evaluable at EOT population. For more details, the reader should refer to the review by the statistical reviewer, Cheryl Dixon, Ph.D.

Results

Impact on efficacy conclusions of poor randomization
Randomization was reasonably balanced between the two treatment arms in all respects. However, in the clinically evaluable population, more patients had Grade 3 endodscopy score at baseline on the fluconazole arm compared to the anidulafungin arm (108/249 [43.4%] versus 124/255 [48.6%]). These differences are small but could potentially place anidulafungin at a slight advantage. This slight imbalance in baseline endoscopy grade persisted even when limited to the follow-up population.

Duration of randomized treatment in the clinically evaluable population was balanced with a median of 14 days on both arms and a mean of 14.4 ± 1.4 and 14.4 ± 1.5 days on the anidulafungin and fluconazole arms, respectively. The duration of therapy was also similar in the ITT population (13.4 ± 3.2 and 13.6 ± 3.1 days for the two arms, respectively).

Impact of imbalances in important prognostic factors among treatment groups
Of the 601 enrolled subjects, HIV test was performed on 280 (47%) subjects. Of these, 237 (85%) tested positive (114/300 [38%] and 123/301 [41%] of patients randomized to anidulafungin and fluconazole arms, respectively). Use of prior antifungal therapy was balanced between the two arms. On the anidulafungin arm, 32 (10.7%) patients used prior antifungal agents compared to 35 (11.6%) on the fluconazole arm. Of these 67 patients, 33 were on oral nystatin and 12 on oral clotrimazole. Only 10 patients had received prior triazole antifungal agent (fluconazole 9 [4 on anidulafungin arm and 5 on fluoconazole arm], itraconazole 1 [on anidulafungin arm]).

Similarly, only 10 (1.7%) of the 601 subjects were on any prior antiretroviral therapy (ART), 4 on anidulafungin arm versus 6 on fluconazole arm. The corresponding distribution of the various classes of ART on the anidulafungin and fluconazole arms were as follows: nucleoside reverse transcriptase (NRTI) 3 versus 5, non-nucleoside reverse transcriptase (NNRTI) 0 versus 2, and protease inhibitors (PI) 1 versus 3. Although majority of patients received no ART, use of ART increased slightly during the

study period. A total of 51 (8.5%) patients were on concurrent ART (18 (6.0% on anidulafungin arm and 33 (11.0%) on fluconazole arm). The corresponding distribution of the various classes of ART used concurrently on the anidulafungin and fluconazole arms were as follows: nucleoside reverse transcriptase (NRTI) 18 versus 33, non-nucleoside reverse transcriptase (NNRTI) 6 versus 12, and protease inhibitors (PI) 5 versus 20. Given the opportunistic nature of esophageal candidiasis, the imbalance in concurrent use of ART could potentially confer an advantage to the fluconazole arm.

Medical Officer's Comment: *Overall, the lack of adequate anti-HIV therapy would make this population more susceptible to relapse. As noted earlier in this review, the population enrolled in this study is somewhat dissimilar to the HIV-infected population in the US, given that most patients with AIDS in the US would likely be receiving HAART. However, a small number of patients could present with esophageal candidiasis leading to the diagnosis of their underlying AIDS.*

Relevance and acceptability of the way subject dropouts and missing data was handled by the applicant in analyzing the study

A total of 1198 patients were screened of which 601 (50.2%) were randomized. Among the 601 randomized patients, 488 (81.2%) completed the study as shown in Table 11. The most common reasons for screen failure were: lack of presence of esophageal candidiasis (n=192), patient not sufficiently reliable (n=72), presence of ulcerative lesions on endoscopy (n=36), and age over 65 years (n=36). *The MO reviewer could not find data on the demographic and other characteristics of screen failures to assess their comparability with those randomized and thus generalizability to the target population.*

Table 11 provides details of discontinuations from the study and reasons for their discontinuation.

Table 11: Patient Discontinuation and Reason for Discontinuation, Intent-to-Treat Population

		Anidulafungin	Fluconazole	Total
		N=300	N=301	N=601
Total discontinued		55	58	113
Reason for discontinuation	Adverse event	29	23	52
	Lost to follow-up	7	13	20
	CMV/HSV positive	6	8	14
	Baseline lab value outside specified range	6	5	11
	Non-compliance	4	4	8
	By request	2	3	5
	Change in condition	1	1	2
	Unknown	0	1	1

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 10 of Study report)

Subjects who terminated prematurely were not replaced. The protocol treated missing outcome data as indeterminate outcome, which mapped to an outcome of failure, except for the analysis of endoscopic response at EOT and FU, which was performed with no indeterminate category. Furthermore, certain protocol violations were criteria for exclusion from the clinically evaluable population at end of therapy. The criteria included:

1. Patients with fewer than 10 total days of therapy (not consecutive days).
2. Patients lacking an EOT endoscopy.
3. Patient receiving systemic anti-fungal therapy within the week prior to enrollment.
4. Patient receiving systemic or topical (mouth only) anti-fungal therapy during the period of active treatment.
5. Patients with an EOT visit > 7 days from the last dose of study drug.

The size of each analysis population and the reasons for exclusion from an analysis population is shown in Table 12.

Table 12: Reasons for Exclusion from Each Analysis Population

Analysis Population and Reasons for Exclusion		**Treatment Arm**	
		Anidulafungin n/N (%)	**Fluconazole n/N (%)**
Randomized		300	301
Intent to treat		300	301
Clinically evaluable at end of therapy		249 (83.0)	255 (84.7)
Excluded		51 (17.0)	46 (15.3)
Reason for exclusion	Less than 10 days of therapy	28 (9.3)	22 (7.3)
	Anti-fungal agent during treatment period, other than for failure	16 (5.3)	11 (3.7)
	No end of therapy endoscopy	5 (1.7)	6 (2.0)
	Misdose	2 (0.7)	0
	Prior systemic anti-fungal agent	0	3 (1.0)
	Baseline ulcerative lesions	0	1 (0.3)
	End of therapy visit outside window	0	1 (0.3)
	No baseline yeast confirmation	0	1 (0.3)
	No informed consent information	0	1 (0.3)
Clinically evaluable at follow-up		233 (77.7)	229 (76.1)
Excluded		67 (22.3)	72 (23.9)
Reason for exclusion	Not clinically evaluable at end of therapy	51 (17.0)	46 (15.3)
	No follow-up endoscopy	14 (4.7)	22 (7.3)
	Anti-fungal agent during follow-up, other than for failure	2 (0.7)	3 (1.0)
	Follow-up visit outside window	0	1 (0.3)
Mycological intent to treat		219 (73.0)	223 (74.1)
Excluded		81 (27.0)	78 (25.9)
Reason for exclusion	No baseline *Candida* species	81 (27.0)	78 (25.9)
Mycologically evaluable at end of therapy		180 (60.0)	186 (61.8)

Excluded		120 (40.0)	115 (38.2)
Reason for exclusion	No baseline *Candida* species	69 (23.0)	69 (22.9)
	Not clinically evaluable at end of therapy	51 (17.0)	46 (15.3)
Mycologically evaluable at follow-up		168 (56.0)	167 (55.5)
Excluded		132 (44.0)	134 (44.5)
Reason for exclusion	No baseline *Candida* species	65 (21.7)	62 (20.6)
	Not clinically evaluable at follow-up	67 (22.3)	72 (23.9)

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 7 of Study report)

Credibility of results that subgroup the data by protocol completer, compliers or other stratifications

Given the nature of the disease, the design of the study, and the need for objectivity in data interpretation, the sponsor's exclusion of patients without confirmed esophageal candidiasis and/or those without endoscopic assessment is credible and typical of this kind of trial. Of the 601 randomized, 504 (83.4%) were clinically evaluable at the end of therapy. The main reasons for being unevaluable at end of therapy were less than 10 days of therapy and use of systemic antifungal therapy during study period (for reasons other than treatment failure). Rates of premature discontinuation and clinical unevaluability at the end of therapy were balanced between the two groups. This degree of premature study termination and unevaluability is typical of such studies.

Subject Disposition

The review examined enrollment and outcomes at the various study sites in order to assess to what extent the study and outcomes were driven by the size of enrollment and response at particular study sites. The investigators and the number of subjects they randomized are shown on Table 13 for the intent-to-treat population.

Table 13: Number of Patients Randomized by Treatment and Site, Intent-to-Treat Population

	Treatment Arm		
Site	**Anidulafungin**	**Fluconazole**	**Total**
1	2	2	4
2	2	2	4
4	56	57	113
6	31	31	62
7	2	1	3
8	1	2	3
9	7	7	14
10	76	76	152
12	13	13	26
13	20	20	40
16	16	16	32
17	12	12	24
18	10	10	20

19	24	23	47
20	1	2	3
21	2	1	3
22	2	2	4
23	1	3	4
24	0	1	1
25	3	2	5
26	2	2	4
27	4	3	7
28	3	3	6
29	6	6	12
30	1	1	2
31	3	3	6
Total	300	301	601

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 8 of Study Report)

The review also evaluated the region of location of study sites as shown on Table 14.

Table 14: Patient Enrollment by Country of Pivotal Study Site Location

Country	Total Number of Sites	Total Enrollment
South Africa	11	453
Thailand	3	91
Argentina	10	51
United States	2	6
Total	26	601

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 9 of Study Report)

Medical Officer's Comment: *The top 5 sites enrolled a total of 414 (68.9%) of the 601 patients. The two highest enrolling sites (152 and 113 patients) were located in South Africa*

Baseline characteristics (demographics, target disease characteristics, and relevant underlying medical conditions) were very similar between the two treatment arms in both the ITT and the clinically evaluable at EOT populations. The mean patient age was approximately 37 years with a range of 18 to 69 years. There were more females than males in both groups. Of the patients who agreed to HIV testing, 114 of 136 patients (83.6%) in the anidulafungin group were positive, and 123 of 143 patients (86.0%) in the fluconazole group were positive. Tuberculosis was a frequent concomitant illness with between 26 and 28% of patients receiving concomitant medications for active tuberculosis. As noted earlier, although 67 (11.1%) of the 601 patients in the trial received prior anti-fungal medications, only 9 patients (4 and 5 on anidulafungin and fluconazole arms, respectively) received prior treatment with fluconazole. Majority of the patients that received prior antifungal therapy took nystatin or clotrimazole and there were no relevant differences between the two treatment arms.

As shown on Table 15, slightly more patients had grade 3 esophageal candidiasis on the fluconazole arm compared to anidulafungin arm (48.8% versus 42.3%) although the difference was not statistically significant.

Table 15: Endoscopy Grade at Baseline

Grade 1	61 (20.3)	53 (17.6)
Grade 2	112 (37.3)	101 (33.6)
Grade 3	127 (42.3)	147 (48.8)

Source: Adapted from Applicant's Submission (NDA 21-632, Study VER002-4 Table 13 of Study Report). Data reviewed prior to exclusion of site #19.

Furthermore, no significant differences occurred in the baseline isolates between the two treatment arms as shown on Table 16. Of note, 91.2% of subjects with baseline fungal isolates had *Candida albicans* in this pivotal study. This compares with 74.2% in the caspofungin pivotal trial.

Table 16: Baseline Isolates by Species

		Treatment Arm		
Population	**Species**	**Anidulafungin**	**Fluconazole**	**Total**
Mycological ITT population n (%)	N (total isolates)	229	237	466
	C. albicans	212 (92.6)	213 (89.9)	425 (91.2)
	C. glabrata	11 (4.8)	13 (5.5)	24 (5.2)
	C. krusei	1 (0.4)	2 (0.8)	3 (0.6)
	C. lusitaniae	0	1 (0.4)	1 (0.2)
	C. pelliculosa	0	1 (0.4)	1 (0.2)
	C. tropicalis	1 (0.4)	2 (0.8)	3 (0.6)
	C. species	4 (1.7)	5 (2.1)	9 (1.9)
Mycologically evaluable at end of therapy population n (%)	N (total isolates)	189	198	387
	C. albicans	177 (93.7)	182 (91.9)	359 (92.8)
	C. glabrata	8 (4.2)	11 (5.6)	19 (4.9)
	C. krusei	1 (0.5)	2 (1.0)	3 (0.8)
	C. tropicalis	1 (0.5)	1 (0.5)	2 (0.5)
	C. species	2 (1.1)	2 (1.0)	4 (1.0)
Mycologically evaluable at follow-up population n (%)	N (total isolates)	177	178	355
	C. albicans	165 (93.2)	163 (91.6)	328 (92.4)
	C. glabrata	8 (4.5)	10 (5.6)	18 (5.1)
	C. krusei	1 (0.6)	2 (1.1)	3 (0.8)
	C. tropicalis	1 (0.6)	1 (0.6)	2 (0.6)
	C. species	2 (1.1)	2 (1.1)	4 (1.1)

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 14 of Study Report). Data reviewed prior to exclusion of site #19.

As noted above, protocol violation was a reason for exclusion from clinically evaluable population at EOT. The major reasons for exclusion from this analysis population were less than 10 days of therapy and the administration of an anti-fungal agent during the treatment period [other than for failure] (97 and 50 patients on anidulafungin and fluconazole arms, respectively with no significant differences between the two arms).

Efficacy Endpoint Outcomes

Population PK samples were drawn from 46% of randomized patients. In the course of data audit, DSI found measurable levels of both active and comparator drugs in samples from 8 of the 26 sites. Such dual drug levels occurred sporadically among the 8 sites, except site 19 (a site in Thailand) that involved 32% of samples drawn. Moreover, levels of the drug to which the patient was not randomized were very low in the other 7 sites. The Division elected to exclude data from site #19 in their analyses of efficacy. The Division also reanalyzed the data limiting analyses to only patients that had PK samples drawn, tested, and results available. However, none of these reanalyses altered the outcome reported by the sponsor in any significant way. Efficacy outcomes presented in this review show outcomes with and without site #19 while safety outcomes include site #19. (For further details of the DSI investigation, the reader should please see section VI (c) Integrated Review of Efficacy, Detailed Review of Efficacy, Amendment 3 of June 15, 2001, Randomization Incident and Data Integrity. The full report of DSI findings is archived in the Agency's Division Filing System.)

Primary Efficacy Outcome

Primary efficacy outcome was defined as endoscopic success in clinically evaluable patients at EOT. Success encompassed endoscopic cure and improvement as noted in the study design section. Results of the primary efficacy outcome are shown on Table 17.

Table 17: Primary Efficacy Outcome Including Site 19

Response	Anidulafungin N= 249	Fluconazole N= 255	Treatment difference	95% CI
Success n, (%)	242 (97.2)	252 (98.8)	-1.6%	-4.1%, 0.8%
Cure	219 (88.0)	238 (93.3)	-5.3%*	-10.8%, 0.2%*
Improvement	23 (9.2)	14 (5.5)		
Failure n, (%)	7 (2.8)	3 (1.2)		

Data are from applicant's analysis. Those with asterisk (*) are FDA calculations. Data includes site 19 and was derived prior to receipt of DSI inspection findings

Data Reanalysis with the Exclusion of Site 19

Ina submission dated January 23, 2004 in response to FDA request dated January 14, 2004, the applicant reported the result of their reanalysis of primary efficacy outcome that excluded site #19. The results of the applicant's primary efficacy reanalysis is consistent with reanalysis conducted by the FDA statistical reviewer, which is shown on Table 18.

Table 18: Primary Efficacy Outcome Excluding Site 19

Response	Anidulafungin N= 231	Fluconazole N= 236	Treatment difference	95% CI
Success n, (%)	225 (97.4)	233 (98.7)	-1.3%	-4.2%, 1.6%
Cure	204 (88.3)	221 (93.6)	-5.3%	-10.9%, 0.3%
Improvement	21 (9.1)	12 (5.1)		
Failure n, (%)	6 (2.6)	3 (1.3)		

Data are from FDA Statistical Reviewer's Reanalysis.

Medical Officer's Comments: *The primary efficacy outcome were very similar when cure and improvement are combined. However when only cures are considered, the difference in outcome was larger with the lower bound of the 95% confidence interval of the difference between the two treatment arms of -10.9%, favoring fluconazole in the Agency's reanalysis of data excluding site #19. As noted above, exclusion of site19 had no impact on the results because of the relatively small number of patients involved.*

Additional Analyses on Primary Efficacy Outcome
Spread of Primary Outcomes form the Top Five Enrolling Sites

Given the need to ensure that outcome of the study is not driven by the results obtained from any specific investigator site, this review assessed primary efficacy outcomes from the top five sites from which most patients were enrolled. The primary efficacy outcomes for the top five enrolling sites are summarized in Table 19.

Table 19: Primary Efficacy Outcome from the 5 Top Enrolling Sites

Site Number	Total # Enrolled	Clinical Evaluable at EOT	Endoscopic Success at EOT by Treatment Arm*			
			Anidulafungin		Fluconazole	
			Clinical Evaluable	ITT	Clin Eval	ITT
4	113	94	49/50 (98.0%)	51/56 (91.1%)	44/44 (100.0%)	49/57 (86.0%)
6	62	49	24/25 (96.0%)	27/31 (87.1%)	23/24 (95.8%)	24/31 (77.4%)
10	152	134	61/64 (95.3%)	63/76 (82.9%)	70/70 (100.0%)	72/76 (94.7%)
13	40	32	15/16 (93.8%)	15/20 (75.0%)	16/16 (100.0%)	17/20 (85.0%)
19	47	37	17/18 (94.4%)	20/24 (79.2%)	19/19 (100.0%)	20/23 (87.0%)

*Endoscopic success (includes cure plus improvement but excludes indeterminate). Derived from Applicant's Dataset 'Endo'. Data reviewed prior to availability of DSI inspection findings.

Endoscopy Response at EOT by Endoscopy Grade at Baseline
The statistical reviewer, Cheryl Dixon, Ph.D., examined how the endoscopy grades at EOT differed from baseline endoscopy grades between the two treatment arms. The results of that analysis is shown on Table 20.

Table 20: Change in Endoscopy Grade at EOT Relative to Baseline

Endoscopy Grade at Baseline		Endoscopy Grade at End of Therapy				
		0	1	2	3	Total
Anidulafungin						
	1	48	2	0	0	50
	2	82	6	3	0	91
	3	89	13	4	2	108
	Total	219	21	7	2	249
Fluconazole						
	1	43	1	0	0	44
	2	84	3	0	0	87
	3	111	8	3	2	124
	Total	238	12	3	2	255

Analysis includes data from site #19. Data reviewed prior to availability of DSI inspection findings.

Overall, the shifts in endoscopy grades at end of therapy versus baseline were comparable between the two treatment arms, although there was a trend favoring fluconazole.

