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APPLICATION NUMBER

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NDA 21-948

Statistical Review(s)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-948

Drug Name: Eraxis™ (anidulafungin) for Injection

Indication(s): Candidemia and other forms of Invasive Candidiasis

Applicant: Vicuron Pharmaceuticals Inc., a subsidiary of Pfizer, Inc.

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Biometrics Division: Division of Biometrics III

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The efficacy of anidulafungin for the treatment of candidemia in primarily non-neutropenic patients was supported by one controlled study. This study demonstrated that the overall efficacy (as assessed by the global response rate at the end of IV therapy) of anidulafungin is non-inferior to fluconazole assuming a non-inferiority margin of 20%. A small subgroup of patients in this study had candidiasis at other sites or in addition to their candidemia. There was a favorable outcome in these patients. It is left to the clinical reviewer to determine any labeling claims regarding additional infections due to *Candida* that may be made based on this data.

1.2 Brief Overview of Clinical Studies

One pivotal study, VER002-9, has been submitted to provide support for the use of anidulafungin in the treatment of candidemia. VER002-9 was a Phase 3, randomized, double-blind comparative study to evaluate the safety and efficacy of anidulafungin versus fluconazole in the treatment of candidemia and other forms of invasive candidiasis. The study was conducted at sites in the United States, Canada, Belgium, Germany, Italy, and the Netherlands. Subjects were randomized to receive either IV anidulafungin or IV fluconazole in a 1:1 ratio. Anidulafungin was administered as a loading dose of 200 mg on day 1 followed by maintenance doses of 100 mg daily thereafter. IV fluconazole was administered as a loading dose of 800 mg on day 1 followed by maintenance doses of 400 mg IV daily thereafter. Therapy was to continue for at least 14 days after the time of the last positive culture and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Patients in either group could be switched to oral fluconazole (400mg / day) after at least 10 days of IV therapy if certain criteria were met. The primary efficacy endpoint was the global response at the end of IV therapy.

1.3 Statistical Issues and Findings

A total of 261 patients were randomized to receive treatment in VER002-9. The modified intent to treat (MITT) population included 245 patients (127 in the anidulafungin group and 118 in the fluconazole group). The rates of global response at the end of IV therapy in the MITT population were 75.6% for anidulafungin and 60.2% for fluconazole. A 95% confidence interval about the difference between the success rates (anidulafungin – fluconazole) was calculated to demonstrate the non-inferiority of anidulafungin to fluconazole. The lower bound of this confidence interval was greater than the non-inferiority margin of -20%. Although the lower bound of this confidence interval was greater than zero, a claim of clinical superiority is not accepted since confirmatory evidence from a second comparative study has not been provided. The results at 2- and 6- weeks follow-up support the claim of non-inferiority of anidulafungin compared to fluconazole.

2. INTRODUCTION

2.1 Overview

This is an NDA submission for anidulafungin. Anidulafungin belongs to the echinocandin class of antifungal agents. The indication being sought by the applicant in this NDA is the treatment of candidemia and other forms of invasive candidiasis. The proposed therapeutic dose and regimen of anidulafungin for this indication is a 200 mg intravenous (IV) loading dose on the first day, followed by 100 mg IV once daily thereafter (200/100mg). NDA 21-632 for anidulafungin was previously submitted for the treatment of esophageal candidiasis and is approvable pending labeling at the time of this review.

The development program for candidemia and invasive candidiasis consisted of a single pivotal study, VER002-9. VER002-9 is a phase 3 study of the safety and efficacy of anidulafungin versus fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis. Supportive data is provided by VER002-6, an open label, dose ranging study of 3 doses (100/50 mg, 150/75 mg, and 200/100mg) of anidulafungin, and VER002-9B, an open label non-comparative extension study of VER002-9.

Reviewer's Comment: This review will focus on the pivotal candidemia study, VER002-9. Studies VER002-6 and VER002-9B are briefly mentioned in Section 5.1. For a complete discussion of these studies, please refer to the Medical Officer review by Elizabeth O'Shaughnessy, M.D.

2.2 Data Sources

The data analyzed in this review comes from the Phase 3 study of the treatment of candidemia and other forms of invasive candidiasis submitted as the pivotal evidence to support the efficacy of anidulafungin for the treatment of candidemia and other forms of invasive candidiasis. The VER002-9 study report and datasets provided in the electronic submission were reviewed. These can be found in the cross-referenced electronic submission located at:

\\Cdsesub1\n21632\N_000\2005-05-27.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study VER002-9 was a Phase 3, double-blind, randomized, non-inferiority study of anidulafungin versus fluconazole in the treatment of candidemia and other forms of invasive candidiasis. The study was conducted at 47 centers in the United States and internationally. The majority of the subjects (185) were enrolled in the United States, followed by Canada which enrolled 59 subjects. The remaining countries enrolled few subjects: Belgium (2),

Germany (3), Italy (6), and the Netherlands (1). Subjects were randomized to receive either IV anidulafungin or IV fluconazole. Therapy was to continue for at least 14 days after the time of the last positive culture and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Total duration was not to exceed 42 days.

Anidulafungin was administered as a loading dose of 200 mg IV followed by maintenance doses of 100 mg IV from day 2 onward. Fluconazole was administered as a loading dose of 800 mg IV followed by maintenance doses of 400 mg IV from day 2 onward. It was encouraged that therapy be completed with IV study medication, if possible. Patients in either group could be switched to oral fluconazole (400 mg/ day) after at least 10 days of IV therapy if all of 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.

Patients 16 years or older were enrolled in the study if they had at least one positive blood culture or positive culture of a specimen from a normally sterile site for *Candida* within 96 hours and at least one of the following:

- a fever defined as an oral/tympanic temperature $\geq 100.4^{\circ}$ F, rectal temperature $\geq 101.4^{\circ}$ F, or an axillary temperature $\geq 99.4^{\circ}$ F.
- hypothermia defined as a temperature less than 96.8° F
- 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.

Subjects were randomized to anidulafungin or fluconazole in a 1:1 ratio and stratified according to their APACHE II score (≤ 20 and >20) and absolute neutrophil count (ANC) (≤ 500 and >500).

Blood samples were taken at baseline, 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 follow-up visits. Additional cultures could be obtained at the investigator's discretion as clinically indicated. For patients whose baseline isolates (or histological evidence of infection) were obtained from samples other than blood, culture or histology from the same site was repeated as clinically indicated. Microbiological response was assessed as a success if the baseline pathogen was eradicated or presumed eradicated. A patient was considered a microbiological failure if the baseline pathogen was persistent or presumed persistent, a documented or presumed recurrence, if they had a superinfection or new infection, or if the culture data was not available.