Secondary Efficacy Outcomes

The following tables summarize secondary efficacy outcomes in study VER002-4 based on the applicant's analysis populations and inclusive of site 19, unless otherwise specified. Overall, findings from these secondary endpoints are consistent with those of the primary endpoint. However, the detailed review of these secondary endpoints were considered necessary as some of them may be clinically relevant and quite important in understanding the impact of the overall response of patients with esophageal candidiasis following treatment with anidulafungin.

Endoscopic Response at Follow-up in Clinically Evaluable At Follow Up Population
The applicant's analyses (with and without site #19) of endoscopic response in the clinically evaluable at follow-up population are presented in Tables 21 and 22. As further discussed later in this section, the "evaluable at follow-up population" was defined by the applicant after completion of the study before the data lock.

Table 21: Endoscopic Response at Follow-Up in Clinically Evaluable at Follow-Up Population

Response	Anidulafungin N= 233	Fluconazole N= 229	Treatment difference	95% CI	p-value[1]
Success n, (%)	150 (64.4)	205 (89.5)	-25.1%	-32.5%, - 17.8%	< 0.001
Cure	89 (38.2)	170 (74.2)			
Improvement	61 (26.2)	35 (15.3)			
Failure n, (%)	83 (35.6)	24 (10.5)			

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 22 of Study Report). Includes Site #19

As calculated by the FDA statistical reviewer, Dr. Dixon, the difference in endoscopic cure between anidulafungin (38.2%) and fluconazole (74.2%) is -36.0% with a 95% confidence interval of -44.9%, to 27.1%, p-value <0.001. This analysis includes data from site #19. The same result is shown in Table 22 with data from site #19 excluded.

Table 22: Endoscopic Response at Follow-Up in Clinically Evaluable at Follow-Up Population Excluding site #19

Response		Anidulafungin N= 216	Fluconazole N= 210	Treatment difference	95% CI
Success n, (%)		141 (65.3)	190 (90.5)	-25.2	-32.7, - 17.7
	Cure	85 (39.4)	161 (76.7)		
	Improvement	56 (25.9)	29 (13.8)		
Failure n, (%)		75 (34.7)	20 (9.5)		

Source: Applicant's reanalysis of data to exclude site 19 (submitted February 6, 2004)

The reader should recall that the applicant uses two evaluable populations to analyze data in this application, one at end of therapy and another at follow-up. The Division's statistical review team used the pre-specified evlauable population at end of therapy.

Sustained Successful Outcome

The statistical reviewer examined endoscopy response at follow-up and how the endoscopy grades at end of therapy differed from baseline endoscopy grades between the two treatment arms. In these analyses, relapse is defined as worsening of endoscopy grade between end of therapy and follow-up. Failures at end of therapy are carried over to follow-up. The results of these analyses are shown on Tables 23 and 24 with and without site #19.

Table 23: Endoscopic Response at Follow-up in Clinically Evaluable Population Excluding Site 19

	Anidulafungin	Fluconazole	Difference (95% CI)	p-value*
Sustained Success at follow-up, n/N (%)	94/249 (37.8)	172/255 (67.5)	-29.7 (-38.4, -21.0)	<0.0001
Relapse, n/N (%)	132/242 (54.5)	55/252 (21.8)	32.7 (24.2, 41.1)	<0.0001
Relapse or Indeterminate, n/N (%)	148/242 (61.2)	80/252 (31.7)	29.5 (20.7, 38.3)	<0.0001

*Fisher's Exact Test
Relapse indicates success at end of therapy and failure at Follow-up visit
Data are from FDA Statistical Reviewer's Analysis and includes site #19.

Table 24: Endoscopic Response at Follow-up in Clinically Evaluable Population Excluding Site 19

	Anidulafungin	**Fluconazole**	**Difference (95% CI)**	**p-value***
Sustained Success at follow-up, n/N (%)**	90/231 (39.0)	163/236 (69.1)	-30.1 (-39.1, -21.1)	<0.0001
Relapse, n/N (%)	120/225 (53.3)	45/233 (19.3)	34.0 (25.3, 42.7)	<0.0001
Relapse or Indeterminate, n/N (%)	135/225 (60.0)	70/233 (30.0)	30.0 (20.9, 39.1)	<0.0001

*Fisher's Exact Test. Data are from FDA Statistical Reviewer's Analysis. **Denominator includes failures at EOT (6 on anidulafungin and 3 on fluconazole arms)

Given the higher numbers of indeterminate outcomes at follow-up in the fluconazole arm, incorporating patients with indeterminate outcome is the most conservative approach to assessment of outcome at follow-up. Even so, there are significantly more relapses on the anidulafungin arm compared to the fluconazole arm.

Another way to examine the endoscopy response at follow-up is to assess the change in endoscopy grade at follow-up relative to the original endoscopy grade at baseline as shown in Table 25.

Table 25: Change in Endoscopy Grade at Follow-up Relative to Baseline

		Endoscopy Grade at Follow-up					
		0	1	2	3	Missing	Total
Endoscopy Grade at Baseline							
Anidulafungin							
	1	22	16	6	3	1	48
	2	42	17*	15	6	8	88
	3	25	18#	26	30	7	106
	Total	89	51	47	39	16	242
Fluconazole							
	1	32	4	2	0	5	43
	2	65	9	3	2	8	87
	3	74	15	11¶	10	12	122
	Total	171	28	16	12	25	252

Analysis by FDA Statistical Reviewer *16 Relapse, 1 Not relapse # 14 Relapse, 4 Not relapse ¶ 10 Relapse, 1 Not relapse. Analysis includes data from site 19.

Overall, a larger proportion of patients on the anidulafungin arm had residual endoscopy findings of esophageal candidiasis at follow-up compared to those on the fluconazole arm (61% versus 25%). In addition, endoscopy grade worsened for 15 patients on the anidulafungin arm (9 went from 1 at baseline to grades 2 or 3 at follow-up and 6 went from 2 at baseline to 3 end of therapy) compared to 4 on the fluconazole arm (2 patients went from 1 at baseline to 2 at end of therapy and another 2 went from 2 at baseline to 3 at EOT. Furthermore among those that relapsed, proportionally more patients on anidulafungin arm had a worsening of their endoscopy score from baseline as shown in Table 26.

Table 26: Relapse Severity of Endoscopic Grade Relative to Baseline

Change in Endoscopy Grade	Anidulafungin n=132	Fluconazole n=55	p-value
Less Severe	56	34	-
Same or Worse	76 (57.6%)	21 (38.2%)	0.017
Same	61	17	
Worse	15	4	

Analysis by FDA Statistical Reviewer. Includes site 19.

Endoscopic Response at End of Therapy and Follow-Up in Intent-to-Treat Population

In the ITT population at EOT, endoscopic success in the anidulafungin group was 86.7%, and in the fluconazole group was 88.0%. Among patients in the anidulafungin arm 76.7% were cured while 10% improved. Outcomes for patients on the fluconazole arm were 83.4% and 4.7% for cure and improved categories, respectively.

In the ITT population at FU, endoscopic success in the anidulafungin group was

55.0%, and in the fluconazole group was 72.1%. Among patients in the andilafungin arm 33.0% were cured while 22.0% improved. Outcomes for patients on the fluconazole arm were 59.5% and 12.6% for cure and improved categories, respectively.

Overall, endoscopic results in the ITT closely paralleled those obtained from the clinically evaluable at EOT and at follow-up.

Clinical Response at End of Therapy and Follow-Up in Clinically Evaluable Patients
Tables 27 show clinical outcomes at end of therapy and at follow-up in clinically evaluable patients while Table 28 shows the same data excluding site #19 in a revised analysis submitted by the applicant on February 6, 2004. The reader should be reminded that two distinct analysis populations are involved at the two time points: 'clinically evaluable at end of therapy population' and 'clinically evaluable at follow-up population'. Again, the results closely reflect the endoscopic outcomes at both time points.

Table 27: Clinical Response at End of Therapy and Follow-Up in Clinically Evaluable Patients

		Anidulafungin	Fluconazole	Treatment difference	95% CI	p-value[1]
Clinically evaluable at end of therapy population		249	255			
End of therapy visit	Success n, (%)	246 (98.8)	254 (99.6)	-0.8%	-2.4%, 0.7%	
	Cure	242 (97.2)	250 (98.0)			
	Improvement	4 (1.6)	4 (1.6)			
	Failure n, (%)	3 (1.2)	1 (0.4)			
Clinically evaluable at follow-up population		233	229			
Follow-up visit	Success n, (%)	130 (55.8)	190 (83.0)	-27.2%	-35.2%, -19.2%	< 0.001
	Cure	125 (53.6)	186 (81.2)			
	Improvement	5 (2.1)	4 (1.7)			
	Failure n, (%)	103 (44.2)	39 (17.0)			
	Failure	100 (42.9)	38 (16.6)			
	Indeterminate	3 (1.3)	1 (0.4)			

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 24 of Study Report).

Table 28: Clinical Response at End of Therapy and Follow-Up in Clinically Evaluable Patients Excluding Site 19

Clinical Response at End of Therapy and Follow-Up, Excluding Site 19						
			Anidulafungin	**Fluconazole**	**Treatment difference**	**95% CI**
Clinically evaluable at end of therapy population			231	236		
End of therapy visit	Success n, (%)		229 (99.1)	235 (99.6)	-0.5	-2.0, 1.0
		Cure	225 (97.4)	231 (97.9)		
		Improvement	4 (1.7)	4 (1.7)		
	Failure n, (%)		2 (0.9)	1 (0.4)		
Clinically evaluable at follow-up population			216	210		
Follow-up visit	Success n, (%)		124 (57.4)	182 (86.7)	-29.3	-37.3, -21.3
		Cure	120 (55.5)	178 (84.8)		
		Improvement	4 (1.9)	4 (1.9)		
	Failure n, (%)		92 (42.6)	28 (13.3)		
		Failure	89 (41.2)	27 (12.8)		
		Indeterminate	3 (1.4)	1 (0.5)		

Source: Applicant's reanalysis of data to exclude site 19 (submitted February 6, 2004)

Clinical Response at End of Therapy and Follow-Up in Clinically Evaluable Populations

Clinical success rates in the clinically evaluable patients at EOT were very high for both arms, 98.8% and 99.6% for anidulafungin and fluconazole arms, respectively. Majority of the patients on both arms were clinical cures (97.2% and 98.0% for anidulafungin and fluconazole arms, respectively).

Clinical response rate in the clinically evaluable patients at follow up remained durable at 83.0% for fluconazole but less durable for anidulafungin (55.8%). The difference between these response rates was -27.2% with a 95% confidence interval around the difference -35.2% and -19.2% ($p < 0.001$).

Clinical Response at End of Therapy and Follow-Up in Intent-to-Treat Population

As for other outcomes assessed in this study, results in the ITT closely paralleled those obtained from clinically evaluable population.

Medical Officer's Comment: *The reader should recall that clinically evaluable at follow-up population is a population defined post hoc by the applicant prior to data lock. The Division's statistical review team note that only one pre-specified clinically evaluable population is acceptable. With this in mind, the statistical review team assessed*

durability of response at follow-up. In doing so, the team defined sustained success for both endoscopic and clinical outcomes as either patients who were cure at end of therapy and remained cure at follow-up or were improved at end of therapy and were cure or remain improved at follow-up without further deterioration in grade or clinical symptoms. The statistical team used the clinically evaluable at end of therapy as the population for analysis at both end of therapy and follow-up time points. The FDA statistical reviewer's reanalysis of clinical response at end of therapy in clinically evaluable at end of therapy population was consistent with the applicant's reanalysis shown in the top portion of Table 28. However, given the differences between the FDA and the applicant in the definition of and approach to analysis population at follow-up, clinical response at follow-up reanalyzed by the FDA to exclude site #19 shown in Table 29 is at variance with the applicant's reanalysis shown in the bottom of Table 28.

Table 29: Clinical Response at Follow-up in Clinically Evaluable at End Of Therapy Population

	Anidulafungin	**Fluconazole**
Sustained success, n/N (%)	120/231 (51.9)	181/236 (76.7)
Relapse, n/N (%)	93/229 (40.6)	30/235 (12.8)
Relapse + indeterminate, n/N (%)	109/229 (47.6)	54/235 (23.0)

Data are from FDA Statistical Reviewer's Analysis. Site 19 excluded.

Table 30 summarizes clinical response at end of therapy in all treated population. This analysis is presented here for completeness of the review and also to show that, like the endoscopic response, the clinical response at end of therapy was similar in the two treatment arms, even in a conservative analysis such as presented here.

Table 30: Clinical Response at End Of Therapy in the All Treated Population

Response		**Anidulafungin N= 276**	**Fluconazole N= 278**
Success n, (%)		242 (87.7)	247 (88.8)
	Cure	237(85.9)	242 (87.1)
	Improvement	5 (1.8)	5 (1.8)
Failure n, (%)		6 (2.2)	3 (1.1)
Indeterminate		28 (10.1)	28 (10.1)

Data are from FDA Statistical Reviewer's Analysis. Site 19 excluded.

Clinical Outcome at End of Therapy

For completeness of this review, outcomes of specific clinical symptoms (odynophagia/dysphagia and retrosternal) are summarized in the Tables 31 through 35. All analyses were performed by Dr. Dixon and include site 19 except otherwise specified.

Table 31: Odynophagia/Dysphagia at Baseline

	Anidulafungin N=249	Fluconazole N=255
Absent	7	6
Mild	48	44
Moderate	107	131
Severe	87	73
Missing	0	1

Table 32: Odynophagia/Dysphagia at End of Therapy

	Anidulafungin N=249	Fluconazole N=255
Absent	248	250
Mild	1	5

Table 33: Odynophagia/Dysphagia at Follow-up

	Anidulafungin N=249	Fluconazole N=255	p-value
Relapse of Symptom	45	12	< 0.0001
Same or worse compared to baseline	22	7	
Missing Follow-up Data	18	25	

Table 34: Retrosternal Pain at Baseline

	Anidulafungin N=249	Fluconazole N=255
Absent	50	61
Mild	56	61
Moderate	79	85
Severe	64	47
Missing	0	1

Table 35: Retrosternal Pain at End of Therapy

	Anidulafungin N=249	Fluconazole N=255
Absent	245	253
Mild	4	2

Table 36: Retrosternal Pain at Follow-up

	Anidulafungin N=249	Fluconazole N=255	p-value
Relapse of Symptom	25	8	< 0.0019
Same or worse compared to baseline	17	2	
Missing Follow-up Data	18	25	

Even with smaller absolute numbers than endoscopy outcome, at follow-up patients on anidulafungin arm still had significantly worse clinical outcome compared to those on fluconazole arm.

Time to Resolution of Symptoms

The mean and median times to resolution of symptoms in the clinically evaluable patients at EOT were identical for both treatment arms (median of 5 days for each arm and mean of 5.31 and 5.46 days for the anidulafungin and fluconazole arms, respectively). Similar results were obtained in the ITT population. Kaplan-Meier curves for time to resolution of symptoms showed minimal divergence between the two treatment arms.

Duration of Therapy

The mean and median duration of therapy in the clinically evaluable patients at EOT were identical for both treatment arms (median of 14 days for each arm and mean of 14.2 and 14.3 days for the anidulafungin and fluconazole arms, respectively). Similar results were obtained in the ITT population.

Per-Patient Mycological Outcomes

Patients with esophageal candidiasis could be clinically and endoscopically cured yet still harbor *Candida* organisms in their esophagus. Patients with sustained immunosuppression, such as those in this study, could potentially relapse from persisting *Candida* isolates in their upper gastrointestinal tract. Table 36 presents the applicant's analyses of per-patient mycological outcomes in mycologically evaluable populations at end of therapy and at follow-up.

Table 36: Per-Patient Mycological Outcomes and Responses in Mycologically Evaluable Populations

			Anidulafungin	Fluconazole
End of Therapy	N		180	186
	Success		156 (86.7)	169 (90.9)
		Proven eradication	152 (84.4)	156 (83.9)
		Presumed eradication	3 (1.7)	4 (2.2)
		Colonization	1 (0.6)	9 (4.8)
	Failure		24 (13.3)	17 (9.1)
		Proven persistence	23 (12.8)	12 (6.5)
		Presumed persistence	0	0
		Superinfection	1 (0.6)	5 (2.7)
Follow-up	N		168	167
	Success		75 (44.6)	121 (72.5)
		Proven eradication	72 (42.9)	115 (68.9)

		Presumed eradication	2 (1.2)	2 (1.2)
		Colonization	1 (0.6)	4 (2.4)
	Failure		93 (55.4)	46 (27.5)
		Proven persistence	10 (6.0)	6 (3.6)
		Presumed persistence	4 (2.4)	0
		Proven recurrence	66 (39.3)	34 (20.4)
		Presumed recurrence	1 (0.6)	0
		Superinfection	12 (7.1)	6 (3.6)

Source: Applicant's Submission (NDA 21-632, Study VER002-4 Table 26 of Study Report)

As with endoscopic and clinical outcomes, the per-patient mycologic outcomes atend of therapy are similar between the two treatment arms but successful outcome at follow-up is significantly inferior on anidulafungin arm relative to fluconazole arm. Twenty-one mycologically evaluable patients at end of therapy had more than one baseline isolates. The per-patient success rate among this population at end of therapy was 88.9% versus 75.0% for anidulafungin and fluconazole arms, respectively and at follow-up 22.2% versus 36.4% for anidulafungin and fluconazole arms, respectively. However, the absolute numbers of patients with more than one baseline isolates are too small for any meaningful comparison.

Per-Pathogen Mycological Outcome

It is pertinent to assess the outcome of anidulafungin treatment of those patients with both *albicans* and non-*albicans Candida* isolates. Although the most frequent isolate in esophageal candidiasis is *Candida albicans*, patients infected with the non-*albicans* isolates may be more difficult to treat. Table 37 summarizes the per-pathogen outcomes at end of therapy in mycologically evaluable population.