Clinical assessments were performed at baseline, on Day 10 of IV medication, at the end of IV medication, at the end of oral study medication (if applicable), and at 2-week and 6-week follow-up visits. This assessment included a recording of the signs and symptoms of candidemia and invasive candidiasis (e.g. endophthalmitis, hemodynamic instability,

cutaneous lesions, abdominal/flank pain, nausea, vomiting, anorexia, etc). Clinical response was assessed by the investigator as the following:

- Day 10 of IV therapy
 - Success: Improvement or no worsening of signs and symptoms of the *Candida* infection
 - Failure: Worsening of signs and symptoms of the *Candida* infection
- End of IV therapy
 - Success:
 - Cure: Resolution of sign and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or oral fluconazole required to complete the course of therapy.
 - Improvement: Significant but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or oral fluconazole required
 - Failure:
 - Failure: No significant improvement in signs and symptoms of the *Candida* infection or death due to the *Candida* infection. Patient must have received at least 3 doses of study medication to be classified as a failure
 - Indeterminate: Circumstances prevented an evaluation from being made (lost to follow-up or death which could not be documented due to candidiasis or candidemia). Patients who received fewer than 3 doses of study medication had a clinical efficacy response of indeterminate.
- End of Oral Therapy
 - Success: Complete resolution or significant improvement of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment required
 - Failure:
 - Failure: No significant improvement in signs and symptoms of the *Candida* infection and additional systemic antifungal therapy was required, or death due to the *Candida* infection
 - Indeterminate: Same as for End of IV therapy.
- Follow-up visits
 - Success:
 - 2 week FU visit: a success at end of IV therapy, end of oral therapy (if applicable) and required no additional antifungal therapy
 - 6 week FU visit: a success at end of IV therapy, end of oral therapy (if applicable), 2 week FU visit, and required no additional antifungal therapy
 - Failure:
 - Failure: a failure at any previous timepoint, or a previous success with worsening signs and symptoms requiring additional antifungal therapy, or death due to the *Candida* infection
 - Indeterminate: as above

Reviewer's Comment: *As stated above, the investigator could assign patients whose death could not be documented due to candidiasis or candidemia as clinically indeterminate. For the purpose of the analyses presented in this review, these patients will be considered as failures rather than indeterminate. The implication of classifying these patients as a failure rather than indeterminate occurs primarily when determining the efficacy evaluable population (see discussion of analysis populations below).*

The primary objective of the study was to determine if anidulafungin is at least as effective as fluconazole with the respect to the global response at the end of IV therapy in the treatment of subjects with candidemia and/or other forms of invasive candidiasis. Anidulafungin was considered non-inferior to fluconazole if the lower limit of the approximate two-sided 95% confidence interval for the difference between the global response success rates (anidulafungin - fluconazole) was at least -20%, the non-inferiority margin agreed to during protocol development. Assuming a global response success rate of 70% for both treatment groups, a sample size of 222 patients was needed to demonstrate non-inferiority with 90% power. It was assumed that less than 10% of the subjects would not have a *Candida* species at baseline and would be excluded from the microbiological intent to treat (MITT) population. Therefore, 248 patients were to be enrolled. It was also assumed that 25% of the enrolled subjects would not be evaluable. With 186 evaluable patients, the study would still have sufficient power (>80%) to make statistical comparisons in this evaluable population.

The primary efficacy analysis was based on the MITT population. This population included all patients who received at least 1 dose of study medication and had a positive culture of a *Candida spp.* from a sample taken in the 96 hours prior to study entry. An efficacy evaluable population was also defined to provide supportive data to confirm the results of the MITT analysis. The efficacy evaluable population consisted of patients who met all the inclusion and exclusion criteria; received at least 7 days of IV therapy, unless declared a failure after 3 doses of study medication; did not receive additional protocol prohibited antifungal therapy; had a positive baseline culture for *Candida spp.* within 96 hours before enrollment into the study; and had a clinical or microbiological response other than indeterminate. The ITT/safety population consisted of all patients who received at least one dose of study treatment.

Reviewer's Comment: *The protocol defined the efficacy evaluable population as above. However, the Statistical Analysis Plan and Clinical Study Report define 5 separate efficacy evaluable populations, one for each of the time points. It is usually the Division's practice to define a single efficacy evaluable population based on the primary time point.*

The primary efficacy endpoint is the global response at the end of IV therapy. A subject is considered a success if they are both a clinical success and microbiological success. A subject is considered a failure if they are either a clinical or microbiological failure. A subject is considered indeterminate if there is a clinical and/or microbiological response that is indeterminate and neither response is a failure. The primary analysis is a two-step comparison of the proportion of global success between treatment groups at the end of IV

therapy. A two-sided 95% confidence interval calculated using the normal approximation to the binomial was used to estimate the difference in success rates between the treatment groups. In the first step, non-inferiority will be concluded if the lower limit of the confidence interval is not less than -0.20. The second step will be to determine if the lower limit is greater than zero. If the second step is satisfied, then anidulafungin will be considered strict-sense superior to fluconazole. Secondary endpoints included global response at the other time points, clinical response at all time points, and patient level microbiological response at all time points.

3.1.2 Patient Demographics

A total of 261 patients were randomized into the study, 132 patients were randomized to receive anidulafungin and 129 to receive fluconazole. Of the patients randomized into the study, 131 and 125 patients received at least one dose of anidulafungin and fluconazole, respectively. The MITT population included 245 patients (127 in the anidulafungin group and 118 in the fluconazole group). The FDA efficacy evaluable population consisted of 109 anidulafungin patients and 101 fluconazole patients. The most common reasons for exclusion from the efficacy evaluable population were received less than 7 days of IV therapy and not a clinical failure (12 anidulafungin and 9 fluconazole), did not have a positive baseline culture for *Candida* (4 anidulafungin and 7 fluconazole), clinical response of indeterminate at end of IV therapy (2 anidulafungin and 3 fluconazole). The remaining patients were excluded due to having ≥ 3 days of prior anti-fungal therapy but not considered a clinical failure, a violation of inclusion/exclusion criteria, and patient unblinded but not a clinical failure.

Reviewer's Comment: The above FDA efficacy evaluable population is slightly different than the efficacy evaluable at end of IV therapy population defined by the Applicant in the Clinical Study Report. The Applicant's population excluded an additional 6 anidulafungin and 10 fluconazole patients. All of these patients died but the death was not considered due to candidemia or invasive candidiasis. In the Applicant's analysis, these patients were considered clinically indeterminate or not a failure, thus meeting a reason for exclusion from the population. However, in the Division's analyses these patients are treated as failures and included in the efficacy evaluable population.

Table 1 summarizes the demographic and baseline characteristics of the MITT population. There were no significant differences across treatment groups. The study population was evenly divided between males and females. Most of the patients were white. The mean age of the patients was 57 years for the anidulafungin patients and 59 years for the fluconazole patients. Approximately 20% of the anidulafungin patients and 17% of the fluconazole patients had Apache II scores > 20 . Very few ($< 4\%$) of the patients were neutropenic (ANC ≤ 500). Approximately 3% of the patients had another site of infection in addition to candidemia and between 5 and 10% of the patients had an infection at a site other than the blood. The most common invasive candidiasis risk factors were the presence of a central venous catheter, the use of broad spectrum antibiotics, and recent surgery. All of the risk

factors observed occurred similarly across treatment groups with the exception of the use of immunosuppressive therapy which was slightly higher in the fluconazole patients.