Table 37: Per-Pathogen Mycological Outcome at End of Therapy in Mycologically Evaluable Population

		Anidulafungin	Fluconazole
All species	N	189	198
	Success n, (%)	165 (87.3)	186 (93.9)
	Proven eradication	161 (85.2)	182 (91.9)
	Presumed eradication	4 (2.1)	4 (2.0)
	Failure n, (%)	24 (12.7)	12 (6.1)
	Proven persistence	24 (12.7)	12 (6.1)
	Presumed persistence	0	0
C. albicans	N	177	182
	Success n, (%)	155 (87.6)	172 (94.5)
	Proven eradication	152 (85.9)	168 (92.3)
	Presumed eradication	3 (1.7)	4 (2.2)
	Failure n, (%)	22 (12.4)	10 (5.5)
	Proven persistence	22 (12.4)	10 (5.5)
	Presumed persistence	0	0
C. Non*albicans*	N	12	16
	Success n, (%)	10 (83.3)	14 (87.5)
	Proven eradication	9 (75.0)	14 (87.5)
	Presumed eradication	1 (8.3)	0

	Failure n, (%)	2 (16.7)	2 (12.5)
	Proven persistence	2 (16.7)	2 (12.5)
	Presumed persistence	0	0

Source: Adapted from Applicant's Submission (NDA 21-632, Study VER002-4 Table 28 of Study Report)

The mycological responses at follow-up paralleled clinical and endoscopic responses at the follow-up time point. Successful mycological outcome (proven eradication and presume eradication) were 54.2% (96/177) and 76.4% (136/178) on the anidulafungin and fluconazole arms respectively.

Activity of Anidulafungin Against Non-albicans Candida

In Study VER002-4, a total of 28 non-albicans *Candida* species were documented (12 and 16 on anidulafungin and fluconazole arms, respectively). The success rate was similar between the two arms (83.3% versus 87.5% for anidulafungin and fluconazole arms, respectively). Of note, the two cases of *Candida krusei* on the fluconazole arm were proven eradication while the single case on the anidulafungin arm was proven persistence. As noted later in this review, data from Study VER002-11 enclosed in the current NDA [redacted]

Additional Analyses by the Medical Officer

As noted earlier during review of the primary efficacy outcome, it was essential to assess the potential for the outcomes of a few study sites to drive the outcome of the study. Evaluation of study outcomes by specific investigator site also allows selection of sites for data audit. Tables 38 and 39 present relevant secondary outcomes from the top five enrolling sites.

Table 38: Clinical Cure from the Top 5 Enrolling Sites

Site Number	Total # Enrolled	ClinEval at EOT	Clinical Cure at EOT by Treatment Arm*			
			Anidulafungin		Fluconazole	
			Clin Eval	ITT	Clin Eval	ITT
4	113	94	50/50 (100.0%)	52/56 (92.9%)	43/44 (97.7%)	48/57 (84.2%)
6	62	49	24/25 (96.0%)	26/31 (83.9%)	24/24 (100.0%)	25/31 (80.7%)
10	152	134	62/64 (96.9%)	63/76 (82.9%)	70/70 (100.0%)	71/76 (93.4%)
13	40	32	16/16 (100.0%)	16/20 (80.0%)	16/16 (100.0%)	17/20 (85.0%)
19	47	37	17/18 (94.4%)	21/24 (87.5%)	19/19 (100.0%)	20/23 (87.0%)

*Excludes improvement. Indeterminates were nonevaluable. Derived from Applicant's Dataset 'Endo'

Table 39: Mycological Success at EOT from the Top 5 Enrolling Sites

Site Number	Total # Enrolled	ClinEval at EOT	Mycologic Success at EOT by Treatment Arm*			
			Anidulafungin		Fluconazole	
			Clin Eval	ITT	Clin Eval	ITT
4	113	94	48/50 (96.0%)	50/52 (96.1%)	44/44 (100.0%)	50/50 (100.0%)
6	62	49	23/25 (92.0%)	24/27 (88.9%)	19/24 (79.2%)	19/26 (73.1%)
10	152	134	58/64 (90.6%)	59/66 (89.4%)	67/70 (95.7%)	70/72 (97.2%)
13	40	32	14/16 (87.5%)	14/16 (87.5%)	16/16 (100.0%)	17/17 (100.0%)
19	47	37	15/18 (83.3%)	17/23 (73.9%)	17/19 (89.5%)	18/21 (85.7%)

*Mycologic Success = Eradication and Presumed Eradication. Derived from Applicant's Dataset 'Endo'

Medical Officer's Comments: *Since outcomes from these sites are consistent across sites and similar to overall outcome, the two largest sites were selected for inspection. As noted earlier, dual drug levels were later found in 32% of samples drawn from site19 and that site was excluded from a number of analyses.*

Outcomes in Special Populations

There were no interactions by age, gender, race, or study site at EOT. However at follow-up, race and age appeared to be significant predictors of endoscopic outcome in a logistic model constructed with baseline characteristics. Endoscopic response rates at follow-up showed a significant trend of being higher the older the subjects in the model. Similarly, patients classified as Other had increased chance of follow-up endoscopic success compared to White patients that had success rates comparable to Black patients. Asian patients on the other hand, had a decreased chance of follow-up endoscopic success relative to White patients. For more details on these findings, the reader should see the review by the Statistical Reviewer, Cheryl Dixon, Ph.D.

This study was performed in adults and at the time of this review no data is available to assess outcome of anidulafungin in the treatment of children with esophageal candidiasis.

Conclusions Regarding Efficacy Data in Study VER002-4

In all analyses, findings from this single large adequate and well-controlled study of esophageal candidiasis shows that at the end of therapy, anidulafungin met the protocol-specified primary endpoint with 97.4% endoscopic success in evaluable patients at end of therapy compared to 98.7 % for fluconazole. The success rate in the anidulafungin arm is much higher than would be expected for placebo at the end of therapy time point. At the two week post-therapy follow-up visit anidulafungin was found to be statistically significantly inferior to fluconazole for the endpoint of endoscope success [39.0% (anidulafungin) vs. 69.1% (fluconazole)]

While the protocol-specified primary endpoint was endoscopic response at end of therapy, for antimicrobial drugs we typically utilize a primary endpoint that is assessed at

a time point removed from the time at which antimicrobial drug therapy is completed (e.g., 5 half-lives post completion of therapy). The clinical course of disease for patients with esophageal candidiasis can be a course of relapsing or recurrent disease over the weeks to months following successful treatment, particularly in a population such as was studied in trial that received very limited treatment for AIDS before and during the trial.

Study H4A-MC-XBAF

This study was conducted by the original sponsors of the IND, Eli Lilly and Company. Study H4A-MC-XBAF was entitled "a phase 2, randomized, open-label, non-comparator, multicenter evaluation of safety and efficacy of two intravenously administered 14- to 21-days dosage regimens of anidulafungin in the treatment of patients with esophageal candidiasis co-infected with HIV."

The study was planned for enrollement in 17 centers in the United States, Western Europe, Argentina, and South Africa. Only 12 of these centers enrolled patients, a total of 36 male and female patients $\geq$ 12 years of age. The two dose regimens studied were: an intravenous loading dose of 50 mg on first day followed by daily intravenous maintenance infusions of 25 mg (50/25 mg dose) and an intravenous loading dose of 70 mg followed by daily intravenous maintenance infusions of 35 mg (70/35 mg dose). Follow-up assessment was done at four weeks (± 7 days) post-therapy or earlier if clinically relapsed. Endoscopy at the follow-up visit was only performed if clinically relapsed. A total of 19 and 17 patients were enrolled in the 50/25 mg and 70/35 mg dose groups, respectively.

The primary objective of the study was to evaluate the safety and efficacy of two intravenous dose regimens of anidulafungin in the treatment of patients with esophageal candidiasis. The secondary objectives were to evaluate the mycologic response of the two dose regimens, identify potentially efficacious dose regimen for future trials in patients with candidiasis, and to determine PK characteristics of anidulafungin in this patient population and attempt to correlate PK with efficacy and safety outcomes.

Enrollment criteria were standard for studies of esophageal candidiasis. Although the title suggests only HIV-infected patients with esophageal candidiasis were studied, the inclusion criteria allowed enrollment of patients with risk factors for esophageal candidiasis other than HIV-infection. Patients were consented and screened if they presented with typical symptoms of esophagitis (odynophagia/dysphagia and/or retrosternal pain, which were graded as absent, mild, moderate, or severe). Patients were randomized based on endoscopic finding of grade 1 or higher and microscopic or culture confirmation of yeast. Endoscopy and mycologic studies should have been done within four days prior to enrollment. Materials for mycology were obtained by scraping or biopsy during endoscopy. Endoscopic grading was 0, 1, 2, and 3 based on the modified criteria of Kodsi et al (1976).[5] Patients with positive baseline or end of therapy human cytomegalovirus (CMV) or herpes simplex virus (HSV) esophagitis were enrolled but excluded from "qualified patients" analysis dataset. Other key exclusion criteria were:

- Evidence of systemic fungal infection other than esophageal candidiasis
- Patients who, in the investigator's opinion, was expected to survive for <2 months from time of study entry or whose underlying condition would not reasonable assure ability ot complete study
- Receipt of effective systemic antifungal therapy for a duration greater than 2 days within one week prior to treatment with study drug, unless the infecting *Candida* species was resistant (in vitro or inherently) to such antifungal agent. Oral or topical non-absorbable antifungal agents were allowed
- Patients in whom treatment of underlying disease could potentially interfere with assessment of response
- Most recent laboratory results within 30 days prior to enrollment showing absolute neutrophil count <500 PMNs/mm^3 or <1000 PMNs/mm^3 and expected to fall to <500 PMNs/mm^3 during the study
- Patients with ulcerative esophageal lesions found on endoscopy

Analysis populations included an ITT and safety population comprising all patients assigned to treatment group. In addition, efficacy analysis was also performed on qualified patients (clinically evaluable patients), defined as all patients except those meeting the following criteria:

- Did not meet entry criteria at time of enrollment
- Had an end of therapy clinical response of "Indeterminate"
- Did not receive at least 5 of 7 doses of study drug during the first week of treatment
- Had a baseline or end of therapy endoscopy lesion positive for CMV or HSV

The primary efficacy endpoint was proportion of "qualified patients" with clinical success (cure of and improvement in clinical symptoms) based on investigator-assessed clinical response at end of therapy. Clinical response at end of therapy were classified as cure, improvement, failure, and indeterminate. At follow-up, clinical responses were classified as cure, improvement, relapse, and indeterminate.

Secondary efficacy endpoints were not clearly defined but the following analyses were performed:

- Clinical response rate at end of therapy in all patients
- Clinical response rate at follow-up in all patients
- Clinical response rate at follow-up in qualified patients
- Mycologic response in all patients at end of therapy
- Mycologic response in qualified patients at end of therapy
- Summary of endoscopy grades at end of therapy and follow-up in all patients
- Summary of endoscopy grades at end of therapy and follow-up in qualified patients
- Correlation of clinical and mycologic efficacy outcome in all patients

• Correlation of clinical and mycologic efficacy outcome in qualified patients

In Study XBAF, endoscopy was required at baseline and at end of therapy but was repeated at the follow-up visit only in the event of clinical relapse. To reflect the primary endpoint in Study VER002-4, the applicant performed additional analysis post hoc to assess the proportion of patients with endoscopic cure or improvement in the two dose groups. All treated patients with baseline and end of therapy endoscopy were included in the analysis. Evaluability criteria were similar to those in the original analysis. In the applicant's analysis, success was defined as complete cure plus improvement in endoscopic grade.

Statistical Hypothesis
No statistical hypothesis was tested in this open-label noncomparative study.

Results
The primary efficacy endpoint, proportion of evaluable ("qualified") patients with clinical success (cure of and improvement in clinical symptoms) at end of therapy is shown on Table 40. Table 41 sumarizes clinical response rate at follow-up in evaluable (qualified) patients.

Table 40: Clinical Success at End of Therapy in Evaluable Patients in Study XBAF

Anidulafungin IV Dose Group	Clinical Outcome in Evaluable Patients n/N (%)		
	Cured	Improved	Success
50/25 mg	11/16 (68.8)	5/16 (31.3)	16/16 (100)
70/35 mg	9/11 (81.1)	0/11 (0.0)	9/11 (81.8)

Success = clinical response of cured (absence of symptoms) or improvement
Source: Adapted from Applicant's submission Tables XBAF 11.11-11.14

Table 41: Clinical Success at Follow up in Evaluable Patients in Study XBAF

Anidulafungin IV Dose Group	Evaluable Patients
	Follow-up n/N (%)
50/25 mg QD	6/16 (37.5)
70/35 mg QD	6/11 (54.5)

Success = clinical response of cured (absence of symptoms) or improvement
Source: Adapted from Applicant's submission Tables XBAF 11.11-11.14

Of the 16 evaluable patients in the 50/25 mg dose group, 11 (68.8%) were clinical cures and 5 (31.3%) were clinically improved. Of the 11 evaluable patients in the 70/35 mg dose group, 9 (81.1%) were clinical cures and 2 (18.2%) clinical failures. When clinical cure (absence of symptoms) alone is considered, there was evidence of a dose-response relationship at end of therapy with the 70/35 mg group performed consistently better than the 50/25 mg dose. Table 42 summarizes the endoscopic response at end of therapy in evaluable patients while Tables 43 and 44 show proportion of patients with clinical cure at end of therapy or follow-up with the respective proportions with grade of 0 endoscpic

finding at end of therapy and follow-up in all patients and in qualified patients as adapted from the applicant's submission.

Table 42: Endoscopic Success at End of Therapy in Evaluable Patients

Anidulafungin IV Dose Group	Endoscopic Success in Evaluable Patients n/N (%)		
	Cured	Improved	Success
50/25 mg	7/14 (50.0)	4/14 (28.6)	11/14 (78.6)
70/35 mg	7/9 (77.8)	1/9 (11.1)	8/9 (88.9)

Source: Adapted from NDA Table XBAF (1a) Page 3 of Study H4A-MC-XBAF

Table 43: Proportions of Patients with Clinical Cure (Absence of Symptoms) and Endoscopic Cure (Endoscopy Grade 0) in the All Patients Population

	50/25 mg Dose Group	70/35 mg Dose Group
End of Therapy		
Proportion with Absence of Symptoms (%)	73.7	82.4
Proportion with Endoscopic Grade 0 (%)	42.1	52.9
Follow-up		
Proportion with Absence of Symptoms (%)	47.1	38.5

Source: Applicant's submission Tables XBAF 11.8

Table 44: Proportions of Patients with Clinical Cure (Absence of Symptoms) and Endoscopic Cure (Endoscopy Grade 0) in the Qualified Patient Population

	50/25 mg Dose Group N=16	70/35 mg Dose Group N=11
End of Therapy		
Proportion with Absence of Symptoms (%)	68.8	81.8
Proportion with Endoscopic Grade 0 (%)	43.8	63.6
Follow-up		
Proportion with Absence of Symptoms (%)	46.7	44.4

Source: Applicant's submission Tables XBAF 11.9

The proportions of patients without any symptoms of esophageal candidiasis at end of therapy and follow-up in both dose groups are lower than similar outcome in the anidulafungin arm of Study VER002-4 (97.2% and 95.2% in clinically evaluable and ITT [indeterminate category excluded] populations at end of therapy, respectively and 53.6% in both populations at follow-up per sponsor's analysis inclusive of site 19). A higher dose of anidulafungin (100/50 mg) was used in Study VER002-4 which could explain the differences. In addition, patients were followed up four weeks post-end of therapy in Study XBAF, which further explains the poorer durability of clinical response in that study. Taken together, both studies are consistent in showing a relative lack of durability of clinical response in patients treated with anidulafungin.

Although the numbers are small, the endoscopic success rates in both treatment arms are lower than that obtained for the anidulafungin arm in Study VER002-4 (protocol-defined success rate 97.2% [cure 88%, improved 9.2%]) as was noted above for clinical response. The reason for the difference is not clear but might be due to the higher dose (100/50 mg) of anidulafungin used in Study VER002-4. An additional analysis was performed in this review to capture change in endoscopic grade at end of therapy compared to baseline as shown in Table 45, an analysis similar to what was done in Study VER002-4.

Table 45: Change in Endoscopy Grade at EOT Relative to Baseline

Endoscopy Grade at Baseline		**Endoscopy Grade at End of Therapy**					
		0	1	2	3	Missing	Total
50/25 mg Dose							
	1	2	1	0	0	0	3
	2	3	0	1	0	1	5
	3	3	1	4	1	2	11
	Total	8	2	5	1	3	19
70/35 mg Dose							
	1	2	0	1	0	0	3
	2	2	0	0	0	1	3
	3	5	1	1	1	3	11
	Total	9	1	2	1	4	17

Analysis by FDA Medical Reviewer

Of the 16 patients with baseline endoscopy grades 2 or 3 in the 50/25 dose group, 6 were grade 0 at end of therapy, 5 improved in grade, 2 patients had the same grade, while endoscopy data were not available for 3 at end of therapy. The response was higher in the 70/35 mg dose group. Of the 14 patients with endoscopy grades 2 or 3 in the 70/35 mg dose group, 7 were grade 0 at end of therapy, two improved in grades, one remained the same, while in four patients end of therapy endoscopy data were missing. Of note, one patient in the 70/35 mg dose group had a worsening of endsocpic grade from grade 1 at baseline to 2 at end of therapy, a finding more common in the anidulafungin arm of Study VER002-4 compared to the fluconazole arm.

Only three patients (all in the 50/25 mg dose group) had endoscopy performed at follow-up. One of the three patients had endoscopy grade 3 at baseline, end of therapy, and at follow-up. Another patient had grade 2 at baseline and 0 at end of therapy and follow-up. The third patient had grade 2 at baseline, 0 at end of therapy and 2 at follow-up. The small number of patients with endoscopy assessment at the three time points does not allow adequate assessment of the durability of endoscopic response to anidulafungin. Furthermore, this study fails to provide any reasonable additional data to suggest anidulafungin's durability of response is any better than found in Study VER002-4.

Mycologic Response in All and Qualified Patients at End of Therapy
Table 46 summarizes mycologic response in all and qualified patients at end of therapy in Study XBAF.

Table 46: Summary of Mycologic Response in All and Qualified Patients at EOT

	N	Eradication n (%)	Presumed Eradication n (%)	Colonization n (%)	Persistence n (%)	Indeterminate n (%)
All Patients						
50/25 mg	19	4 (21.1)	2 (10.5)	5 (26.3)	7 (36.8)	1 (5.3)
70/35 mg	17	3 (17.6)	2 (11.8)	6 (35.3)	1 (5.9)	5 (29.4)
Qualified Patients						
50/25 mg	16	4 (25.0)	2 (12.5)	4 (25.0)	6 (37.5)	0 (0)
70/35 mg	11	2 (18.2)	2 (18.2)	6 (54.5)	0 (0)	1 (9.1)

At EOT in all patients mycologic success (eradication, presumed eradication, and colonization) were 57.9% (11/19) and 64.7% (11/17) in the 50/25 mg and 70/35 mg dose groups, respectively. The corresponding mycologic success rates in qualified patients were 62.5% (10/16) and 90.9% (10/11), respectively in the two dose groups. Among qualified patients, six (60%) of the 10 successes in the 70/35 mg dose group were assessed to be colonized at end of therapy as were 4 (40%) of 10 successes in the 50/25 mg dose group. It should be noted that colonization was defined as isolation of new or baseline *Candida* species in the absence of mucosal lesions.