Table 1
Demographic and Baseline Characteristics (MITT)

# Patients	Treatment Group	
	anidulafungin	fluconazole
	127	118
Gender		
Male	65 (51.2)	60 (50.8)
Female	62 (48.8)	58 (49.2)
Age mean (SD)	57 (17.1)	59.2 (16.5)
Min, max	16, 89	24, 91
Race		
White	92 (72.4)	87 (73.7)
Black	23 (18.1)	25 (21.2)
Other	12 (9.4)	6 (5.1)
Apache II Score		
≤ 20	101 (79.5)	98 (83.1)
> 20	26 (20.5)	20 (16.9)
Absolute Neutrophil Count		
> 500	124 (97.6)	114 (96.6)
≤ 500	3 (2.4)	4 (3.4)
Site of Infection		
Candidemia only	116 (91.3)	103 (87.3)
Candidemia and Invasive Candidiasis	4 (3.1)	4 (3.4)
Invasive Candidiasis only	7 (5.5)	11 (9.3)
Invasive Candidiasis Risk Factors		
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)
Other	16 (12.6)	14 (11.9)
Country		
United States	86 (67.7)	90 (76.3)
Canada	35 (27.6)	23 (19.5)
Italy	4 (3.1)	2 (1.7)
Germany	2 (1.6)	1 (0.9)
Belgium	0	1 (0.9)
Netherlands	0	1 (0.9)

3.1.3 Efficacy Results

Table 2 summarizes the results of the primary endpoint, global response at the end of IV therapy, for the MITT and FDA efficacy evaluable populations. For the MITT population, the success rate was 75.6% for anidulafungin and 60.2% for fluconazole. The lower limit of

the 95% confidence interval about the difference in response rates is greater than the non-inferiority margin of -20%. Since the lower limit of the confidence interval is greater than 0, it can be said that anidulafungin was statistically superior to fluconazole in the MITT population. The FDA efficacy evaluable results support the claim of non-inferiority of anidulafungin compared to fluconazole.

Table 2
Global Response at End of IV Therapy

	Anidulafungin	fluconazole	Difference and 95% CI*
MITT	96/127 (75.6)	71/118 (60.2)	15.4 (3.0, 27.8)
FDA Evaluable	90/ 109 (82.6)	68/101 (67.3)	15.3 (2.8, 27.8)

*A difference (anidulafungin- fluconazole) and 95% confidence interval is reported.

Reviewer's Comment: The 95% confidence intervals reported in this review are slightly different than those reported in the Applicant's study report since a continuity correction is applied in the calculation of the confidence intervals presented in this review. The conclusions drawn, however, are the same.

Table 3 summarizes the global response rates at the follow-up visits for the MITT population. At both follow-up visits, anidulafungin was non-inferior to fluconazole for the proportion of patients with global success.

Table 3
Global Response at Follow-up Visits (MITT population)

	anidulafungin n=127	fluconazole n=118	Difference and 95% CI*
2 week follow-up	82 (64.6)	58 (49.2)	15.4 (2.3, 28.5)
6 week follow-up	71 (55.9)	52 (44.1)	11.8 (-1.5, 25.1)

*A difference (anidulafungin- fluconazole) and 95% confidence interval is reported.

Global response at follow-up in the FDA evaluable population and clinical and microbiological response at all time points showed consistent results. (results not shown)

3.2 Evaluation of Safety

A total of 130 patients (99.2%) in the anidulafungin group and 122 patients (97.6%) in the fluconazole group had at least one clinical adverse event. Serious adverse events were reported in 65 (49.6%) anidulafungin patients and 71 (56.8%) fluconazole patients. There were 68 deaths during the study, 29 patients (22.1%) from the anidulafungin group and 39 patients (31.2%) from the fluconazole group. One additional anidulafungin patient died after the 6-week follow-up visit. Although the number of deaths are numerically fewer in the anidulafungin arm, the difference does not reach statistical significance (p=0.16).

For a detailed review of the safety data, please see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The following table summarizes the number of patients who had a successful global response at the end of IV therapy for gender, race, and age. There are no significant treatment by subgroup interactions. Anidulafungin subjects had higher success rates than fluconazole patients in all subgroups with the exception of black subjects where fluconazole treated subjects had a slightly higher success rate.

Table 4
Subgroup Analyses Global Response at End of IV Therapy
MITT Population

	Treatment Group	
	anidulafungin	fluconazole
Gender		
Male	48/65 (73.9)	39/60 (65.0)
Female	48/62 (77.4)	32/58 (55.2)
Age		
≤ 65	62/84 (73.8)	45/72 (62.5)
> 65	34/43 (79.1)	26/46 (56.5)
Race		
White	73/92 (79.4)	52/87 (59.8)
Black	14/23 (60.9)	16/25 (64.0)
Others	9/12 (75.0)	3/6 (50.0)

4.2 Other Special/Subgroup Populations

The study was stratified at randomization by Apache II score and ANC. There were too few subjects with an ANC ≤ 500 to make any conclusions by ANC. For patients with an Apache II score ≤ 20 at baseline, global success at end of IV therapy was 82/101 (81.2%) for patients treated with anidulafungin and 60/98 (61.2%) for patients treated with fluconazole. The global response rate at end of IV therapy for patients with an Apache II score >20, which is indicative of a sicker population, was similar between treatment groups: 14/26 (53.9) anidulafungin vs. 11/20 (55.0) fluconazole.

The study was primarily performed on a population of subjects with candidemia. There was a small proportion of subjects who had another site of infection with or without candidemia. The global response rates at end of IV therapy for the subgroup of patients with candidemia only was 88/116 (75.9%) anidulafungin vs. 63/103 (61.2%) fluconazole. The success rate for patients with other forms of invasive candidiasis was 8/11 (72.7%) anidulafungin patients and 8/15 (53.5%) fluconazole subjects.

The study was an international study though primarily conducted in the United States. The global response rates for the patients treated in the United States were similar to that of the overall population. MITT patients in the United States treated with anidulafungin had a

global response of 73.3% compared to 61.1% for MITT patients in the United States treated with fluconazole. The difference between treatment groups was 12.2% (95% CI: -2.7, 27.1). This treatment comparison only supports non-inferiority of anidulafungin compared to fluconazole. The global response rate for MITT patients in the remaining countries treated with anidulafungin (80.5%) was greater than that seen for the overall population. Whereas those MITT patients in the remaining countries treated with fluconazole had global response rates (57.1%) lower than those seen for the overall population. Upon further investigation of the individual study sites, it was noted that Site 41 from Canada which enrolled the largest number of patients in the study (10% of the study population) had near perfect global success rates for anidulafungin (14/15) compared to only 50% for fluconazole treated patients (5/10). When this site is excluded from the analysis, the global response rates for patients treated in the remaining countries is similar to those seen in the United States (73.1% anidulafungin and 61.1% fluconazole).

Table 5 summarizes the global response rates at end of IV therapy for the additional subgroups discussed above for the MITT population.

Table 5
Additional Subgroup Analyses Global Response at End of IV Therapy
MITT Population

	Treatment Group	
	anidulafungin	fluconazole
Apache II		
≤ 20	82/101 (81.2)	60/98 (61.2)
>20	14/26 (53.9)	11/20 (55.0)
Type of Infection		
Candidemia only	88/116 (75.9)	63/103 (61.2)
Other forms of Invasive Candidiasis	8/11 (72.7)	8/15 (53.5)
Country		
United States	63/86 (73.3)	55/90 (61.1)
Non-US	33/41 (80.5)	16/28 (57.1)
Excluding site 41	19/26 (73.1)	11/18 (61.1)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The results of the single pivotal study (VER002-9) submitted to support the use of anidulafungin for the treatment of candidemia and other forms of invasive candidiasis suggest that anidulafungin is superior to fluconazole as assessed by the global response at end of IV therapy for the MITT population. Since only a single comparative study was submitted, confirmatory evidence to support the claim of superiority to fluconazole has not been provided. As discussed in Section 4.2, it appears that Site 41 which enrolled the largest number of patients in the study (10% of the study) may be driving the statistical significance. The demographic and baseline characteristics of Site 41 do not differ from that of the overall

MITT population, with the exception that fluconazole patients treated at this site were slightly older than the overall population (mean age of fluconazole patients at Site 41 was 67 years), to explain why this site may have had such favorable results for anidulafungin or less favorable results for fluconazole. When Site 41 is excluded from the analysis of the overall MITT population, the global response rate is 73.2% (82/112) for anidulafungin treated patients and 61.1% (66/108) for fluconazole treated patients. The 95% confidence interval about the difference of 12.1% is (-1.1, 25.3). This treatment comparison supports only a claim of non-inferiority. Due to this finding and the lack of a confirmatory study, superiority of anidulafungin compared to fluconazole has not been clearly demonstrated for the treatment of candidemia and other forms of invasive candidiasis.

Additional evidence that anidulafungin is effective in the treatment of candidemia and other forms of invasive candidiasis comes from the dose ranging trial, VER002-6, of 3 doses of anidulafungin in invasive candidiasis including candidemia and the open label non-comparative extension study of VER002-9. Study VER002-6 enrolled and treated 120 patients to each of the three dose groups (100/50 mg, 150/75 mg, and 200/100mg). The sponsor concluded that the efficacy data indicated a trend favoring the 2 higher doses. However, there was not enough power to detect either a statistically significant trend among all three doses or a statistically significant difference between the lowest dose and the 200/100 mg dose, their proposed dose in this indication. VER002-9 enrolled 33 patients of which 31 were included in the MITT population. Global response at the end of IV therapy was 21 of 31 (67.7%) patients. For a complete discussion of these studies see the Medical Officer review.

5.2 Conclusions and Recommendations

In a single Phase 3 study of anidulafungin versus fluconazole in the treatment of candidemia in primarily non-neutropenic patients, anidulafungin was shown to be non-inferior to fluconazole. The majority of the subjects in this study had candidemia without more invasive involvement. There was a favorable outcome in a small subgroup of subjects who had candidiasis at other deep tissue sites. The decision as to whether these subjects are sufficient to make any labeling claims regarding additional infections due to *Candida* is left to the clinical reviewer.

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Statistical Reviewer's Memorandum

To: NDA 21-632

From: Cheryl Dixon, Ph.D.
Biostatistician, Division of Biometrics III

Through: Karen Higgins, Sc.D.
Statistical Team Leader, Division of Biometrics III

Re: Addendum to Statistical Review dated March 29, 2004

Date: November 15, 2005

General

The original NDA for anidulafungin was submitted April 25, 2003. On May 21, 2004, an approvable letter was sent to the Applicant. The Action Letter stated that a satisfactory risk/benefit ratio for the use of anidulafungin for the treatment of esophageal candidiasis had not been demonstrated. This was due to a possible signal for hepatotoxicity and that the esophageal candidiasis study (VER002-4) demonstrated that anidulafungin had a higher relapse rate at the two-week post therapy visit than the comparator therapy (see Statistical Review and Evaluation dated March 29, 2005 for a complete review of Study VER002-4). In order to address the concern regarding hepatotoxicity, the Applicant was required to further characterize the safety profile of anidulafungin. In order to address the concern regarding the efficacy of anidulafungin, the Applicant was required to provide additional clinical data to address the observed high relapse rate of anidulafungin and/or provide supportive evidence of anidulafungin's efficacy as an anti-candidal agent. An adequate and well-controlled study that demonstrated the efficacy of anidulafungin in another infection due to *Candida* spp. would not support labeling of anidulafungin as initial therapy in esophageal candidiasis, however, since this study would not be able to address the high relapse rate observed in Study VER002-4 which studied esophageal candidiasis.

On May 27, 2005, the Applicant provided a complete response to the approvable action letter. Included in this submission are efficacy and safety data from several studies including study VER002-9. VER002-9 is a phase 3 study of the safety and efficacy of anidulafungin versus fluconazole in the treatment of patients with candidemia and other forms of invasive candidiasis. This study was submitted to provide the supportive evidence of anidulafungin efficacy in other *Candida* infections. Thus, the Applicant has revised the indication being sought in this submission to second line treatment of esophageal candidiasis. The proposed dose and regimen of anidulafungin for esophageal candidiasis is a 100 mg IV loading dose on the first day followed by 50 mg IV once daily for 14 to 21 days.

The remainder of the memorandum will provide a brief review of the efficacy data from study VER002-9. For a complete review of this study, please see the Statistical Review and Evaluation of NDA 21-948. Please see the Medical Officer review for the review of the safety data in the resubmission which addresses the Division's concern regarding the possible signal for hepatotoxicity.

VER002-9

Study VER002-9 was a Phase 3, double-blind, randomized, non-inferiority study of anidulafungin versus fluconazole in the treatment of candidemia and other forms of invasive candidiasis. The study was conducted at 47 centers in the United States and internationally. The majority of the subjects (185) were enrolled in the United States, followed by Canada which enrolled 59 subjects. The remaining countries enrolled few subjects: Belgium (2), Germany (3), Italy (6), and the Netherlands (1). Subjects were randomized to receive either IV anidulafungin or IV fluconazole. Therapy was to continue for at least 14 days after the time of the last positive culture and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Total duration was not to exceed 42 days. Anidulafungin was administered as a loading dose of 200 mg IV followed by maintenance doses of 100 mg IV from day 2 onward. Fluconazole was administered as a loading dose of 800 mg IV followed by maintenance doses of 400 mg IV from day 2 onward. It was encouraged that therapy be completed with IV study medication, if possible. Patients in either group could be switched to oral fluconazole (400 mg/ day) after at least 10 days if protocol specified criteria were met.

Patients enrolled in the study were 16 years or older who had at least one positive blood culture or positive culture of a specimen from a normally sterile site for *Candida* within 96 hours and at least one of the following clinical features: a fever defined as an oral/tympanic temperature $\geq 100.4^{\circ}$ F, rectal temperature $\geq 101.4^{\circ}$ F, or an axillary temperature $\geq 99.4^{\circ}$ F; hypothermia defined as a temperature less than 96.8° F; 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. Subjects were randomized to anidulafungin or fluconazole in a 1:1 ratio and stratified according to their APACHE II score (≤ 20 and >20) and absolute neutrophil count (ANC) (≤ 500 and >500).

Blood samples were taken at baseline, 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 follow-up visits. Additional cultures could be obtained at the investigator's discretion as clinically indicated. For patients whose baseline isolates (or histological evidence of infection) were obtained from samples other than blood, culture or histology from the same site was repeated as clinically indicated. Microbiological response was assessed as a success if the baseline pathogen was eradicated or presumed eradicated. A patient was considered a microbiological failure if the baseline pathogen was persistent or presumed persistent, a documented or presumed

recurrence, if they had a superinfection or new infection, or if the culture data was not available.