Correlation of clinical and mycologic efficacy outcome at end of therapy in all and in qualified patients
Among all patients in the 50/25 mg dose group, 7 (38.9%) of the 18 patients who were clinical successes (cure or improvement and excluding indeterminate category) were mycologic persistence while 5 (27.8%) of the 18 were colonization. For the 70/35 mg dose group, the corresponding proportions of mycologic persistence and colonization were 9.1% (1/11) and 54.5% (6/11), respectively. The proportions among the qualified patients were similar to those among all patients in the two dose groups. It is worth noting that one patient in the 70/35 mg dose group was a clinical failure but mycologic eradicaction.

Conclusion Regarding Efficacy Data in Study XBAF
Although anidulafungin doses used in the Phase 2 dose-ranging esophageal candidiasis Study XBAF were smaller than that used in the Phase 3 esophageal candidiasis study (VER002-4), the efficacy outcomes show a similar pattern of relatively high rate of success at end of therapy but marginally sustained success at follow-up. In addition, there was a dose-response in clinical and endoscopic cure at end of therapy. Overall, the degree of success noted with the smaller doses are still better than would be expected for placebo.

Study VER002-6

Study VER002-6 is titled "A phase 2, open-label, randomized, dose-ranging study of the safety and efficacy of intravenous anidulafungin in the treatment of patients with invasive candidiasis." The study was conducted in 24 centers in north America over a period of about 14 months (August 31, 2001 to November 6, 2003).[2]

The objectives of the study were:

- To determine the clinical and microbiological efficacy of various dose regimens of anidulafungin (100/50 mg, 150/75 mg, and 200/100 mg) administered intravenously to patients with invasive *Candida* species infections
- To determine the safety of the dose regimens in this patient population
- To characterize the relationship between anidulafungin concentrations and specific indices of safety and efficacy by performing population pharmacokinetic analysis on plasma samples from patients with invasive To determine the *Candida* species infections.

The study enrolled adult patients only. Patients were randomly assigned to one of the three dose regimens, 100 mg, 150 mg, or 200 mg initial loading dose on Day 1 followed respectively by 50 mg, 75 mg, or 100 mg daily maintenance dose from Day 2 to a maximum duration of treatment of 14 days. A post-therapy follow-up evaluation was done 2 weeks after end-of-therapy or earlier in the event of failure or use of another systemic antifungal agent.

The primary endpoint was the global response at follow-up in the evaluable at follow-up population.

Secondary endpoints were:

- The global response at end of therapy in the evalubale at end of therapy population
- The global response at end of therapy in the evalubale at end of therapy and follow-up in the MITT population
- The clinical response at end of therapy in the evalubale at end of therapy population
- The clinical response at follow-up in the evaluable at follow-up population
- The gclinical response at end of therapy and follow-up in the ITT population
- The microbiological response at end of therapy in the evaluable at end of therapy population
- The microbiological response at follow-up in the evaluable at follow-up population
- The microbiological response at end of therapy and follow-up in the MITT population

Efficacy of anidulafungin was based on clinical and microbiological outcomes (success or failure) at end of therapy and follow-up. Analysis population comprised ITT (all

[2] Findings from this study were presented at the 13th European Congress of ClinicalMicrobiology and Infectious Diseases held in Glasgow, United Kingdom on May 10-13, 2003.

patients who received any amount of anidulafungin [these were included in the analysis of safety and pharmacokinetics]); MITT (microbiological ITT [all patients in the ITT population who also had baseline microbiological or microscopy evidence of *Candida* species infection]); evaluable at end of therapy (patients who completed a course of therapy, received an end of therapy assessment, had a clinical outcome criterion other than unable to determine, and did not have any protocol violations up to the end of therapy visit that impacted the assessment of efficacy, had baseline microbiological or microscopy evidence of *Candida* species infection, and had a microbiological outcome other than unable to determine); and evaluable at follow-up population (patients who were evaluable at end of therapy, had a follow-up assessment with a clinical outcome other than unable to determine, and did not have any protocol violations between end of therapy and follow-up that would impact the assessment of efficacy, had baseline microbiological or microscopy evidence of *Candida* species infection, and had a microbiological outcome other than unable to determine).

A total of 123 patients were randomized, 120 treated (40 patients per dose regimen) and 68 (56.7%) of 120 treated patients completed the study. Median age of the 120 patients treated was 54 years and 56.7% were females, 58.3% white, 34.2% black, and a median APACHE score of 14.0. The mean and median APACHE scores were highest in the 150/75 mg dose group and least in the 100/50 dose group.

Relevant baseline medical conditions were similar across the three dose groups. Immunosuppressed/immunological disorders occurred in 50 patients, diabetes mellitus in 36, and peripheral vascular disease in 10 patients. Only 5 patients had baseline neutrophil count < 500 cells/mm.^{3} Of the 116 MITT patients, 109 had candidemia, 12 had invasive tissue infection, and 5 had both candidemia and tissue infection. In other words, 104 (89.7%) of the 116 patients had candidemia alone. Eighteen invasive tissue samples were documented in the 12 patients as follows: 3 specimens each from abdominal wall wound, retroperitoneal fluid, sinus contents, and abscesses (right hip, right hand/forearm, abdominal wall); and one each from peritoneal fluid, peritoneal dialysate, pleural fluid, extravascular, back tissue, and esophageal biopsy.

Eighty-two (68.3%) of the 120 treated patients had received prior systemic antifungal medication prior to Day 1 of study. Sixty-five (79.3%) of those patients exposed to prior systemic antifungal agent took fluconazole. Most of the prior systemic antifungal medications were used in the week immediately prior to enrollment.

Among the MITT population, the 5 predominant baseline isolates were *Candida albicans* (53.4%), *Candida glabrata* (31.0%), *Candida parapsilosis* (9.5%), *Candida tropicalis* (8.6%), and *Candida krusei* (4.3%). Nine patients had two baseline isolates and one patient had three baseline isolates.

Patient disposition

Table 47 summarizes patient disposition and reasons for discontinuation.

Table 47: Patient Disposition and Reason for Discontinuation

	100/50 mg (N=42) n (%)	150/75 mg (N=40) n (%)	200/100 mg (N=41) n (%)	Total (N=123) n (%)
Total Randomized	42(100.0)	40(100.0)	41(100.0)	123(100.0)
Total Completed Study	18(42.9)	29(72.5)	21(51.2)	68(55.3)
Total Discontinued	24(57.1)	11(27.5)	20(48.8)	55(44.7)
Reason for Discontinuation				
Adverse Event	13(31.0)	8(20.0)	9(22.0)	30(24.4)
At the Request of the Patient, Investigator, or Versicor	7(16.7)	3(7.5)	6(14.6)	16(13.0)
Other	3(7.1)	0	5(12.2)	8(6.5)
Patient Noncompliance	1(2.4)	0	0	1(0.8)

Source: Table 4.1 of Study Report for Study VER-002-6 from Applicant's submission

Medical Officer's Comments: *There were a total of 42 (34.1%) protocol violations among the 123 patients. Three (2.4%) patients did not take any study medication, 28 (22.8%) had < 10 days of anidulafungin, 10 (8.1%) took concomitant systemic antifungal therapy during study other than for failure, and in 4 (3.3%) patients, there was no baseline Candida or diagnosis was not adequately confirmed. Of note, the study report states that several exceptions were made for patients who accidentally received a single dose of a systemic antifungal and such patients were not exclude from the evaluable population. In addition, from the study report, patients who were improved at EOT were allowed to take another systemic antifungal after at end of therapy. These patients were considered to be evaluable at end of therapy, but not evaluable at follow-up (with a clinical response noted as "unable to determine"). The medical officer considers these patients failures. Other patients who took another systemic antifungal between at end of therapy and follow-up were excluded from the evaluable population unless they were a failure.*

Primary Efficacy Outcome

The Primary efficacy outcomes, global response rates at follow-up in the evaluable at follow-up population, were 72.2%, 84.6%, and 83.3% for the 100/50 mg, 150/75 mg, and 200/100 mg arms, respectively giving a response of 80.9% for the entire group. However, response rates among 200/100 mg dose group were consistently lower than for the 150/75 mg dose group. These findings are relevant to the dose used in study VER002-4, which might suggest that the right dose for that study could have been 150/75 mg, although it could be argued that esophageal candidiasis is less invasive (i.e., less serious) relative to candidemia and that a dose of 100/50 mg should be adequate. This numerically lower response rate in the 100/50 mg group were observed with the secondary outcome measures as summarized in Table 48 below.

Table 48: Clinical Outcome and Response at End-of-Therapy and Follow-up

	100/50 mg	150/75 mg	200/100 mg	Total
ITT Population At End of Therapy	[N=40]	[N=40]	[N=40]	[N=120]
Success (n, %)	26(65.0)	30(75.0)	27(67.5)	83(69.2)
Cure (n,%)	19(47.5)	25(62.5)	21(52.5)	65(54.2)
Improvement (n, %)	7(17.5)	5(12.5)	6(15.0)	18(15.0)
Failure (n, %)	14(35.0)	10(25.0)	13(32.5)	37(30.8)
Failure (n, %)	3(7.5)	3(7.5)	4(10.0)	10(8.3)
Unable to Determine (n, %)	11(27.5)	7(17.5)	9(22.5)	27(22.5)
ITT Population At Follow-up	[N=40]	[N=40]	[N=40]	[N=120]
Success (n, %)	14(35.0)	23(57.5)	20(50.0)	57(47.5)
Cure (n,%)	13(32.5)	23(57.5)	20(50.0)	56(46.7)
Improvement (n, %)	1(2.5)	0	0	1(0.8)
Failure (n, %)	26(65.0)	17(42.5)	20(50.0)	63(52.5)
Failure (n, %)	3(7.5)	3(7.5)	4(10.0)	10(8.3)
Worsening of EOT Cure or Improvement	1(2.5)	1(2.5)	1(2.5)	3(2.5)
Unable to Determine (n, %)	22(55.0)	13(32.5)	15(37.5)	50(41.7)
Evaluable At End of Therapy Population	[N=25]	[N=30]	[N=28]	[N=83]
Success (n, %)	22(88.0)	27(90.0)	25(89.3)	74(89.2)
Cure (n,%)	19(76.0)	24(80.0)	20(71.4)	63(75.9)
Improvement (n, %)	3(12.0)	3(10.0)	5(17.9)	11(13.3)
Failure (n, %)	3(12.0)	3(10.0)	3(10.7)	9(10.8)
Failure (n, %)	3(12.0)	3(10.0)	3(10.7)	9(10.8)
Evaluable At Follow-up Population	[N=18]	[N=26]	[N=24]	[N=68]
Success (n, %)	13(72.2)	22(84.6)	20(83.3)	55(80.9)
Cure (n,%)	12(66.7)	22(84.6)	20(83.3)	54(79.4)
Improvement (n, %)	1(5.6)	0	0	1(1.5)
Failure (n, %)	5(27.8)	4(15.4)	4(16.7)	13(19.1)
Failure (n, %)	3(16.7)	3(11.5)	3(12.5)	9(13.2)
Worsening of EOT Cure or Improvement	1(5.6)	1(3.8)	1(4.2)	3(4.4)
Unable to Determine (n, %)	1(5.6)	0	0	1(1.5)

Source: Table 5.5 of Study Report for Study VER-002-6 from Applicant's submission

Outcome by *Candida* species

Considering all *Candida* species in the microbiologically evaluable population, the success rate at EOT was 99/127 (78.0% [proven eradication 23.6%, presumed eradication 54.3%]) and failure rate was 28/127 (22.0% [proven persistence 2.4%, presumed persistence 5.5%, and unable to determine 14.2%]). Corresponding rates at follow-up in the, microbiologically evaluable population were success 76/127 (59.8% [proven eradication 50.4%, presumed eradication 9.4%]) and failure rate was 51/127 (40.2% [proven persistence 7.9%, presumed persistence 0.8%, and unable to determine 31.5%]).

For *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, and *Candida tropicalis*, the four most common species observed in this study, the response rates for all dose groups at EOT and follow-up are as shown on Table 49.

Table 49: Per Pathogen Microbiological Response of the MITT at EOT and Follow-up for Top Four *Candida* Isolates (All Dose Groups Combined)

	Success	Proven Eradication	Presumed Eradication	Failure	Proven Persistence	Presumed Persistence	Unable to Determine
End of Therapy							
Candida albicans N=62	47 (75.8)	14 (22.6)	33 (53.2)	15 (24.2)	2 (3.2)	3 (4.8)	10 (16.1)
Candida glabrata N=36	30 (83.3)	9 (25.0)	21 (58.3)	6 (16.7)	0	1 (2.8)	5 (13.9)
Candida parapsilosis N=11	10 (90.9)	5 (45.5)	5 (45.5)	1 (9.9)	0	1 (9.1)	0
Candida tropicalis N=10	6 (60.0)	1 (10.0)	5 (50.0)	4 (40.0)	0	1 (10.0)	3 (30.0)
Follow-up							
Candida albicans N=62	36 (58.1)	29 (46.8)	7 (11.3)	26 (41.9)	5 (8.1)	1 (1.6)	20 (32.3)
Candida glabrata N=36	23 (63.9)	19 (52.8)	4 (11.1)	13 (36.1)	0	1 (2.8)	12 (33.3)
Candida parapsilosis N=11	8 (72.7)	7 (63.6)	1 (9.1)	3 (27.3)	0	1 (9.1)	2 (18.2)
Candida tropicalis N=10	6 (60.0)	6 (60.0)	0	4 (40.0)	0	1 (10.0)	3 (30.0)

Source: Adapted from Table 5.6 of Study Report for Study VER-002-6 from Applicant's submission

Conclusion Regarding Efficacy in Study VER002-6

All three doses of anidulafungin demonstrated sustained efficacy in this phase 2 study of primarily candidemia patients with immunocompromising conditions (a relatively more serious infection). These patients were treated for a duration up to 42 days with a median duration of 14.5 days. Although the outcomes showed no clear evidence of dose-response, the study supports the conclusion that anidulafungin has activity against documented candida infections.

Study VER002-11

This open-label, non-randomized study is ongoing. The objective is to evaluate the safety and efficacy of anidulafungin 100/50 mg for 14-21 days in patients with fluconazole-refractory mucosal candidiasis. The primary endpoints are:

For orpharyngeal candidiasis: clinical response at end of therapy in clinically evaluable population

For esophageal candidiasis: endoscopic response at end of therapy in clinically evaluable population. The sponsor plans to enroll 20 patients. In the preliminary results from 5 patients submitted in the NDA, all were fluconazole refractory (3 with oropharyngeal candidiasis, 2 had both oropharyngeal and esophageal candidiasis). Three of the 5 had fluconazole non-susceptible C. albicans at baseline. Both patients with esophageal candidiasis were endoscopic successes at EOT and clinical cures at follow-up.

D. Efficacy Conclusions

Findings from the single large Phase 3 esophageal candidiasis study show that at the end of therapy, anidulafungin met the protocol-specified endpoint with 97.4% endoscopic success in evaluable patients at end of therapy compared to 98.7 % for fluconazole. The success rate in the anidulafungin arm is much higher than would be expected for placebo or an ineffective therapy. However, in a study population expected to be more susceptible to relapse based on lack of HAART, a difference was shown at follow-up with

anidulafungin significantly inferior to fluconazole in the proportion of patients with sustained success. Additional data from the smaller Phase 2 esophageal candidiasis and invasive candidiasis studies are supportive of the activity of anidulafungin against *Candida* infections and results are consistent with findings from the large Phase 3 study.

Labeling Issues

Sponsor's proposed INDICATION AND USAGE section reads:
"TRADENAME is indicated for the treatment of esophageal candidiasis."

Regarding the findings at follow-up in the CLINICAL STUDIES section, the sponsor's proposed labeling states:

[ ]

Possible Wording of Labeling Should Anidulafungin Be Approved

Anidulafungin (or TRADENAME) is indicated for treatment of esophageal candidiasis. [

]

VII. Integrated Review of Safety

VII.1 Brief Statement of Findings

At the intended dose of anidulafungin and for the proposed indication, there appears to be no major safety concerns other than mild (< 3 x ULN) dose-dependent and temporal trends to elevated liver transaminases and a dose-dependent elevation of alkaline phosphatase (clinical pharmacology study VER002-5 using doses up to 260/130 mg). In addition, there were no safety flags when the safety database was analyzed by gender and underlying diseases/conditions. The total number of subjects enrolled is insufficient to adequately characterize the safety of anidulafungin by race, age, and geographic location. Further, the review did not reveal any safety issues among subjects on concomitant calcineurin inhibitors (cyclosporine and tacrolimus) or corticosteroid. Notwithstanding, a potential might exist for anidulafungin to cause hepatotoxicity, given animal data from preclinical studies performed with anidulafungin and data from the postmarketing safety review of another echinocandin, caspofungin. Furthermore, at the proposed dose, only 331 patients have been exposed for ≥ 14 days in the safety database. Uncommon serious toxicities of anidulafungin cannot be excluded until many more people have been exposed to the drug either in subsequent trials or in the event that the product is approved and marketed.

VII.2 Materials Utilized in the Review and Safety Review Methodology

- Medical Officer review (MOR) of safety of caspofungin in the caspofungfin NDA
- Post-marketing adverse events reported for caspofungin reviewed by Sarah Singer, R.Ph. Safety Evaluator, Division of Drug Risk Evaluation, CDER.
- Safety data of anidulafungin in NDA 21-632
- Literature search for safety of echinocandin antifungal drug class

Given that anidulafungin is in the same class as caspofungin (the only approved echinocandin), the medical officer review of safety of caspofungin was closely examined. In reviewing safety in the caspofungin NDA, the Medical Officer concluded that caspofungin is "frequently associated with systemic symptoms such as fever, myalgias, flu-like symptoms, nausea, and vomiting." The review further noted that "local infusional toxicities are also frequent, including phlebitis, pain, erythema and rash" and that "transaminase elevations occurred at a frequency and magnitude similar to that seen with fluconazole." However, the review also noted that caspofungin is "rarely associated with renal toxicity and electrolyte abnormalities are less frequent than those seen with amphotericin B."

7.3 Demographics in Anidulafungin Safety Database

Table 50 shows the demographics and some baseline characteristics of subjects treated with anidulafungin in the NDA database.