Clinical assessments were performed at baseline, on Day 10 of IV medication, at the end of IV medication, at the end of oral study medication (if applicable), and at 2-week and 6-week follow-up visits. This assessment included a recording of the signs and symptoms of candidemia and invasive candidiasis (e.g. endophthalmitis, hemodynamic instability, cutaneous lesions, abdominal/flank pain, nausea, vomiting, anorexia, etc). Clinical response was assessed by the investigator at the end of IV therapy as the following:

- Success:
 - Cure: Resolution of sign and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or oral fluconazole required to complete the course of therapy.
 - Improvement: Significant but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or oral fluconazole required
- Failure:
 - Failure: No significant improvement in signs and symptoms of the *Candida* infection or death due to the *Candida* infection. Patient must have received at least 3 doses of study medication to be classified as a failure
 - Indeterminate: Circumstances prevented an evaluation from being made (lost to follow-up or death which could not be documented due to candidiasis or candidemia). Patients who received fewer than 3 doses of study medication had a clinical efficacy response of indeterminate.

At the follow-up visits, clinical response was assessed by the investigator as:

- Success:
 - 2 week FU visit: a success at end of IV therapy, end of oral therapy (if applicable) and required no additional antifungal therapy
 - 6 week FU visit: a success at end of IV therapy, end of oral therapy (if applicable), 2 week FU visit, and required no additional antifungal therapy
- Failure:
 - Failure: a failure at any previous timepoint, or a previous success with worsening signs and symptoms requiring additional antifungal therapy, or death due to the *Candida* infection
 - Indeterminate: as defined at end of IV therapy.

Reviewer's Comment: *As stated above, the investigator could assign patients whose death could not be documented due to candidiasis or candidemia as clinically indeterminate. For the purpose of the analyses presented in this review, these patients will be considered as failures rather than indeterminate. The implication of classifying*

these patients as a failure rather than indeterminate occurs primarily when determining the efficacy evaluable population (see discussion of analysis populations below).

The primary objective of the study was to determine if anidulafungin is at least as effective as fluconazole with respect to the global response at the end of IV therapy in the treatment of subjects with candidemia and/or other forms of invasive candidiasis. Anidulafungin was considered non-inferior to fluconazole if the lower limit of the approximate two-sided 95% confidence interval for the difference between the global response success rates (anidulafungin - fluconazole) was at least -20%, the non-inferiority margin agreed to during protocol development. Assuming a global response success rate of 70% for both treatment groups, a sample size of 222 patients was needed to demonstrate non-inferiority with 90% power. It was assumed that less than 10% of the subjects would not have a *Candida* species at baseline and would be excluded from the microbiological intent to treat (MITT) population. Therefore, 248 patients were to be enrolled. It was also assumed that 25% of the enrolled subjects would not be evaluable. With 186 evaluable patients, the study would still have sufficient power (>80%) to make statistical comparisons in the evaluable population.

The primary efficacy analysis was based on the MITT population. This population included all patients who received at least 1 dose of study medication and had a positive culture of a *Candida spp.* from a sample taken in the 96 hours prior to study entry. An efficacy evaluable population was also defined to provide supportive data to confirm the results of the MITT analysis. The efficacy evaluable population consisted of patients who met all the inclusion and exclusion criteria; received at least 7 days of IV therapy, unless declared a failure after 3 doses of study medication; did not receive additional protocol prohibited antifungal therapy; had a positive baseline culture for *Candida spp.* within 96 hours before enrollment into the study; and had a clinical or microbiological response other than indeterminate. The ITT/safety population consisted of all patients who received at least one dose of study treatment.

Reviewer's Comment: The protocol defined the efficacy evaluable population as above. However, the Statistical Analysis Plan and Clinical Study Report define 5 separate efficacy evaluable populations, one for each of the time points. It is usually the Division's practice to define a single efficacy evaluable population based on the primary time point.

The primary efficacy endpoint is the global response at the end of IV therapy. A subject is considered a success if they are both a clinical success and microbiological success. A subject is considered a failure if they are either a clinical or microbiological failure. A subject is considered indeterminate if there is a clinical and/or microbiological response that is indeterminate and neither response is a failure. The primary analysis is a two-step comparison of the proportion of global success between treatment groups at the end of IV therapy. A two-sided 95% confidence interval calculated using the normal approximation to the binomial distribution was used to estimate the difference in success rates between the treatment groups. In the first step, non-inferiority will be concluded if the lower limit of the confidence interval is not less than -0.20. The second step will be

to determine if the lower limit is greater than zero. If the second step is satisfied, then anidulafungin will be considered strict-sense superior to fluconazole. Secondary endpoints included global response at the other time points, clinical response at all time points, and patient level microbiological response at all time points.

- **Results**

A total of 261 patients were randomized into the study, 132 patients were randomized to receive anidulafungin and 129 to receive fluconazole. Of the patients randomized into the study, 131 and 125 patients received at least one dose of anidulafungin and fluconazole, respectively. The MITT population included 245 patients (127 in the anidulafungin group and 118 in the fluconazole group). The FDA efficacy evaluable population consisted of 109 anidulafungin patients and 101 fluconazole patients. The most common reasons for exclusion from the efficacy evaluable population were received less than 7 days of IV therapy and not a clinical failure (12 anidulafungin and 9 fluconazole), did not have a positive baseline culture for *Candida* (4 anidulafungin and 7 fluconazole), clinical response of indeterminate at end of IV therapy (2 anidulafungin and 3 fluconazole). The remaining patients were excluded due to having ≥ 3 days of prior anti-fungal therapy but not considered a clinical failure, a violation of inclusion/exclusion criteria, and patient unblinded but not a clinical failure.

Reviewer's Comment: The above FDA efficacy evaluable population is slightly different than the efficacy evaluable at end of IV therapy population defined by the Applicant in the Clinical Study Report. The Applicant's population excluded an additional 6 anidulafungin and 10 fluconazole patients. All of these patients died but the death was not considered due to candidemia or invasive candidiasis. In the Applicant's analysis these patients were considered clinically indeterminate or not a failure, thus meeting a reason for exclusion from the population. However, in the Division's analyses these patients are treated as failures and included in the efficacy evaluable population.

Table 1 summarizes the demographic and baseline characteristics of the MITT population. There were no significant differences across treatment groups. The study population was evenly divided between males and females. Most of the patients were white. The mean age of the patients was 57 years for the anidulafungin patients and 59 years for the fluconazole patients. Approximately 20% of the anidulafungin patients and 17% of the fluconazole patients had Apache II scores > 20 . Very few ($< 4\%$) of the patients were neutropenic ($ANC \leq 500$). Approximately 3% of the patients had another site of infection in addition to candidemia and between 5 and 10% of the patients had an infection at a site other than the blood. The most common invasive candidiasis risk factors were the presence of a central venous catheter, the use of broad spectrum antibiotics, and recent surgery. All of the risk factors observed occurred similarly across treatment groups with the exception of the use of immunosuppressive therapy which was slightly higher though not statistically significant in the fluconazole patients.

Table 1**Demographic and Baseline Characteristics (MITT)**

	Treatment Group	
	anidulafungin	fluconazole
# Patients	127	118
Gender		
Male	65 (51.2)	60 (50.8)
Female	62 (48.8)	58 (49.2)
Age mean (SD)	57 (17.1)	59.2 (16.5)
Min, max	16, 89	24, 91
Race		
White	92 (72.4)	87 (73.7)
Black	23 (18.1)	25 (21.2)
Other	12 (9.4)	6 (5.1)
Apache II Score		
≤ 20	101 (79.5)	98 (83.1)
> 20	26 (20.5)	20 (16.9)
Absolute Neutrophil Count		
> 500	124 (97.6)	114 (96.6)
≤ 500	3 (2.4)	4 (3.4)
Site of Infection		
Candidemia only	116 (91.3)	103 (87.3)
Candidemia and Invasive Candidiasis	4 (3.1)	4 (3.4)
Invasive Candidiasis only	7 (5.5)	11 (9.3)
Invasive Candidiasis Risk Factors		
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)
Other	16 (12.6)	14 (11.9)
Country		
United States	86 (67.7)	90 (76.3)
Canada	35 (27.6)	23 (19.5)
Italy	4 (3.1)	2 (1.7)
Germany	2 (1.6)	1 (0.9)
Belgium	0	1 (0.9)
Netherlands	0	1 (0.9)

Table 2 summarizes the results of the primary endpoint, global response at the end of IV therapy, for the MITT and FDA efficacy evaluable populations. For the MITT population, the success rate was 75.6% for anidulafungin and 60.2% for fluconazole. The lower limit of the 95% confidence interval about the difference in response rates is greater than the non-inferiority margin of -20%. Since the lower limit of the confidence interval is greater than 0, it can be said that anidulafungin was statistically superior to fluconazole in the MITT population. The results of the FDA efficacy evaluable population support the results of the MITT population.

Table 2

Global Response at End of IV Therapy

	anidulafungin	fluconazole	Difference and 95% CI [*]
MITT	96/127 (75.6)	71/118 (60.2)	15.4 (3.0, 27.8)
FDA evaluable	90/ 109 (82.6)	68/101 (67.3)	15.3 (2.8, 27.8)

^{*}A difference (anidulafungin- fluconazole) and 95% confidence interval is reported.

Reviewer's Comment: *The 95% confidence intervals reported in this review are slightly different than those reported in the Applicant's study report since a continuity correction is applied in the calculation of the confidence intervals presented in this review. The conclusions drawn, however, are the same.*

The study was an international study though primarily conducted in the United States. The global response rates for the MITT patients treated in the United States were similar to that of the overall MITT population. MITT patients in the United States treated with anidulafungin had a global response of 73.3% compared to 61.1% for MITT patients in the United States treated with fluconazole. The difference between treatment groups was 12.2% (95% CI: -2.7, 27.1). This treatment comparison only supports non-inferiority of anidulafungin compared to fluconazole. The global response rate for MITT patients in the remaining countries treated with anidulafungin (80.5%) was greater than that seen for the overall MITT population. Whereas those MITT patients in the remaining countries treated with fluconazole had a global response rate (57.1%) lower than that seen for the overall population. Upon further investigation of the individual study sites, it was noted that Site 41 from Canada which enrolled the largest number of patients in the study had near a perfect global success rate for anidulafungin (14/15) compared to only 50% for fluconazole treated patients (5/10). When this site is excluded from the analysis, the global response rates for patients treated in the remaining countries is similar to those seen in the United States (73.1% anidulafungin and 61.1% fluconazole). When Site 41 is removed from the analysis of the overall MITT population, the global response rate is 73.2% (82/112) for anidulafungin and 61.1% (66/108) for fluconazole treated patients. The 95% confidence interval about the difference of 12.1% is (-1.1, 25.3). This treatment comparison supports a claim of non-inferiority.

Table 3 summarizes the global response rates at the follow-up visits for the MITT population. At both follow-up visits, anidulafungin was non-inferior to fluconazole for the proportion of patients with global success.

Table 3

Global Response at End of IV Therapy (MITT population)

	anidulafungin n=127	fluconazole n=118	Difference and 95% CI [*]
2 week follow-up	82 (64.6)	58 (49.2)	15.4 (2.3, 28.5)
6 week follow-up	71 (55.9)	52 (44.1)	11.8 (-1.5, 25.1)

^{*}A difference (anidulafungin- fluconazole) and 95% confidence interval is reported.

Conclusions and Recommendations

As previously discussed (see original Statistical Review and Evaluation dated March 29, 2005), anidulafungin was shown to be as effective as oral fluconazole in the treatment of esophageal candidiasis when measured at the end of therapy. The results of study VER002-9 provide the supportive evidence of the efficacy of anidulafungin for the treatment of other *Candida* infections primarily candidemia. This study, however, did not address the high relapse rate of anidulafungin observed in the esophageal candidiasis study. Any labeling of anidulafungin for the treatment of esophageal candidiasis, second line or not as initial treatment, should clearly describe the significantly higher relapse rate that was observed 2 weeks following end of therapy with anidulafungin.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 21-632

Drug Name: anidulafungin for injection

Indication(s): Treatment of esophageal candidiasis

Applicant: Vicuron Pharmaceutical Inc

Date(s): Stamp date: April 25, 2003
Original PDUFA date: February 25, 2004
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Biometrics Division: Division of Biometrics III (HFD-725)

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Keywords: clinical studies, NDA review, one study application, robustness of evidence, anti-fungal, esophageal candidiasis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In a single Phase 3 study of anidulafungin (100/50 mg) versus fluconazole (200/100 mg) in the treatment of esophageal candidiasis, anidulafungin was shown to be non-inferior to fluconazole at the End of Therapy (EOT). However, by 2 weeks following EOT, significantly more patients who received anidulafungin relapsed compared to those patients who received fluconazole.

The dose of anidulafungin chosen for this Phase 3 study was based on a small dose ranging study that tested two doses (70/35 mg and 50/25 mg) that were lower than the dose used in this study. There is also preliminary evidence from a dose ranging study of invasive candidiasis that a higher dose (200/100 mg) may be needed for that indication. Due to the significant increase in relapse only two weeks following end of treatment, it is of concern as to whether the appropriate dose has been chosen for the treatment of esophageal candidiasis. It is therefore recommended that an additional dose ranging study be performed including the dose studied in this Phase 3 study and at least one higher dose. This study would investigate whether the amount of relapse can be improved upon with increased doses. It may also be useful to include a fluconazole arm to provide a positive control.

1.2 Brief Overview of Clinical Studies

One pivotal study, VER002-4, has been submitted to provide support for the use of anidulafungin in the treatment of esophageal candidiasis. Study VER002-4 was a Phase 3 randomized, double-blind, double-dummy, non-inferiority study of anidulafungin versus fluconazole. The study was conducted at sites in South Africa, Argentina, Thailand, and the United States/ Puerto Rico. The majority of the patients were enrolled in South Africa. Subjects were randomized to receive either IV anidulafungin + PO placebo or IV placebo + oral fluconazole. Anidulafungin was administered as a loading dose of 100 mg on Day 1 followed by maintenance doses of 50 mg daily from Day 2. Fluconazole was administered orally as a 200 mg loading dose on Day 1 followed by maintenance doses of 100 mg orally from Day 2. Therapy was to be discontinued between Days 14 and 21 for patients who had remained symptom free for exactly 7 days. The primary efficacy endpoint was endoscopic response at end of therapy (EOT). Secondary endpoints included endoscopic response at follow-up (FU), clinical response at EOT and FU, and mycological response at EOT and FU.