Table 50: Demographic and Baseline Characteristics: Phase 2/3 Clinical Studies in Candidiasis or Aspergillosis

	Anidulafungin			Fluconazole
	Candidiasis[+]	Aspergillosis[#]	All Patients	Candidiasis[@]
Characteristic	**(N=456)**	**(N= 17)**	**(N=473)**	**(N=301)**
Age, years				
N	456	17	473	301
Mean	42.1	54.7	42.6	37.0
Standard Deviation	15.0	16.1	15.2	9.5
Median	38.0	59.0	38.0	36.0
Minimum	18.0	21.0	18.0	18.0
Maximum	88.0	79.0	88.0	65.0
Age Group, n (%)				
<65 Years	407 (89.3)	11 (64.7)	418 (88.4)	300 (99.7)
>=65 Years	49 (10.7)	6 (35.3)	55 (11.6)	1 (0.3)
Gender, n (%)				
Male	205 (45.0)	14 (82.4)	219 (46.3)	145 (48.2)
Female	251 (55.0)	3 (17.6)	254 (53.7)	156 (51.8)
Race, n (%)				
Black	190 (41.7)	1 (5.9)	191 (40.4)	144 (47.8)
Caucasian	139 (30.5)	14 (82.4)	153 (32.3)	41 (13.6)
Asain	46 (10.1)	0 (0.0)	46 (9.7)	46 (15.3)
Hispanic	16 (3.5)	1 (5.9)	17 (3.6)	2 (0.7)

Other	64 (14.0)	1 (5.9)	65 (13.7)	68 (22.6)
Unknown	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Location of Study, n (%)				
US	126 (27.6)	7 (41.2)	133 (28.1)	3 (1.0)
Non-US	330 (72.4)	10 (58.8)	340 (71.9)	298 (99.0)

+ From Studies H4A-MC-XBAF, VER002-4, AND VER002-6
# From Study VER002-7; Anidulafungin co-administered with AmBisome®
@ From Study VER002-4

The demographics of subjects enrolled in the Phases 2 and 3 studies in this application are generally comparable to the demographics of the HIV/AIDS population in the USA with the notable exception of the large number of females enrolled in the studies. In the US at the end of 2001, there were approximately 360,000 adults and adolescents living with AIDS; of which 79% were males and 21% were females. In 2001, 49% of persons living with AIDS were Black, 31% White, 19% Hispanic and 1-2% other.[3]

Additional demographic information from Phase 1 studies in the application is shown in healthy volunteers who received at least one dose of anidulafungin (Table 51), in subjects with hepatic impairment (Table 52), and in those with renal impairment (Table 53).

[3] http://www.cdc.gov/hiv/graphics/images

Table 51: Demographic Characteristics for Subjects Who Received at Least One Dose of Intravenous Anidulafungin: Phase 1 Clinical Studies in Healthy Subjects

Demographic Characteristics	H4A-JE-101L	H4A-EW-XBAE	H4A-EW-XBAU	VER002-1	VER002-5	VER002-8	VER002-10	All Studies
Number of subjects	18	25	12	12	30	12	9	118
Age, years								
Mean	24.6	27.4	23.1	26.2	40.7	35.3	32.1	31.0
Minimum	20	19	20	19	19	18	21	18
Maximum	30	55	27	36	64	50	45	64
Gender, N (%)								
Male	18 (100.0)	21 (84.0)	12 (100.0)	7 (58.3)	15 (50.0)	3 (25)	9 (100.0)	85 (72.0)
Female	0	4 (16.0)	0	5 (41.7)	15 (50.0)	9 (75)	0	33 (28.0)
Ethnicity, N (%)								
White	0	24 (96.0)	0	0	22 (73.3)	7 (58.3)	7 (77.8)	60 (50.8)
Black	0	1 (4.0)	0	0	3 (10.0)	2 (16.7)	2 (22.2)	8 (6.8)
Asian	18 (100.0)	0	0	0	0	0	0	18 (15.3)
Hispanic	0	0	0	0	3 (10.0)	3 (25.0)	0	6 (5.1)
Other	0	0	0	0	2 (6.6)	0	0	2 (1.7)
Not collected	0	0	12	12	0	0	0	24 (20.3)

Source: Applicant's submission

Table 52: Selected Demographic Parameters Presented for Subjects Hepatic Impairment (by Hepatic Cohort) and All Control Subjects in Study VER002-2

		Group A	Group B	Group C	Total	
	Statistic	Mildly Impaired (N= 6)	Moderately Impaired (N= 6)	Severely Impaired (N= 8)	All Impaired (N=20)	All Controls (N= 7)
Age (yrs)						
	n	6	6	8	20	7
	Median	59.0	50.0	51.5	51.0	52.0
	Mean (SD)	59.3 (11.2)	51.8 (8.4)	52.0 (8.9)	54.2 (9.7)	54.0 (10.6)
	Min, Max	47.0, 73.0	44.0, 68.0	41.0, 64.0	41.0, 73.0	41.0, 72.0
Gender						
Male	n (%)	4 (66.7)	3 (50.0)	6 (75.0)	13 (65.0)	3 (42.9)
Female	n (%)	2 (33.3)	3 (50.0)	2 (25.0)	7 (35.0)	4 (57.1)
Ethnicity						
Caucasian	n (%)	5 (83.3)	1 (16.7)	0	6 (30.0)	0
Hispanic/Latino	n (%)	1 (16.7)	5 (83.3)	8 (100)	14 (70.0)	7 (100)

SD Standard deviation
Source: Applicant's submission

Table 53: Selected Demographic Parameters Presented for Subjects with Renal Impairement (by Renal Cohort) and All Control Subjects in Study VER002-3

		Group A	Group B	Group C	Group D		Totals	
		Mildly Impaired	Moderately Impaired	Severely Impaired	End-Stage Pre-Dialysis Infusion	End-Stage Post-Dialysis Infusion	Renally Impaired	Controls
	Statistic	(n = 8)	(n = 6)	(n = 6)	(n = 3)	(n = 3)	(N = 26)	(N = 8)
Age (yrs)								
	n	8	6	6	3	3	26	8
	Median	54.5	65.0	61.5	64.0	50.0	59.5	60.0
	Mean (SD)	54.8(11.8)	64.5 (7.3)	57.7(12.8)	60.7(12.3)	49.0 (9.5)	57.7 (11.2)	58.4 (9.0)
	Min, Max	34.0, 70.0	55.0, 72.0	33.0, 68.0	47.0. 71.0	39.0, 58.0	33.0, 72.0	44.0, 67.0
Gender								
Male	n (%)	6 (75.0)	3 (50.0)	3 (50.0)	2 (66.7)	2 (66.7)	16 (61.5)	7 (87.5)
Female	n (%)	2 (25.0)	3 (50.0)	3 (50.0)	1 (33.3)	1 (33.3)	10 (38.5)	1 (12.5)
Ethnicity								
African-American	n (%)	1 (12.5)	1 (16.7)	2 (33.3)	2 (66.7)	3 (100)	9 (34.6)	0
Asian	n (%)	0	1 (16.7)	0	0	0	1 (3.8)	0
Caucasian	n (%)	7 (87.5)	4 (66.7)	4 (66.7)	1 (33.3)	0	16 (61.5)	7 (87.5)
Hispanic/Latino	n (%)	0	0	0	0	0	0	1 (12.5)

SD Standard deviation

VII.4 Extent of Anidulafungin Exposure (intravenous and oral) in Subjects

VII.4.1 Intravenous Anidulafungin Exposure

This section is excerpted from the applicant's submission. A total of 660 subjects (subjects or patients) received at least one dose of IV anidulafungin: 179 subjects in the nine Phase 1/Phase 2 special population studies and 481 subjects in the six Phase 2-3 clinical studies in candidiasis or aspergillosis. Subjects received a single loading dose of IV anidulafungin followed by one or more maintenance doses. A total of 412 subjects received a maintenance dose of ≥50 mg for at least 10 days, with 331 subjects receiving a maintenance dose of ≥ 50 mg for at least 14 days.

Exposure to IV anidulafungin is presented by anidulafungin maintenance dose level and duration of treatment in Table 54. A total of 298 subjects (45.2%) received IV anidulafungin for less than 14 days; 340 subjects (51.5%) received IV anidulafungin from 14 to 21 days, and 22 subjects (3.3%) received IV anidulafungin for more than 21 days. Of these, one subject received 60 days of IV anidulafungin in the invasive candidiasis study VER002-6, and one subject received 90 days of IV anidulafungin in invasive Aspergillosis study VER002-7. A more detailed breakdown shows that 94 patients received anidulafungin at or above the proposed dose for over 14 days [72 for 15-21 days, 12 for 22-28 days, 2 for 29-35 days, 5 for 36-42 days, and 3 for over 42 days, including one patient treated for 90 days]).

Table 54: Exposure to Intravenous Anidulafungin by Dose Level and Duration

Study	Indication/Description	Phase	IV Dose Level	# of Subjects with Indicated Duration of Exposure (days)			
Phase 2-3 Clinical Studies In Candidiasis or Aspergillosis							
Candidiasis				< 14	14-21	> 21	Total
VER002-4	Esophageal Candidiasis	3	100/50 mg	44	256	0	300
H4A-MC-XBAF	Esophageal Candidiasis	2	50/25 mg	3	14	0	17
			70/35 mg	3	16	0	19
VER002-6	Invasive Candidiasis/ Candidemia	2	100/50 mg	21	15	4	40
			150/75 mg	17	19	4	40
			200/100 mg	22	14	4	40
VER002-11	Fluconazole-Refractory Mucosal Cnadidiasis	2/3	100/50 mg	2	3	0	5
H4A-MC-XBAG	Invasive Candidiasis/ Candidemia	2	50/35 mg	2	0	0	2
			70/35 mg	0	1	0	1
Aspergillosis							
VER002-7	Invasive Aspergillosis	2/3	200/100 mg	5	2	10	17
Subtotal				119	340	22	481
Phase 1/Special Population Studies							
Healthy Subjects							
H4A-EW-101L	Single-Ascending Dose	1	0.1–1.3 mg /kg	18			18
H4A-EW-XBAE	Single-Ascending Dose	1	0.1–1.3 mg mg /kg	25			25
H4A-EW-XBAU	Multiple-Ascending	1	30/15 mg	6			6

	Dose		70/35 mg	6			6
VER002-1	Multiple-Ascending Dose Optimization	1	100/70 mg	6			6
			140/100 mg	6			6
VER002-5	Multiple-Ascending, Maximum Tolerated Dose	1	150/75 mg	10			10
			200/100 mg	10			10
			260/130 mg	10			10
VER002-10	Mass Balance	1	^{14}C-100 mg	9			9
Drug Interaction Study							
VER002-8	Cyclosporine Drug Interaction	1	200/100 mg	12			12
Special Population Studies							
VER002-2	Hepatic Impairment	2	50 mg	27			27
VER002-3	Renal Impairment	2	50 mg	34			34
			Subtotal	179			179
			Total	298	340	22	660

Exposure to IV anidulafungin is presented by anidulafungin maintenance dose level in Table 55. The majority of subjects (90.6%; 598/660) received anidulafungin maintenance doses ≥50 mg; and approximately 9.4% (62/660) received maintenance doses <50 mg.

Table 55: Exposure to Intravenous Anidulafungin by Dose Level

Study Number	Indication/description	Phase	Number of Subjects With Exposure to Indicated IV Anidulafungin Dose Level (Mg)+						Total
			<50	50	70	75	100	130	
Phase 2-3 Clinical Studies in Candidiasis or Aspergillosis									
Indication: Candidiasis									
VER002-4	Esophageal Candidiasis	3		300					300
H4A-MC-XBAF	Esophageal Candidiasis	2	36						36
VER002-6	Invasive Candidiasis/ Candidemia	2		40		40	40		120
VER002-11	Fluconazole-Refractory Mucosal Cnadidiasis	2/3		5					5
H4A-MC-XBAG	Invasive Candidiasis/ Candidemia	2	3						3
Indication: Aspergillosis									
VER002-7	Indication: Aspergillosis	2/3					17		17
		Subtotal	39	345	0	40	57	0	481
Phase 1/Phase 2 Special Population Studies									
Healthy Subjects									
H4A-EW 101L	Single-Ascending Dose	1		6	6		6		18
H4A-EW XBAE	Single-Ascending Dose	1	11	1	6		7		25
H4A-EW XBAU	Multiple-Ascending Dose	1	12						12
VER002-1	Multiple-Ascending Dose Optimization	1			6		6		12
VER002-5	Multiple-Ascending, Maximum Tolerated Dose	1				10	10	10	30
VER002-10		1					9		9

Drug Interaction Study									
VER002-8	Cyclosporine Drug Interaction	1					12		12
Special Population Studies									
VER002-2	Hepatic Impairment	2		27					27
VER002-3	Renal Impairment	2		34					34
		Subtotal	23	68	18	10	50	10	179
		Total	62	413	18	50	107	10	660

+ For Single-Dose Studies; Dose Levels are Presented for Single Doses. For Multiple-Dose Studies, Dose Levels are Presented By Maintenance Dose Level.

A summary of the subjects who received anidulafungin maintenance dose of ≥50 mg for at least 10 days is provided in Table 56.

Table 56: Exposure to Intravenous Anidulafungin – Subjects Who Received ≥ 100/50 mg for ≥ 10 days

Study Number	Indication/Decsription	Phase	Number of Subjects who Received IV Anidulafungin ≥100/50 mg for ≥10 Days +
Phase 2-3 Clinical Studies in Candidiasis or Aspergillosis			
VER002-4	Esophageal Candidiasis	3	272
VER002-6	Invasive Candidiasis	2	87
VER002-11	Fluconazole-Refractory Mucosal Candidiasis	2/3	5
VER002-7	Invasive Aspergillosis	2/3	13
		Subtotal	377
Phase 1 Studies			
VER002-1	Ascending Dose Optimization	1	6
VER002-5	Ascending, Maximum Tolerated Dose	1	29
		Subtotal	35
		Total	412

+ For Single-Dose Studies; Dose Levels are Presented for Single Doses. For Multiple-Dose Studies, Dose Levels are Presented By Maintenance Dose Level.

Medical officer's comment: *The size of the relevant dose and duration of treatment with anidulafungin in this application is relatively large compared to other recent applications for the indication of esophageal candidiasis although the earlier applications had been marketed prior to their approval for treatment of esophageal candidiasis .*

VII.4.2 Oral formulation of Anidulafungin

Safety of the oral formulation of anidulafungin is not evaluated in detail in this review because this formulation was ultimately found not to be orally bioavailable to any

remarkable extent. The Medical Officer reviewed the summaries of oral formulation studies included in the application and agrees with the conclusions of the applicant regarding the oral formulation. Accordingly, the following section is excerpted from applicant's submission.

A total of 131 subjects (38 healthy subjects, 15 HIV-infected subjects, and 78 HIV-infected patients with candidiasis) received up to 1200 mg per day of oral anidulafungin (LY303366) in 5 Phase 1-2 clinical studies. The results of these studies demonstrate that oral anidulafungin showed low bioavailability and high variability; therefore, the IV formulation was selected for Phase 3 clinical development.

Eighty-eight of the 131 subjects (67 %) treated with oral anidulafungin reported at least 1 treatment-emergent AE. No deaths were reported following oral administration of anidulafungin. Non-fatal SAEs were reported for 2 (1.5%) subjects who had received oral anidulafungin, and 2 (1.5%) subjects discontinued treatment because of AEs. Most subjects had AEs that were mild or moderate in intensity, and most had AEs that were not related to treatment.

In general, the most frequently reported AEs were those affecting the gastrointestinal system. Gastrointestinal effects (e.g., diarrhea and abdominal pain) were dose-limiting after oral administration. Two HIV-infected patients with candidiasis had non-fatal SAEs requiring hospitalization: 1 patient had life-threatening dyspnea that occurred 1 month after treatment with oral anidulafungin (200 mg/100 mg); and 1 patient had increased serum transaminase levels after oral treatment with anidulafungin (300 mg/150 mg). The dyspnea was considered by the investigator to be unrelated to study treatment. The elevations in liver enzymes were considered possibly related to study drug; however, the patient was later diagnosed with chronic hepatitis C. One HIV-infected subject and 1 HIV-infected patient with candidiasis discontinued treatment with oral anidulafungin because of drug-related AEs (rash and maculopapular rash).

No substantive differences were observed in the proportions of subjects with AEs among healthy subjects, HIV-infected subjects or HIV-infected patients with candidiasis. There were no clinically significant changes in vital signs, ECGs, or clinical laboratory test results.

VII.4.3 Safety Review in Study VER002-4

Given the disparate patient population enrolled in the different studies included in the NDA (data from healthy volunteers and patients with mucosal candidiasis, invasive candidiasis, or invasive aspergillosis), and the fact that the bulk of the data for safety is derived from the large randomized study in esophageal candidiasis (VER002-4), this safety review focuses primarily on Study VER002-4. In addition, Study VER002-4 is the only Phase 2/3 study with an active comparator. Moreover, Study VER002-4 is the only phase 2/3 study with a substantial number of patients exposed to the proposed dose of anidulafungin that also incorporates a comparator. However, the review will briefly evaluate safety from other studies. Another reason to rely on Study VER002 is that it is

the only double blind study in the application, an important point to consider when assessing subjective symptoms and evaluating the investigators' assessment of causality.

The following tables summarize safety findings in VER002-4 per the applicant's analysis.

Table 57: Summary of Safety in Study VER002-4

Safety Parameter	Treatment Arm		Total
	Anidulafungin N=300	Fluconazole N=301	N=601
Total number of adverse events	871	916	1787
Patients with at least one adverse event	237 (79.0)	226 (75.1)	463 (77.0)
Patients with at least one adverse event of mild intensity	169 (56.3)	156 (51.8)	325 (54.1)
Patients with at least one adverse event of moderate intensity	165 (55.0)	161 (53.5)	326 (54.2)
Patients with at least one adverse event of severe intensity	57 (19.0)	39 (13.0)	96 (16.0)
Patients with at least one adverse event of life-threatening intensity	16 (5.3)	22 (7.3)	38 (6.3)
Patients with at least one serious adverse event	60 (20.0)	44 (14.6)	104 (17.3)
Patients with at least one adverse event leading to discontinuation	29 (9.7)	23 (7.6)	52 (8.7)
Patients with at least one adverse event of the following relationship to study drug			
Unrelated	218 (72.7)	212 (70.4)	430 (71.5)
Unlikely	36 (12.0)	50 (16.6)	86 (14.3)
Possible	19 (6.3)	27 (9.0)	46 (7.7)
Probable	10 (3.3)	12 (4.0)	22 (3.7)
Unknown	16 (5.3)	16 (5.3)	32 (5.3)
Deaths	23 (7.7)	20 (6.6)	43 (7.2)

Adapted from NDA 21-632 Study VER002-4 Study Report Tables 36. Data includes site #19.

Table 58: Treatment-Emergent Adverse Events Occurring in ≥ 10 Patients in a Treatment Group in Study VER002-4

	Treatment Arm, n (%)	
	Anidulafungin N= 300	Fluconazole N= 301
Number of patients with at least one AE	237 (79.0)	226 (75.1)
Preferred Term		
Pyrexia	26 (8.7)	26 (8.6)
Headache NOS	25 (8.3)	20 (6.6)
Diarrhea NOS	23 (7.7)	24 (8.0)
Vomiting NOS	20 (6.7)	28 (9.3)

Nausea	19 (6.3)	22 (7.3)
Dyspepsia	18 (6.0)	15 (5.0)
Phlebitis NOS	16 (5.3)	25 (8.3)
Anemia NOS	15 (5.0)	11 (3.7)
Hypokalaemia	14 (4.7)	15 (5.0)
Oral candidiasis	13 (4.3)	10 (3.3)
Leukopenia NOS	11 (3.7)	13 (4.3)
Cough	11 (3.7)	4 (1.3)
Anemia NOS aggravated	10 (3.3)	10 (3.3)
Lymphopenia	10 (3.3)	7 (2.3)
Liver function tests abnormal	10 (3.3)	4 (1.3)
Neutropenia	9 (3.0)	14 (4.7)
Constipation	9 (3.0)	10 (3.3)
Herpes simplex	7 (2.3)	12 (4.0)
Dizziness	6 (2.0)	13 (4.3)
Abdominal pain NOS	5 (1.7)	13 (4.3)
Aspartate aminotransferase increased	4 (1.3)	10 (3.3)

Source: Adapted from NDA Study VER002-4 Table 37. Data includes site #19.

Table 59: Life-Threatening and Severe Intensity Adverse Events Occurring in ≥ 2 Patients Overall

	Treatment Arm, n(%)	
Preferred Term	**Anidulafungin N= 300**	**Fluconazole N= 301**
Life-threatening		
Number of patients with at least one life-threatening AE	16 (5.3)	22 (7.3)
Cachexia	2 (0.7)	0
Sepsis NOS	1 (0.3)	1 (0.3)
Toxoplasmosis NOS	1 (0.3)	1 (0.3)
Inappropriate antidiuretic hormone secretion	0	2 (0.7)
Sudden death	1 (0.3)	2 (0.7)
Severe		
Number of patients with at least one severe intensity AE	57 (19.0)	39 (13.0)
Lymphopenia	3 (1.0)	3 (1.0)
Dyspnea exacerbated	3 (1.0)	0
Pyrexia	3 (1.0)	0
Dehydration	2 (0.7)	3 (1.0)
Hyponatraemia	2 (0.7)	1 (0.3)
Asthma aggravated	2 (0.7)	0
Cholecystectomy	2 (0.7)	0
Cryptococcosis	2 (0.7)	0
Esophageal candidiasis	2 (0.7)	0
Pneumonia bacterial NOS	2 (0.7)	0
Anemia NOS aggravated	1 (0.3)	5 (1.7)
Aspartate aminotransferase increased	1 (0.3)	3 (1.0)
Disseminated tuberculosis	1 (0.3)	3 (1.0)
Anemia NOS	1 (0.3)	2 (0.7)
Diarrhea aggravated	1 (0.3)	2 (0.7)
Hypokalemia	1 (0.3)	2 (0.7)
Dyspepsia	1 (0.3)	1 (0.3)

Hemoglobin decreased	1 (0.3)	1 (0.3)
HIV infection NOS	1 (0.3)	1 (0.3)
Hyperglycemia NOS	1 (0.3)	1 (0.3)
Leukopenia NOS	1 (0.3)	1 (0.3)
Neutropenia	1 (0.3)	1 (0.3)
Pleural effusion	1 (0.3)	1 (0.3)
Pneumonia NOS	1 (0.3)	1 (0.3)
Delirium	0	2 (0.7)
Herpes simplex	0	2 (0.7)

Source: Adapted from NDA Study VER002-4 Table 38. Data includes site #19.

Table 60: Related Adverse Events Occurring in ≥ 2 Patients in a Treatment Group

Preferred Term	Treatment Arm, n (%)	
	Anidulafungin	Fluconazole
	N= 300	N= 301
Number of patients with at least one related adverse event	28 (9.3)	36 (12.0)
Phlebitis NOS	2 (0.7)	4 (1.3)
Nausea	2 (0.7)	3 (1.0)
Headache NOS	2 (0.7)	2 (0.7)
Thrombocytopenia	2 (0.7)	2 (0.7)
Cough	2 (0.7)	1 (0.3)
Thrombophlebitis superficial	2 (0.7)	0
Dyspepsia aggravated	1 (0.3)	3 (1.0)
Dyspepsia	1 (0.3)	2 (0.7)
Aspartate aminotransferase increased	1 (0.3)	2 (0.7)
Vomiting NOS	1 (0.3)	2 (0.7)
Pyrexia	0	3 (1.0)
Pancytopenia	0	2 (1.0)
Hypokalaemia	0	2 (0.7)

Source: NDA Study VER002-4 Table 39. Data includes site #19.

VII.4.4 Additional Analysis by Medical Officer

Using the dataset in Study VER002-4 labeled AE.xpt, this review queried a selection of the MedRA Preferred Term variable (AEPTT) with JMP computer program. The selected AEPTT terms were those considered most relevant to the echinocandin class of antifungal agents. The frequencies of occurrence of these terms on the anidulafungin arm were compared to the fluconazole arm. Patient could have more than one episode of the event and each episode was counted independently.

Table 61: Frequency of Occurrence of Selected Treatment Adverse Events (Using AEPTT variable in AE.xpt Dataset) by Treatment Arm in Study VER002-4 Irrespective of Relationship to Study Drug and Severity

MedRA Preferred Term Variable	Anidulafungin Arm	Fluconazole Arm
Bilirubin in urine	2	0
Hepatotoxcity	0	1

Liver function test abnormal	12	4
ALT Increased	1	6
AST increased	4	13
Gamma glutamyl transferase increased	7	8
Alkaline phosphatase	2	2
Hepatitis or worsening of same	1	2
Infusion site pain	0	1
Injection site problems (pain, edema, extravasation, reactions NOS, erythema, pruritus, hemorrhage)	9	11
Phlebitis/Thrombophlebitis	22	28
Angioneurotic edema	1	1
Tongue edema	0	1
Rash	23	18
Urticaria	2	0
Drug hypersensitivity (Note: none due to study drug)	3	2
Renal failure aggravated, renal failure NOS, renal function tests abnormal, renal impairment NOS, renal failure, acute	3	2
Raised creatinine levels	2	1
Adrenal Insufficiency	1	0
Hematuria	10	5
Blood creatinine phospokinase increased	4	4
Pulmonary embolism	1	0
Dyspnea	10	4
Respiratory Distress	0	1
Chest pain	9	8
Acute Cardiopulmonary failure	1	0
Hypotension	4	10
Sudden death	1	2
Cardiac arrest	0	1
Thrombocytopenia, platelet count decreased, or thrombocytopenia aggravated	7	8
Leukopenia	11	13
Lymphopenia	10	8
Neutropenia	12	14
Anemia or hemoglobin decreased	29	24
Dyspepsia	20	20
Dry mouth	4	2
Vomiting	28	34
Hyponatremia	9	9
Hypokalemia or blood potassium decreased	18	19
Hypocalcemia	2	5
Hypomagnesemia or low magnesium	7	3
Hypoglycemia	2	1

Hyperglycemia	5	7
Impaired GTT	0	1
Uric acid increased	1	4
Headache NOS	30	22
Dizziness	7	14
Insomnia	9	9
Anxiety	7	5
Delirium or agitation	2	3
Confusion	1	2
Encephalopathy	0	1
Encephalitis	0	1
Convulsions		
Depressed level of consciousness	2	1
Edema	5	4
Pyrexia	34	33
Rigors	2	1
Malaise	0	2
Myalgia	2	5
Flu-like illness	0	1
Hot flushes	2	0
Depression or worsening depression	1	1
Summary of Treatment Emergent Adverse Events in Selected dataset		
All non-fatal severe or life-threatening AE in VER002-4	101	97
Possible	*4*	*5*
Probable	*0*	*4*
Unlikely	*4*	*5*
Unrelated	*93*	*80*
Unknown	*0*	*3*

Coding inconsistencies might explain fi8ndings such as the number of patients with liver function abnormalities (12 on anidulafungin arm versus 4 on fluconazole arm), a finding at variance with AST increased (4 on anidulafungin arm versus 13 on fluconazole arm). Of note, the query of the AEPTT variable in the AE dataset did not find any of the following terms: hyperbilirubinemia, torsade des pointes, arrhythmia, prolonged QTc, pulmonary fibrosis, or suicide.

VII.4.5 Conclusion on Adverse Event Profile in Study VER002-4

Overall the adverse event profile of anidulafungin did not differ in any relevant way from that of fluconazole (an established antifungal agent with well-characterized safety profile) in the population studied.

It is noteworthy that a large number of non-fatal severe or life-threatening adverse events were documented but few of the events were considered at least possibly related to study drugs. This finding is most likely a reflection of the study population, a population that

was largely made up of AIDS patients with limited anti-HIV treatment and many with serious co-morbid conditions.

VII.5 Deaths and Discontinuations

A total of 91 deaths occurred in the 20 clinical studies by the cut-off date for this submission; 68 of these occurred in patients on anidulafungin arm (23 [7.7%] among the 300 patients who received anidulafungin in study VER002-4) and 20 in those on fluconazole (all 20 [6.6%] occurred among the 301 patients on fluconazole in study VER002-4). Esophageal candidiasis by itself is rarely a fatal disease. The 1.1% difference in point estimate in the proportion of deaths between anidulafungin and fluconazole in study VER002-4 could simply reflect the subtle imbalances in the severity of the underlying medical conditions in randomized patients.

None of the deaths in patients receiving fluconazole were considered by the investigator to be related to the study drug whereas 2 of the deaths in patients on anidulafungin were thought possibly related to study drug. One of the 2 patients (Patient 13008) died from hepatic necrosis with multisystem failure on the 3rd day of anidulafungin therapy in study VER002-4. The other patient had invasive candidiasis and died from convulsions. Both patients had serious and multiple co-morbidities and were on numerous concomitant medications.

Patient ID #13-008 had hepatic necrosis with multisystem failure that was considered by the investigator to be possibly related to anidulafungin. The patient's liver function tests were normal at screening, although test done 14 days prior to screening revealed ALT 100 U/L. This patient was an alcohol abuser with pulmonary tuberculosis (who completed treatment a few months earlier), bronchiectasis, and right-sided heart failure on several medications. He died on the 3rd day of anidulafungin therapy. The patient was on the following concomitant or recently discontinued medications: Furosemide, Spironolactone, Theophylline, Gaviscon, Lentogesic, Prednisone, Atrovent, Beclate, Fenotenol HBR, Ciprofloxacin (2 courses), Budesonide, Omeprasole, Prochlorperazine.

The investigator initially considered the death due to underlying pulmonary and cardiac conditions. About 3 months later, the investigator revised the cause of death and considered that the jaundice and respiratory failure resulted from hepatic necrosis with multisystem failure, which could possibly be related to anidulafungin.

On February 18, 2004, the Agency requested from the applicant additional information on this patient. Specifically, the Agency requested that the applicant provide any additional information they might have on this patient including, where possible, a copy of the patient's medical records. Information such as the active ingredient (s) and actual amounts in (milligrams or grams) of concomitant medications taken, ingestion of herbal products, and over the counter medications. The Agency also requested that medical information on the patient go back a few weeks prior to enrollment to facilitate evaluation. In general, the additional information on Patient 13-008 provided by the

applicant did not significantly augment information already available in the application. However, the applicant had consulted a hepatologist (Dr. [redacted]) for a review of this patient's data and the entire data on the hepatic profile of anidulafungin. Dr. [redacted] considered that the patient was at risk for ischemic "shock" liver due to the right sided heart failure and distended hepatic veins; that the immediate cause of death was most likely secondary to arrhythmia considering the patient's recent concomitant treatment with ciprofloxacin and theophylline; and that an earlier episode of arrhythmia would explain the enzyme pattern consistent with shock liver.

Internally, two consults were requested from the Office of Drug Safety (ODS) on Patient #13-008. One consult was for the Division of Drug Risk Evaluation (DDRE) to provide information from the DDRE's Adverse Events Reporting System (AERS) on the liver profile of the medications taken concomitantly with anidulafungin or recently discontinued. The consult also asked DDRE to provide updated postmarketing reports of liver toxicity associated with caspofungin, the marketed echinocandin. The review by Sarah J. Singer, R.Ph., Safety Evaluator DDRE, concluded that "AERS provides very little evidence that the six concomitant drugs would have been likely to have caused his fulminant hepatitis. The only concomitant drug with a known hepatotoxic potential which might have been responsible would have been the acetaminophen component of Lentogesic, if given in an overdose situation or with alcohol (neither of which were mentioned in the case summary)."

DDRE review further notes that "the eight AERS cases of caspofungin-associated hepatotoxicity are similar to the anidulafungin case in that they are quite complex and the causal role of the drug is difficult to assess. However, they also share the similarity that LFTs increased quite abruptly within days of starting a course of the echinocandin in four of the caspofungin cases and the anidulafungin case. Although the evidence is not overwhelming, it suggests that there is a possibility the trial patient's newly-introduced echinocandin therapy may have been responsible for his sudden dramatic increase in LFTs and eventual death due to fulminant hepatitis."

Finally, DDRE noted that "the antifungal agents currently approved in the United States for use in systemic mycoses are all associated with significant toxicities. Each clinician should choose the most appropriate drug for a given patient based on a risk/benefit analysis that takes into account the morbidity/mortality of the condition being treated as well as the known adverse event profiles of the possible treatment choices." DDRE then recommended that "if anidulafungin is approved, its labeling should state [redacted] causality remains uncertain."

The other internal consult was sent to John Senior, MD, Associate Director for Science, Office of Pharmaco-epidemiology and Statistical Science (OPSS). Dr. Senior is an expert hepatologist with the FDA.

Dr. Senior concluded that "*the sponsor has sought a variety of alternate explanations for the possibility that their experimental echinocandin agent anidulafungin may have played a role in the fulminant liver injury and death of this patient. The shifting opinions of the investigator do not reassure us that the various attributions of what caused what are accurate. Not to say this is not an easy case to resolve, and there were many confounding factors, as is often the situation It remains true that the patient was chronically ill, was on many medications, and had significant right heart failure that very likely produced centrilobular congestion in the liver and consequent hypoxia at that site. Whether he had an arrthymia, or a pulmonary embolus, or a hypotensive episode, can only be speculated upon. It is entirely possible that a combination of effects produced the acute hepatic failure, with drug toxicity superimposed on impaired liver function from passive congestion. The sudden death suggests final cardiac arrest rather than either liver or respiratory failure. The timing of the events very strongly suggests that taking anidulafungin did something adverse and very bad to this patient. We cannot talk about liver necrosis, for that is a pathologic diagnosis requiring that liver tissue be examined, which was not done. It remains quite likely that this case represents possible hepatotoxicity of anidulafungin.*

Dr. Senior then recommended the following that:

1. This case cannot be dismissed. It must be included in the labeling as a possible case of drug-induced liver injury that was rapid and fatal.
2. Other cases must be looked for in patients treated with this drug. Systemic fungal diseases often occur in otherwise very sick patients who are on other therapies and have underlying problems, which may make them more vulnerable to or less able to recover from additional liver injury caused by anidulafungin.
3. Other agents in this class should be watched carefully as well (caspofingin, micafungin), and full reports of hepatotoxicity, even if relatively rare, be studied thoroughly.

The additional information submitted by the applicant on patient #13-008 and the reviews by Dr. Senior and Ms. Sarah Singer are archived in the Agency's Division Filing System (DFS).

Four (17.4%) of the 23 patients that died on the anidulafungin arm were on concomitant corticosteroids as were 3 (15%) of 20 patients that died on fluconazole arm. Thus, concomitant use of corticosteroid did not appear to play a role in the demise of patients on the anidulafungin arm. This finding is relevant to the concern raised from animal study by Clemons et al.[xiv] that suggested that concomitant use of corticosteroids with anidulafungin resulted in increased mortality among treated rodents. However, the finding is consistent with finding from the animal study done by the applicant at the request of the Division. That study was entitled "acute toxicity study of cortisone acetate, anidulafungin, and cortisone acetate in combination with anidulafungin administered to DBA/2 and BALB/c mice. The study concluded that a single administration of 125 mg/kg (adjusted to 89 mg/kg) cortisone acetate, 10 daily administrations of 25 mg/kg

anidulafungin alone, or the single administration of 125 mg/kg (adjusted to 89 mg/kg) cortisone acetate in combination with 25 mg/kg anidulafungin followed by an additional nine days of anidulafungin administration produced no adverse toxicological findings.

Eight additional cases (4 on each arm) in study VER002-4 died after completion of the follow-up period but within 30 days after the last dose of study drug. These deaths are not included the applicant's integrated safety dataset. These eight deaths are briefly summarized below based on information obtained from the case narratives and CRFs.

Patient 4-056
This patient was on blinded study drug from 07/9/02 to 07/22/02. At screening, the patient had hypotension, sinus tachycardia, hypokalemia, and HIV with cachexia. Screening labs were largely unremarkable except for mild anemia, lymphopenia, elevated liver enzymes considered not clinically significant, hypoalbuminemia, and diarrhea. At end of therapy (07/22/02) patient was noted to have pancytopenia with no improvement 7 days post end of therapy. At the [ ] follow-up visit on [ ], patient was moribund with petechiae and was admitted. Repeat lab tests showed worsened anemia and hypokalemia with minimal improvement in platelet and leucopenia. There was also hypoalbuminemia. Patient was discharged one week later [ ] but status at discharge from hospital is not available. Patient died two days later [ ] from "gastroenteritis."

Patient 4-110
This patient received blinded study drug from 09/12/02 to 09/26/02. At screening, patient was HIV positive and had anemia considered not clinically significant. It should be pointed out that this patient did not meet the entry criteria as screening creatinine was 290 umols/L (> 2.5 x ULN). Patient was admitted with features of pneumonia on [ ] and discharged on [ ]. Here too the condition at discharge is not well documented. Patient died at home on [ ] from pulmonary tuberculosis (TB) per death certificate.

Patient 6-038
This patient received blinded study drug from 09/17/01 to 10/01/01. It is unclear when the patient died. The narrative documents that "the patient experienced pulmonary TB leading to her death on the same day." However, the CIOMS form that captured SAEs documents that the patient died on [ ] but that the patient experienced pulmonary TB from [ ]. Both sources document that from the death certificate patient died from pulmonary TB and PCP. Events leading to death are unknown.