Two additional studies were submitted to provide supportive evidence, XBAF and VER002-6. XBAF was a Phase 2, randomized, dose ranging, proof of concept efficacy study of anidulafungin in esophageal candidiasis. In this study, patients were randomized to either anidulafungin 70/35 mg or 50/25 mg. Both of the doses used in this study are lower than the proposed dose in this NDA. VER002-6 was a dose ranging study of anidulafungin in patients with invasive candidiasis, including candidemia. This study used the dose being

sought in esophageal candidiasis (100/50 mg) as well as 2 higher doses (150/75 mg and 200/100 mg).

1.3 Statistical Issues and Findings

The use of studies XBAF and VER002-6 to support the indication of the treatment of esophageal candidiasis at a daily anidulafungin dose of 50 mg is limited. Study XBAF demonstrated a marginal dose response, with a higher proportion of successful response in the higher dose group. The two doses used in this study, however, are lower than the proposed 50 mg daily dose. VER002-6 also demonstrated a marginal dose response favoring higher doses of anidulafungin. These doses are higher than the proposed 50 mg daily dose.

Thus, the primary evidence to support the indication of the treatment of esophageal candidiasis at a daily dose of 50 mg comes from a single study, VER002-4. A total of 601 patients were randomized to receive study treatment, 300 were randomized to receive anidulafungin and 301 to receive fluconazole. The clinically evaluable population consisted of 249 anidulafungin patients and 255 fluconazole patients. The rates of endoscopic success at EOT for the clinically evaluable population were 97.2% for anidulafungin and 98.8% for fluconazole. A 95% confidence interval about the difference between the success rates (anidulafungin – fluconazole) was calculated to demonstrate the non-inferiority of anidulafungin to fluconazole. The lower bound of the confidence interval was greater than the non-inferiority margin of -10%. The ITT results support the claim of non-inferiority of anidulafungin compared to fluconazole. The results for clinical response at EOT are similar to those seen for endoscopic response. Mycological response rates at EOT are high for both treatment groups. Though not prespecified, this endpoint would not satisfy a claim of non-inferiority of anidulafungin assuming a margin of 10%.

In addition to the EOT assessments, assessments were made a 2 week follow-up visit. Only 37.8% of anidulafungin patients compared to 67.5% of fluconazole patients had a sustained successful endoscopic response at the follow-up visit. The difference between these rates is statistically significant ($p < 0.0001$) indicating that anidulafungin has a lower endoscopic success rate than fluconazole at follow-up. Of the patients who had a successful response at EOT, 54.5% of anidulafungin patients and 21.8% of fluconazole patients relapsed at follow-up. The extent of relapse was characterized by comparing the endoscopy grade at follow-up to baseline. Significantly more of the anidulafungin patients relapsed back to their baseline level or worse compared to fluconazole patients. The results for clinical and mycological response at follow-up support those seen for endoscopic response at follow-up.

Following the completion of the study but prior to unblinding study results, the Applicant notified the Division of an error that occurred with the labeling of the treatment kits that were sent to approximately 70% of the subjects enrolled in the study. The error resulted in a 1:1 reversal of the assignment of the kits to Arm A or Arm B. The Applicant was able to reconstruct a corrected patient treatment assignment table prior to unblinding the study. The Division believes that the Applicant has adequately addressed the kit assignment problem and reconstructed the appropriate patient treatment assignment table. Analyses to confirm this indicate that the results at EOT are robust to the treatment kit assignment problem, while

the results at follow-up using the reconstructed treatment assignments are very much against anidulafungin.

As part of the plan to determine the cause of the kit assignment problem, it was found that some patients had some plasma samples that contained both drugs. Fifty-two percent of these patients were from 1 site, Site 019. Since there was concern about the validity of the data from this site, endoscopic response at EOT and follow-up were reanalyzed excluding this site. The results excluding Site 019 are consistent with the results for the entire study.

Finally, there was concern about having only a single study to support a single indication NDA for a non-life threatening disease. If a conservative alpha of $0.00125 = 2 * (0.05/2)^2$ is applied to this study, non-inferiority of anidulafungin to fluconazole with respect to endoscopic success at EOT and inferiority of anidulafungin at follow-up would still be claimed. Therefore, this study is robust to provide enough evidence that might have been seen had two studies been performed.

2. INTRODUCTION

2.1 Overview

This is the original NDA submission for anidulafungin. Anidulafungin belongs to the echinocandin class and is intended for the treatment of fungal infections. The indication being sought by the applicant in this NDA is the treatment of esophageal candidiasis. The proposed therapeutic dose and regimen of anidulafungin for esophageal candidiasis is a 100 mg intravenous (IV) loading dose on the first day, followed by 50 mg IV once daily for 14 to 21 days (100/50).

One pivotal study, VER002-4, has been submitted to provide support for the use of anidulafungin. VER002-4 was a Phase 3 study to assess the safety and efficacy of anidulafungin for the treatment of esophageal candidiasis. This study was designed to demonstrate that IV anidulafungin (100/50 mg for 14-21 days) is at least as efficacious as the current standard of care, oral fluconazole. Patients received 200/100 mg oral fluconazole for up to 21 days. During the design phase of this study, the Division raised concerns regarding the dose of fluconazole chosen. While 100 mg of fluconazole is an approved dosage, it is lower than what has been used in recent studies. (A study of caspofungin used a fluconazole comparator of 200mg IV and a study of voriconazole used 200 mg oral fluconazole). The sponsor was informed that due to this concern and the fact that only 1 pivotal study would be submitted there would be no room for less than robust findings (January 31, 2002 meeting minutes). In addition, the recommended duration of 100 mg of fluconazole is a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms. The sponsor was also informed that if a large number of fluconazole patients stopped treatment at 14 days and then relapsed that this would cause problems with the interpretation of the study results since fluconazole was given for less than its indicated duration (personal notes from January 12, 2001 teleconference).

Two additional studies were submitted to provide supportive evidence, XBAF and VER002-6. XBAF was a Phase 2, randomized, dose ranging, proof of concept efficacy study of anidulafungin in esophageal candidiasis. In this study, patients were randomized to either anidulafungin 70/35 mg (17 patients) or 50/25 mg (19 patients). A non-significant dose response was demonstrated in this study, with a higher proportion of successful responses in the higher dose group. Both of the doses used in this study, however, are lower than the proposed dose for this NDA. Therefore, this study will not be discussed further in this review. VER002-6 was a dose ranging study of anidulafungin in patients with invasive candidiasis, including candidemia. This study used the dose being sought in esophageal candidiasis (100/50 mg) as well as 2 higher doses (150/75 mg and 200/100 mg). Forty patients were randomized to each dose group. As with XBAF, a dose response favoring the higher doses of anidulafungin was demonstrated in this study. Due to the non-comparative nature of this study and the difference in the populations being studied, this study will not be discussed further in this review. See Medical Officer review for a complete discussion of these studies.

2.2 Data Sources

The data analyzed in this review comes from the pivotal, Phase 3 study submitted as primary support. The VER002-4 study report and datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at:
\\Cdsub1\21632\N_000\2003-04-25.