Patient 10-013
Patient 10-013 received blinded study drug from 06/26/01 to 07/09/01. At the two-week follow-up visit on [ ], patient had no symptoms and examination was unchanged. However, on [ ] patient died at home due to heart failure, ischemic heart disease, hypertension, and diabetes mellitus per the death certificate. ECHO on [ ] had shown poor cardiac function and other cardiac pathology. Moreover patient was on multiple concomitant medications.

Patient 10-034

This patient received blinded study drug from 08/29/01 to 09/11/01. At EOT (09/11/01) patient was found to have elevated AST that was resolving at FU visit on 09/27/01. On that [ ] , patient was found to be dehydrated, wasted, tachypneic, hypothermic, and confused with metabolic acidosis, and ongoing symptoms of EC. Patient became progressively more confused despite adequate hydration and was thought to "probably [be] due to encephalopathy" leading to cardiopulmonary arrest. In addition, patient was dyspneic and tachypneic suggesting pneumonia but was not radiologically confirmed. The patient eventually died on [ ] from AIDS as documented in the death certificate. On review of this patient's CRF, the medical officer notes the patient's alkaline phosphatase, GGT, ALT, AST, and total bilirubin as follows:

Table 62: By Visit Serum Liver Function Parameters in Patient 10-034

Study Day/Visit	Alk Phos	ALT	AST	GGT	Total Bili
Screening	117	57	94	80	10
Day 3	114	49	85	69	12
Day 7	178	68	62	101	10
Day 14	397	318	409	221	10
2-Week Follow-up	342	47	147	104	18

Alk Phos = Alkaline phosphatase. ALT = alanine transaminase. AST = Aspartate transaminase. GGT = gamma glutamyl transpeptidase. Bili = Bilirubin

In addition, creatinine phosphokinase and LDH were slightly elevated during most of the visits. It is important to note that serum bilirubin was never elevated and alkaline phosphatase was elevated later in the course of treatment.

When interpreting clinical laboratory results, the reader should keep in mind that the lag time between blood draw and testing was on average 24 to 48 hours. Nevertheless, it is plausible that in the interval from the end of therapy to the follow-up visit, the patient's liver toxicity was much more profound and, indeed, that the "encephalopathy" was actually a result of fulminant liver failure. This becomes even more relevant as the patient's medical history notes that patient was an alcohol abuser who had stopped drinking in — 2001. More likely though, this patient's condition might have been related to terminal HIV infection.

Patient 10-086

Patient 10-086 was on study drug from 04/02 to 04/24/02. Patient was admitted on [ ] with confirmed cryptococcal meningitis and died the following day.

Patient 12-009

This patient received study drug from 02/18/02 to 03/03/02. At enrollment, the patient had been sick with a three month history of progressive weight and muscle loss and was bedridden with decubitus ulcers. He was HIV infected and on admission was cachectic, anemic, and cyanosed with digital clubbing, peripheral edema, and elevated urea and

creatinine. The patient clinically improved with rehydration and antibiotics although patient had persistent fever of unknown source. Lumber puncture excluded meningitis. On Day 3 of study medication patient had elevated creatinine kinase, LDH, AST, and ALT and ECG (performed routinely as part of the trial) was consistent with myocardial infarction. The patient clinical and laboratory course improved with treatment and patient completed the trial with normal ALT, AST, and kidney function tests on Day 14. However, fever persisted and was considered due to UTI. Patient received an unspecified antibiotic. At follow-up on [redacted] (per the CRF), there was no evidence of EC but the patient died on [redacted] from "septicemia following unsuccessful treatment of a suspected UTI." "The septicemia most likely developed on the day of his death." It is not clear when the subsequent clinical deterioration started in this patient since patient had undergone endoscopy the previous day and would have been sufficiently stable to undergo such procedure. Clinical lab tests on 03/20/02 showed normal bilirubin, CK, alkaline phosphatase, ALT, AST, and GGT but sodium (179 mmol/L), chloride (149 mmol/L), urea (44.7 mmol/L), creatinine (463 umol/L), and uric acid (1120) were elevated while serum bicarbonate was low (10.3 mmol/L). Complete blood count showed profound anemia and thrombocytopenia with neutrophilia and toxic granulations of the neutrophils. Urine analysis showed proteinuria considered not to be clinically significant. Urine culture was not available.

Table 63: By Visit Clinical Chemistry Parameters for Patient #12-009

Study Day/Visit	Na+	K+	Cl-	HCO_3-	Urea	Creat	Uric acid	CK	ALT	AST	GGT	LDH	Alk Phos
Screening	147	3.7	115	14.8	16.3	135	930	486	21	46	18	285	50
Day 3	159	3.9	125	13.9	17.0	243	840	2236	67	157	27	559	65
Day 7	165	3.4	132	14.6	19.2	187	900	436	116	177	41	495	86
Day 14	156	3.7	121	17.1	11.1	131	650	200	55	79	120	370	123
Follow up	179	4.2	149	10.3	44.7	463	1120	161	13	28	19	282	50

Alk Phos = Alkaline phosphatase. ALT = alanine transaminase. AST = Aspartate transaminase. Creat = Creatinine. GGT = gamma glutamyl transpeptidase. LDH = Lactate dehydrogenase.

As noted earlier, interpretation of these lab results requires caution given the lag time from blood draw to testing. However, it is noteworthy that chemistry test from the above table seems to suggest inadequate fluid and electrolyte management in this patient that may have been the immediate cause of death. To what extent study medication contributed to the fluid and electrolyte disturbances is not clear. In the phase 1 multiple dose PK and MTD study (VER002-5) of IV anidulafungin at doses up to 260/130 mg daily for 14 days, there was no evidence of electrolyte and fluid imbalance although there were dose-dependent and temporal trends in ALT and AST elevation (See section VII.4.3 of this review).

Patient 13-013

Patient 13-013 received study drug from 03/14/02 to 03/27/02. Screening medical history included hypotension; abdominal discomfort; urinary tract infection; acquired immune deficiency syndrome (AIDS); swinging fever; cough; pulmonary TB; asthma;

dry mouth; skin rash; lower extremity edema; and weight loss. Patient was readmitted [ ] with sorethroat, diarrhea, odynophagia, and stomach cramps of unspecified cause. He underwent follow-up procedures including endoscopy on [ ] The narrative reports that patient recovered sufficiently to be discharged from hospital on [ ] Patient was readmitted on [ ] comatose, dehydrated, and gasping. Patient died within minutes of admission. Death was attributed to pulmonary TB and organ failure due to progression of AIDS.

VII.6 Additional Evaluation of Liver Profile of Anidulafungin

From animal studies, the liver appears to be a potential target organ of toxicity. Given the findings from Patient #13-008 and the fact that in the Phase 1 maximum tolerated dose study in healthy volunteers (StduyVER002-5), anidulafungin showed a dose-related trend to mild increases in ALT, AST and alkaline phosphates, a thorough review was conducted to provide any potential evidence of liver toxicity contributing to death or discontinuation of study drug. These were exploratory analyses to see if any pattern might emerge to distinguish anidulafungin-treated patients from those treated with fluconazole.Table 64 summarizes fatal cases in Study VER002-4 with at least one potentially significant abnormality of liver function test.

Table 64: Fatal Cases with At Least One Clinically Significant Liver Function Test Abnormalities

Patient ID (duration)	Preferred Term	Relationship to Study Drug*	Alk Phos		ALT		AST		GGT		Total Bili	
			Screen	Peak (Visit)	Screen	Peak (Visit)	Screen	Peak (Visit)	Screen	Peak (Visit)	Screen	Peak (Visit)
Anidulafungin												
9-006 (3 days)	Disseminated Tuberculosis	Unrelated	1231	1231 (0)	48	54 (FU)	100	231 (FU)	274	274 (0)	15	32 (FU)
10-020 (5 days)	Gastric Cancer NOS	Unrelated	263	263 (0)	17	45 (EOT)	29	226 (EOT)	202	202 (0)	21	44 (EOT)
13-008 (3 days)	Hepatic necrosis with multisystem failure	Possibly	76	81 (3)	16	4160 (3)	16	7058 (3)	52	72 (3)	QNS	100 (3)
13-011 (14 days)	HIV Infection NOS	Unrelated	83	196 (FU+9 days)	18	50 (FU+9 days)	37	193 (FU+9 days)	37	37 (0)	6	17 (FU+9 days)
13-016 (10 days)	Pneumonia Aggravated	Unrelated	79	100 (3)	26	87 (3)	82	207 (3)	71	94 (3)	8	8 (0)
17-003 (8 days)	Mycobacterium avium complex	Unrelated	485	1409 (FU)	35	54 (7)	69	115 (7)	168	262 (7)	8	13 (FU)
17-011 (7 days)	Systemic fungal infection	Unrelated	326	1975 (7)	48	79 (7)	168	905 (7)	151	399 (7)	10	23 (7)
Fluconazole												
12-026 (11 days)	Respiratory failure (excluding neonatal)	Unrelated	292	426 (7)	44	93 (EOT+ 1 day)	78	394 (EOT+ 1 day)	147	253 (EOT+ 1 day)	<3	35 (EOT+ 1 day)
13-015 (14 days)	Respiratory failure (excluding neonatal)	Unrelated	70	74 (14)	55	55 (0)	34	99 (7)	26	30 (7)	19	22 (7)
13-018 (8 days)	HIV infection NOS	Unrelated	132	157 (7)	62	62 (0)	71	113 (7)	75	75 (0)	11	12 (3)

*Investigator's assessment of relationship to study drug Visit 0=screening 3=Day three of treatment 7=Day seven of treatment 14=Day fourteen of treatment EOT=End of Therapy FU=Follow-up (14 day post therapy)

Alk Phos Alkaline Phosphatse (units/L) ALT Alanine Transaminase (units/L) AST Aspartate Transaminase (units/L) GGT Gamma Glutamyl Transferase (IUnits/L) LDH Lactate Dehydrogenoase (units/L) Bili Bilirubin (µmols/L) QNS Quantity not sufficient

Additional Information on Patients Presented in Table 64

13-008	Negative HBsAg, Anti-HBs, HCV Ab
13-016	Visit 7 chemistry: lab reports AST and LDH as "Hemolysis". Subsequent lab values are unavailable
17-003	Follow-up visit ALT 33, AST 53, GGT 225, LDH 455
13-015	Visit 14 chemistry: lab reports AST and LDH as "Hemolysis". Subsequent values are unavailable

Discontinuation Due to Adverse Events

Forty six patients were found in the dataset AE.xpt who discontinued randomized therapy due to adverse events (24 on anidulafungin arm and 22 on fluconazole arm). These 46 patients include fatalities whose data have been reviewed for the Table above. Among non-fatal cases were the following patients with at least one clinically significant liver function test:

Anidulafungin

6-059	Received 14 days of therapy. LFTs at screening visit were Alk Phos 166, GGT 221, ALT 69, and AST 75. At time of recurrence of esophageal candidiasis (8 days post-EOT), tests results were Alk Phos 792, GGT 994, ALT 65, AST 107, and total bilirubin 8 µmol/L. GGT further increased to 1177 at 14 day follow-up visit. This patient received fluconazole 400/200 mg from 6 days post-EOT ad was continuing on fluconazole 2 days prior to 14 day follow-up visit.
19-024	Received 12 days of therapy. LFTs at screening visit were ALT 83, and AST 81. AST peaked at Day 3 of treatment at 153 while ALT peaked on Day 7 of treatment at 143. At 14 day follow-up both had gone back to baseline. There were clinically insignificant elevations of Alk Phos and GGT all through treatment phase but total bilirubin remained normal.

Fluconazole

6-002	This patient received a total of 5 days of therapy. Clinically significant elevations in liver function tests at screening were AST 83. On Day 3 of therapy AST was 152. No additional tests for AST were done.

Conclusion from Review of Deaths and Discontinuations Due to Adverse Events

1. Relative to patients on fluconazole, more patients on anidulafungin had clinically significant post-baseline elevation of at least one liver function test.
2. AST appears to be the most sensitive tests but Alkaline Phosphatase, ALT, and total bilirubin may also be affected.
3. These liver abnormalities tend to occur early and in some patients did not resolve at 14 day follow-up visit

4. Abnormal baseline liver function test may increase the risk; however, some patients had normal baseline results.
5. It is unclear to what extent underlying medical conditions and concomitant illnesses contribute to these findings.
6. In the past, the Agency has considered elevations in total bilirubin and transaminases with normal alkaline phosphates as flags for potential significant hepatotoxicity. Besides Patient ID #13008, none of the other patients discussed above meets these criteria.

One caveat in this review relates to the population studied. In a population of patients with advanced AIDS, few of whom were treated with any antiretroviral therapy, opportunistic infections and other AIDS-related conditions would be expected. Such conditions may affect the liver. Most of the abnormalities in liver function tests were grades 2 or less in Study VER002-4, findings that have been found in other trials in a similar population.

Comparative analysis of hepatobiliary clinical laboratory parameters by the applicant suggests no relevant differences in liver function test parameters between anidulafungin and fluconazole, whether examined by mean values (SD) or by pre-defined clinically significant values, as shown on Tables 65 and 66 below:

Table 65: Mean (SD) Hepatobiliary Clinical laboratory Parameters

Parameter		**n**	**Anidulafungin N=300**	**n**	**Fluconazole N=301**
Alkaline Phosphatse	Baseline	296	129.81 (126.99)	294	143.38 (160.85)
	Day 3	266	126.56 (113.37)	266	140.57 (163.20)
	Day 7	253	126.42 (104.22)	262	152.85 (193.46)
	Day 14	236	132.28 (97.71)	246	164.52 (277.92)
	End of therapy	43	175.79 (131.04)	36	336.56 (593.52)
	Follow-up	239	138.14 (121.35)	239	145.31 (163.18)
GGT	Baseline	291	68.59 (97.22)	285	82.55 (115.51)
	Day 3	261	77.84 (176.54)*	266	79.62 (105.98)
	Day 7	251	81.39 (161.59)	258	85.78 (107.76)
	Day 14	234	81.47 (143.33)	241	108.46 (190.15)
	End of therapy	41	94.73 (116.00)	37	160.14 (182.02)
	Follow-up	234	90.66 (148.64)	235	113.62 (179.20)
ALT	Baseline	297	29.38 (21.83)	295	28.55 (33.34)
	Day 3	265	45.69 (255.40)*	268	25.57 (17.38)
	Day 7	258	31.73 (31.32)	260	30.55 (26.82)
	Day 14	237	34.07 (33.69)	243	34.24 (35.70)
	End of therapy	43	36.23 (27.49)	37	46.95 (64.95)
	Follow-up	240	30.63 (26.05)	240	31.74 (29.84)
AST	Baseline	292	41.05 (28.33)	292	41.79 (59.03)
	Day 3	262	69.52 (436.32)*	267	36.50 (23.89)

	Day 7	255	44.77 (61.69)	258	41.96 (33.48)
	Day 14	238	42.82 (35.48)	240	43.87 (38.70)
	End of therapy	43	57.42 (53.04)	37	73.92 (136.82)*
	Follow-up	238	44.88 (40.98)	239	42.34 (44.18)
LDH	Baseline	286	99.96 (151.71)	282	104.90 (136.06)
	Day 3	260	132.56 (677.77)*	257	88.91 (156.36)
	Day 7	249	89.51 (104.64)	251	94.33 (172.12)
	Day 14	230	84.23 (89.17)	234	94.24 (113.89)
	End of therapy	43	96.00 (192.01)	37	81.22 (121.54)
	Follow-up	235	96.96 (122.25)	228	99.20 (134.68)
Total Bilirubin	Baseline	293	9.01 (5.06)	291	9.25 (5.62)
	Day 3	261	9.01 (7.57)	261	8.42 (6.04)
	Day 7	250	8.31 (4.94)	253	8.52 (7.83)
	Day 14	232	8.75 (5.42)	238	9.24 (9.58)
	End of therapy	43	10.47 (6.80)	37	9.65 (10.38)
	Follow-up	237	9.35 (7.84)	235	10.32 (13.41)

*out-of-range maximum values skewed the mean values and generated high standard deviations
Source: Adapted from Table 46 NDA 21-632 Study Report for Study VER002-4

Table 66: Number and Percentage of Patients with Potentially Clinically Significant Increases that were also Clinically Significant Increases from Baseline

	Parameter	n	Anidulafungin N=300	n	Fluconazole N=301
Alkaline Phosphatase	Day 3	266	1/266 (0.38)	267	1/267 (0.37)
	Day 7	254	1/254 (0.39)	262	1/262 (0.38)
	Day 14	237	3/237 (1.27)	246	3/246 (1.22)
	End of therapy	43	0/43	37	0/37
	Follow-up	239	3/239 (1.26)	239	3/239 (1.26)
ALT	Day 3	265	1/265 (0.38)	268	0/268
	Day 7	258	2/258 (0.78)	260	3/260 (1.15)
	Day 14	237	2/237 (0.84)	243	8/243 (3.29)
	End of therapy	43	0/43	37	1/37 (2.70)
	Follow-up	240	2/240 (0.83)	240	5/240 (2.08)
AST	Day 3	262	2/262 (0.76)	267	0/267
	Day 7	255	3/255 (1.18)	258	2/258 (0.78)
	Day 14	238	1/238 (0.42)	240	5/240 (2.08)
	End of therapy	43	2/43 (4.65)	37	1/37 (2.70)
	Follow-up	238	6/238 (2.52)	239	8/239 (3.35)
GGT	Day 3	261	0/261	266	1/266 (0.38)
	Day 7	251	3/251 (1.20)	258	3/258 (1.16)
	Day 14	234	4/234 (1.71)	241	13/241 (5.39)
	End of therapy	41	1/41 (2.44)	37	2/37 (5.41)
	Follow-up	234	14/234 (5.98)	235	16/235 (6.81)

Note: N = number of patients in a treatment group, n, % = number and percentage of patients
* Only parameters with values will be presented
Source: Table 47 NDA 21-632 Study Report for Study VER002-4

Tables 67 and 68 provide additional assessment of potential liver toxicity and also confirm the similarities of the liver profile of anidulafungin to that of fluconazole.

Table 67: Number of Patients with Abnormalities in Pre-Specified Hepatobiliary Parameters at any Time on Therapy

	Anidulafungin N=300		Fluconazole N=301	
	# Patients	% Patients	# Patients	% Patients
ALT > 3 x ULN	16/283	5.6	24/282	8.5
ALT > 5 x ULN	5/283	1.7	7/282	2.4
ALT > 10 x ULN	1/283	0.3	1/282	0.3
ALT > 3 x ULN + bilirubin > 1.5 x ULN	2/193	1.0	2/195	1.0
ALT > 3 x ULN + bilirubin > 2.0 x ULN	1/193	0.5	1/195	0.5
AST > 3x ULN	41/283	14.4	35/281	12.4
AST > 5x ULN	17/283	6.0	14/281	4.9
AST > 10x ULN	4/283	1.4	2/281	0.7
AST > 3 x ULN + bilirubin > 1.5 x ULN	4/193	2.0	4/195	2.0
AST > 3 x ULN + bilirubin > 2.0 x ULN	2/193	1.0	3/195	1.5
Alkaline phosphatase > 1.5 x ULN	46/283	16.2	58/282	20.5

Note: ULN = upper limit normal, ALT = alanine aminotransferase, AST = aspartate aminotransferase
Note: Abnormalities are presented regardless of baseline value
Source: Table 48 NDA 21-632 Study Report for Study VER002-4

Table 68: Number and Percentage of Patients With Prospectively-Defined Abnormalities in Hepatobiliary Parameters on Therapy or Post Therapy Regardless of Baseline Value (Intent-to-Treat Population) in Study VER002-6

	100/50 mg N=40 n (%)	150/75 mg N=40 n (%)	200/100 mg N=40 n (%)
ALT > 3 x ULN	5(12.5)	7(17.5)	3(7.5)
ALT > 5 x ULN	2(5.0)	2(5.0)	0
ALT > 10 x ULN	1(2.5)	1(2.5)	0
ALT > 3 x ULN + Total Bilirubin > 1.5 x ULN	2(5.0)	2(5.0)	2(5.0)
ALT > 3 x ULN + Total Bilirubin > 2.0 x ULN	1(2.5)	1(2.5)	2(5.0)
Alkaline Phosphatase > 1.5 x ULN	22(55.0)	25(62.5)	16(40.0)

Source: Table 6.12 NDA 21-632 Study Report for Study VER002-6

An additional review of line listing of chemistry clinical laboratory data in the single large Phase 3 esophageal candidiasis study was conducted to capture patients with elevated Serum ALT and/or AST (≥ 3 x ULN) who also had elevated total bilirubin (≥ 1.5 x ULN) but with normal alkaline phosphatase ("Hy's law"). With the single patient with hepatic necrosis, 2 patients on each arm met the criteria. When the data was examined without regard to elevation of total bilirubin, an additional 16 patients on

anidulafungin arm and 15 on fluconazole arm were found. In most of these patients, ALT or AST was just greater than 3x ULN.

Overall, the adverse event profile of anidulafungin did not differ in any relevant way from those of fluconazole, an established antifungal agent with well characterized safety profile. However, from study VER002-5, anidulafungin showed a dose-related trend to mild increase in ALT, AST, and alkaline phosphase.

VII.7 Safety issues from animal pharmacology toxicology studies

In characterizing the safety pharmacology of anidulafungin, the applicant assessed the agonist and antagonist activities of the compound in smooth and cardiac muscle tissue bath preparations and purkinje fiber preparations, and by in vivo studies of effects on behavior, gastrointestinal motility, renal function, respiratory rate, and cardiovascular activity. No receptor-selective effects on smooth or cardiac muscle were observed in vitro at an anidulafungin concentration of 1 micromolar or lower. An in vitro study of anidulafungin and purkinje fibers showed no drug-related effects on action potential parameters. Clinically relevant pharmacological effects on any body systems were noted only at anidulafungin IV doses >20 mg/kg.

However, several acute and/or repeated-dose studies identified the liver as a target organ of toxicity as shown by slight to moderate hepatopathy with related elevations in ALT and AST levels.

All clinically important, treatment-related effects observed following long-term IV administration were observed at dosages of 30 to 35 mg/kg/day (monkeys) and 30 to 46 mg/kg/day (rats). Effects at 10 mg/kg/day, including transient, mild infusion-associated adverse events observed in rats, were considered of minor clinical relevance. Thus, the No Observed Adverse Effect Level for both rats and monkeys was considered to be approximately 10 mg/kg/day.

In population PK studies derived from data from the esophageal candidiasis Study VER002-4 and other clinical studies, maximum plasma concentrations were approximately 3.5 mg/L and trough plasma concentrations were greater than 1 mg/L

VII.8 Non-fatal serious adverse events

A total of 120 SAE were reported among the 774 patients in phases 2/3 trials in candidiasis and aspergillosis. In study VER002-4, there were 71 patients with nonfatal SAEs, 37 patients (12.3%) in the anidulafungin group, and 24 patients (8.0%) in the fluconazole group. On both treatment arms, the vast majority of SAEs were associated with conditions commonly seen in immunocompromized patients such as infections with *Cryptococcus neoformans*, *Mycobacterium tuberculosis* and *Pneumocystis carinii*, bacterial pneumonia, other infections, cachexia, and dehydration. There were no

meaningful differences in the frequency of non-fatal SAEs, or in the type of non-fatal SAEs experienced between treatment groups. Non-fatal SAEs from other studies also failed to show any safety flags attributable to anidulafungin or fluconazole.

VII.9 Withdrawals due to Adverse Events

In study VER002-4, a total of 52 patients discontinued treatment due to adverse events. Of these, 40 died from their AEs and are discussed in the section Death. Of the remaining 12 discontinuations, 8 were on anidulafungin arm and 4 on fluconazole arm. Again the significance of the difference is unclear, especially given the small numbers involved, the patient population and the fact that the investigators considered just one and two patients on anidulafungin and fluconazole arms, respectively, to have discontinued due to AE that was possibly related to study medication.

VII.10 Potential Adverse Pregnancy Outcomes

There were no reported pregnancy exposures in the NDA database. Moreover, in rat studies, maternal dose as high as 20 mg/kg/day IV throughout pregnancy and up to 14 days during lactation did not show any adverse effect in offspring although maternal morphology, weight gain, and feed consumption were affected at doses between 6 and 20 mg/kg/day IV. Similarly, the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicities in rabbits was 10 mg/kg/day IV as weight gain was decreased near the end of treatment in the 20 mg/kg/day IV dose group. The 10 mg/kg/day NOAEL is equivalent to about 5 times the highest dose of intravenous anidulafungin administered to humans (260/130 mg) and 13-14 times the dose proposed for esophageal candidiasis. One animal in the rabbit study on 20 mg/kg/day IV of anidulafungin aborted and was terminated from the study on Day 22; this abortion was considered due to the decreased food intake secondary to administration of anidulafungin as the animal was anorectic for 8 days prior to the abortion.

VII.11 Clinical laboratory events

After making allowance for patient population and underlying diseases, only few cases of potentially clinically significant changes from baseline of clinical laboratory occurred and in study VER002-4, these changes were balanced between the two treatment arms. In study VER002-4, the most frequently affected parameter were hemoglobin and hematocrit at follow up in which 4.2% and 3.4% of patients on anidulafungin and fluconazole arms, respectively had potentially clinically significant changes from baseline. Again, the reader should keep in mind the fact that blood samples invariably got to the lab 1-2 or more days following collection.

VII.12 Electrocardiographic events

Since detailed pre-clinical characterization of the electrophysiological effect of anidulafungin was neither done nor required at the early development phase of the product, an extensive electrocardiographic sampling was conducted on all patients in Study VER002-4 at screening and on Day 3 and all ECGs sent to a central laboratory in France for blinded reading. Standard procedures were used for ECG measurement and interpretation. Correction for heart rate employed both Bazett and Fridericia methods. A total of 1176 ECGs were accepted for measurement: 596 at screening and 580 "on therapy" (usually on Day 3). Tables 69, 70, and 71 below, adapted from Appendix 13 of Study VER002-4 of the application, summarize results for ECG evaluation in study VER002-4.

Table 69: Paired Data (Interval Measurements and QT Correction)

Drug	Period	QT (msec)	QTcB (msec)	QTcF (msec)	Delta QTcB (msec)	Delta QTcF (msec)
Anidulafungin N=260	Screen	345	409	386	-1.9 ± 14.7	2.0 ± 15.1
	Day 3	354	407	388		
Fluconazole N=269	Screen	348	413	389	-2.4 ± 13.3	2.4 ± 12.7
	Day 3	358	410	391		

Source: Appendix 13 of Study VER002-4 of applicant's submission

Table 70: Borderline and Outlier (Delta QTc on Paired Data)

Delta QTc	QTcB		QTcF	
	Anidulafungin	Fluconazole	Anidulafungin	Fluconazole
> 60 msec	2	4	4	2
30-60 msec	26	19	28	28

Source: Appendix 13 of Study VER002-4 of applicant's submission

Table 71: Borderline and Outlier Values for QT Interval (Uncorrected and Corrected)

		Baseline			On-Therapy		
Drug	Parameter	>500 msec	>470 msec	>450 msec	>500 msec	>470 msec	>450 msec
Anidulafungin	QT	0	1	2	0	0	1
	QTcB	0	5	12	0	5	17
	QTcF	0	3	4	0	0	1
Fluconazole	QT	0	1	3	0	1	3
	QTcB	0	3	20	0	3	22
	QTcF	0	0	5	0	1	5

Source: Appendix 13of Study VER002-4 of applicant's submission

The intent of these ECG sampling and analysis was to evaluate whether there were any observable drug effects on QT intervals. On both treatment arms in Study VER002-4, no treatment-related signals occurred in ECG. Although drug levels were obtained during

this study, they were not timed to coincide with ECG sampling, which could have better characterize QT interval changes relative to study drugs. Nevertheless, the timing of Day 3 ECG sampling was made to reflect peak concentration at steady state and so the data is reasonably valid and one could conclude that anidulafungin does not seem to be associated with prolonged QT interval. Finally, intravenous anidulafungin had no effect on the ECG data when assessed by age and by underlying diseases/conditions.

VII.13 Drug-Drug Interaction Events

The medical officer's review agrees with the applicant's finding that no pattern exists in the reporting of adverse events for patients who received concomitant medications with potential for drug-drug interaction with anidulafungin (metabolic inhibitors, metabolic inducers, or rifampin-containing medications, antiretroviral therapy, systemic corticosteroids, calcineurin inhibitors, or sirolimus). Indeed, no drug-drug interaction adverse events are reported in this application and given what is known about the pharmacokinetics and the metabolism of anidulafungin, there is a priori no reason to believe that drug-drug interaction would occur.

VII.14 Potential Impact of Demography on Safety

Pediatrics: Anidulafungin is yet to be fully evaluated in the pediatric population. No pediatric patient was exposed to andidulafungin in the current application.

Gender: There is no evidence that a particular gender is at increased risk of adverse events from anidulafungin. Please note that over 50% of subjects in the phases 2 and 3 studies in this application were women. The ability to enroll that number of women into the trials is commendable.

Other demographic characteristics: Patients older that 65 years were excluded from enrollment in study VER002-4 and 44 of the 49 patients > 65 years old included in the integrated summary of safety are drawn from the invasive candidiasis study (VER002-6). Study VER002-6 therefore provides the only opportunity in this application for an evaluation of potential impact of age.

Adverse events were reported for 93.4% (71/76) of patients <65 years and 97.7% (43/44) of patients ≥65 years. The most common AE reported for patients <65 years is vomiting, reported by 17.1% (13/76) of patients <65 years and 4.5% (2/44) of patients ≥65 years. The most common AE reported for patients ≥65 years was sepsis, reported by 18.2% (8/44) of patients ≥65 years and by 5.3% (4/76) of patients <65 years. Adverse events of anemia aggravated, abdominal distension, nausea, vomiting, peripheral edema, pyrexia, rigors, urinary tract infection, dizziness, and dyspnea were more often reported for patients <65 years than for patients ≥65 years, while AEs of sepsis, alkaline phosphatase increased, bilirubin increased, and skin necrosis were more often reported for patients ≥65 years than for patients <65 years. Given the relatively small size of study VER002-6

and the peculiarities of the study population, the data presented here should be interpreted with caution.

Data from the 120-Day Safety Update dated 09/05/03 was reviewed. The Safety Update includes safety information on 11 patients (8 patients from Study VER002-7 [phase 2/3 invasive aspergillosis study], 1 from VER002-11 [phase 2/3 azole-refractory candidiasis], and 2 from VER002-9 [phase 3 invasive candidasis study]). Thirteen SAE were reported for 8 of the 11 patients. Six patients died. None of the SAE or deaths was considered by the investigators to be related to study therapy. In addition, there were no cases of hepatobiliary SAE.

Summary of Critical Safety Findings and Limitations of Data

Review of safety of anidulafungin in the large comparative phase 3 trial did not reveal any relevant differences relative to fluconazole. However, in the maximum tolerated dose Phase 1 study, there was a dose-related and temporal trend towards mild increases in ALT, AST (< 3 x upper limit of normal [ULN]), and Alkaline Phosphatase (<1.5 x ULN). Moreover, a case of fatal hepatic necrosis was seen in the large Phase 3 esophageal candidiasis trial (VER002-4). This case was considered by the investigator to be possibly related to anidulafungin although it was quite confounded by multiple underlying medical conditions and several concomitant or recently discontinued medications that could also have contributed to hepatotoxicity. Given all these, labeling should appropriately mitigate any potential risk.

VIII. Dosing, Regimen, and Administration Issues

Data from the large single Phase 3 and the smaller Phase 2 esophageal candidiasis trials as well as the supportive Phase 2 trial of anidulafungin in patients with invasive candidiasis (predominantly candidemia) suggests a suboptimal dose might have been selected for the Phase 3 trial. In the Phase 2 esophageal candidiasis trial that used doses lower than used in the large Phase 3 study, successful outcomes were generally lower that those in the Phase 3 trial. The Phase 2 dose-ranging trial in invasive candidiasis evaluated three doses, two of which were higher than the currently proposed dose 100/50 mg, 150/75 mg, and 200/100 mg). Outcomes obtained with the 150/75 mg dose were consistently higher than with the currently proposed dose but similar to those obtained with the 200/100 mg dose. No dose-dependent safety signals were observed in the study. This suggests the optimal dose could be about 150/75 mg. Therefore, there appears to be room for the applicant to explore a more effective dose and duration of treatment for the indication of esophageal candidiasis.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

There appears to be no relevant gender effects on safety and efficacy of anidulafungin.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Pharmacology
None of the covariates gender, race, age affect the pharmacokinetics (PK) of anidulafungin. Based on PK studies conducted in patients with renal impairment and hepatic impairment, no dosage adjustment is needed.

Efficacy
There were no interactions by age, gender, race, or study site at EOT. However at follow-up, race and age appeared to have impacted outcomes. Endoscopic response rates showed a significant trend of being higher the older the subjects. Similarly, endoscopic response rates were higher in Hispanics and Asians compared to Whites and Blacks. These findings are not explained by known pharmacology of anidulafungin in humans. The significance of the findings are unclear as the trial was not powered to detect differences in special populations. However, the sponsor should gather data in the post-approval period to provide a better understanding of the efficacy of anidulafungin in these subgroups.

Safety
Given the small size of the database, the variables age, ethnicity, disease status, and geographic location are not sufficiently independent to draw conclusions regarding safety of anidulafungin. Nevertheless, available data suggest there are no discernable safety issues based on these variables.

C. Evaluation of Pediatric Program

There currently is no data on use of anidulafungin in subjects under 18 years of age.

D. Comments on Data Available or Needed in Other Populations

Patients with renal or hepatic impairment appear to tolerate doses of anidulafungin studied in this NDA and thus require no dose adjustment. Similarly, no dose adjustment is required for concomitant administration of cyclosporine.

X. Conclusions and Recommendations

A. Conclusions

Anidulafungin has activity against *Candida* species both in vitro and in vivo. Its activity in esophageal candidiasis is superior to published treatment outcomes for placebo or marginally effective therapies. However, in the predominantly AIDS population with limited anti-HIV therapy studied in the large Phase 3 esophageal candidiasis trial, it is expected that once treatment is stopped, patients will relapse as was seen on both arms although the relapse was significantly worse on the anidulafungin arm relative to the fluconazole arm.

The most common treatment-emergent adverse events considered at least possibly related to study drug included phlebitis, superficial thrombophlebitis, nausea, headache, thrombocytopenia, and cough, occurring in two patients each. Overall, adverse events profiles were similar on the two arms. Nevertheless, animal studies identified the liver as the potential target organ of toxicity for anidulafungin, as shown by slight to moderate hepatopathy with related elevations in serum alanine transominase (ALT) and aspartate transaminase (AST). In the maximum tolerated dose Phase 1 study, there was a dose-related and temporal trend towards mild increases in ALT, AST (< 3 x upper limit of normal [ULN]), and Alkaline Phosphatase (<1.5 x ULN). A case of fatal hepatic necrosis was seen in the large Phase 3 esophageal candidiasis trial (VER002-4). The event was considered possibly related to anidulafungin. This case was greatly confounded by multiple underlying medical conditions and concomitant medications. No similar event occurred on the fluconazole arm; however, a full analysis of hepatobiliary parameters found no relevant differences between the two arms. In addition, evaluation of anidulafungin in patients with varying degrees of hepatic impairment (N=20) revealed no relevant trends compared with unimpaired controls (N=7).

For a patient in whom amphotericin and the azoles are contraindicated, the only available therapeutic option is intravenous (IV) caspofungin. Intravenous anidulafungin provides an alternative to IV caspofungin. Finally, another possible role for anidulafungin is in patients presenting with esophageal candidiasis as the first diagnosis of AIDS requiring the initiation of HAART. Such a patient requires very skilled drug management to minimize potential drug-drug interactions. Treatment of the esophageal candidiasis with an azole would not be ideal, given the increased risk for such interactions.

B. Recommendations

From a clinical perspective, anidulafungin could be approved and appropriately labeled to reflect the inferior durability of response against the lowest approved dose of the comparator (given over a duration shorter than minimum of 21 days in labeling) for a non-inferiority design. Given the animal findings of hepatopathy, the finding of mild elevations in ALT, AST, and alkaline phosphates, the single

case of possibly related hepatic necrosis, and the small size of the safety database, labeling should draw appropriate attention to the potential risk for liver toxicity.

XI. Appendix

A. Other Relevant Materials: Regulatory Briefing Meeting Background Document and Minutes

Given the many issues relating to study integrity, efficacy, and safety of NDA 21-632, the application was presented at the Agency's Regulatory Briefing meeting on February 20, 2004. The Regulatory Briefing background document and meeting minutes are archived in the Division Filing System.

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I have read this review and also considered addtional information including the reviews and consults for NDA 21-632. Please see the Division Director and Deputy Office Director Review for the recommended regulatory action.