3. STATISTICAL EVALUATION

The remainder of this review will focus on the pivotal study VER002-4.

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study VER002-4 was a Phase 3 randomized, double-blind, double-dummy, non-inferiority study of anidulafungin administered intravenously to patients with esophageal candidiasis. The study was conducted at 26 sites in South Africa (11), Argentina (10), Thailand (3), and the United States/ Puerto Rico (2). South Africa randomized the largest number of patients overall, followed by Thailand and Argentina. Subjects were randomized to receive either IV anidulafungin + PO placebo or IV placebo + oral fluconazole. Anidulafungin was administered as a loading dose of 100 mg on Day 1 followed by maintenance doses of 50 mg daily from Day 2. Fluconazole was administered orally as a 200 mg loading dose on Day 1 followed by maintenance doses of 100 mg orally from Day 2. Therapy was to be discontinued between Days 14 and 21 for patients who had remained symptom free for exactly 7 days.

Male or female patients between the ages of 18 and 65 years with esophageal candidiasis were enrolled in the study. The diagnosis of esophageal candidiasis was based on

endoscopic findings (grade 1 or higher), clinical symptoms (odynophagia, dysphagia, and/or retrosternal pain), and mycology (isolation of *Candida* species or evidence of yeast on microscopy). Endoscopies were graded as 0 (normal esophageal mucosa), 1 (individual plaques each ≤ 2 mm in size), 2 (individual plaques each > 2 mm in size), or 3 (confluent plaques and/or increased friability of mucosa). The clinical symptoms were assessed as absent, mild, moderate, or severe. Endoscopic evaluations, clinical evaluations, and cultures were made at baseline, the end of therapy (EOT), and at the earlier of 1) a sign of clinical recurrence and/or requirement for additional systemic antifungal therapy or 2) 2 weeks following EOT.

Intent-to-treat (ITT) and evaluable analysis populations were defined. The ITT population included all patients who were randomized and received at least one dose of study medication. The clinically evaluable population included patients who completed at least 10 days of therapy, received an EOT endoscopy, and did not have any protocol violations that impacted the assessment of efficacy. The mycologically evaluable population included patients who were clinically evaluable and had a positive baseline culture for *Candida* species.

Reviewer's Comments: *In the study report, the Applicant defined evaluable populations at end of therapy and at follow-up. The protocol only stated an evaluable population as defined above. It is not the Division's practice to change the evaluable population based on the timing of the visit. Therefore, all analyses including those at follow-up use the definition of the evaluable population as stated above.*

The clinically evaluable population is the primary analysis population but analyses of the ITT population will be used to test the robustness of the clinically evaluable results.

The primary efficacy endpoint was endoscopic response at end of therapy. A patient was endoscopically assessed as cure (endoscopic grade 0 at EOT), improved (decrease of 1 or more grades from baseline), failure (no change or worsening of endoscopic grade from baseline), or indeterminate (circumstances prevented an evaluation from being made). A successful endoscopic response was defined as cured or improved. Clinical response and mycological response were secondary endpoints. A patient was classified clinically as a cure (absence of symptoms and no additional systemic antifungal required for treatment of study condition), improvement (less severe symptoms compared to baseline evaluations and no additional systemic antifungal required for treatment of study condition), failure (no significant improvement in symptoms following 7 or more days of therapy or requirement for additional systemic antifungal treatment), or indeterminate. Mycology was assessed as eradicated or presumed eradicated (culture negative for *Candida* species present at baseline or no visible lesions on endoscopy), persisted (visible lesions on endoscopy, isolation of baseline *Candida* species with no previous eradication), superinfection (one or more new *Candida* species identified in a patient with visible lesions) or colonization (one or more new *Candida* species identified in a patient with no visible lesions).

Reviewer's Comment: *Assessments were also made at follow-up. Failures at EOT were carried forward as failures at follow-up, regardless of missing or other outcomes. The*

applicant defined endoscopic response at follow-up relative to baseline. In this review, the follow-up assessment will be made relative to end of treatment. Endoscopic response at follow-up was assessed as sustained success (further improvement or no change from EOT in a patient who was an endoscopic success at EOT), relapse (worsening of endoscopic grade from EOT), failure (carried forward from EOT), or indeterminate.

The primary objective of the study was to determine whether anidulafungin was non-inferior to fluconazole. Two-sided 95% confidence intervals, calculated using the normal approximation to the binomial distribution with continuity correction, were used to estimate the difference in the proportion of success between the treatment groups (anidulafungin – fluconazole). The sample size was based on 90% power to show that the lower bound of the two-sided 95% confidence interval for the difference in success rates was no less than –10%. Assuming a success rate of 88% and a dropout rate of 25%, 592 patients were to be enrolled in order to provide evaluable data on 444 patients (222 per treatment group).

3.1.2 Patient Demographics

A total of 601 patients were randomized to receive study treatment, 300 were randomized to receive anidulafungin and 301 to receive fluconazole. A total of 113 patients discontinued the study, 55 (18.3%) from the anidulafungin group and 58 (19.3%) from the fluconazole group. There were no meaningful differences between treatment groups in the reason for discontinuation and most patients discontinued due to an adverse event. All 601 patients were included in the ITT population. The clinically evaluable population consisted of 249 anidulafungin patients and 255 fluconazole patients. The most common reasons for exclusion from the clinically evaluable population were less than 10 days of therapy (28 anidulafungin patients, 22 fluconazole patients) and use of an antifungal agent during the treatment period for a reason other than failure (16 anidulafungin patients, 11 fluconazole patients). The mycologically evaluable population excluded an additional 69 patients from each treatment group who did not have a baseline *Candida* isolate.

Table 1 summarizes the demographic and baseline characteristics of the ITT population. There were no significant differences across treatment groups. More than half of the patients were female. The mean age of the patients was 37 years with a range of 18 to 69 years. AIDS status was positive in 40% of the patients. HIV testing at screening was voluntary and only agreed to by 136 anidulafungin patients and 143 fluconazole patients. HIV status and AIDS status were collected as part of the medical history. Therefore, presumed HIV status can be made for those patients who did not agree to HIV testing within the current study based on this information. Thus, 74.0% of anidulafungin patients and 76.7% of fluconazole patients are HIV positive or presumed to be HIV positive.

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Table 1
Demographic and Baseline Characteristics (ITT)

# Patients	Treatment Group	
	Anidulafungin	Fluconazole
	300	301
Gender		
Male	127 (42.3)	145 (48.2)
Female	173 (57.7)	156 (51.8)
Age mean (SD)		
Min, max	18, 69	18, 65
Race		
White	44 (14.7)	41 (13.6)
Black	146 (48.7)	144 (47.8)
Asian	46 (15.3)	46 (15.3)
Hispanic	1 (0.3)	2 (0.7)
Other	62 (20.7)	68 (15.3)
Missing	1 (0.3)	0
AIDS Status		
Positive	121 (40.3)	122 (40.5)
Negative	179 (59.7)	179 (59.5)
HIV Status		
Positive	114 (38.0)	123 (40.9)
Negative	22 (7.3)	20 (6.6)
No result	0	1 (0.3)
Not done	164 (54.7)	157 (52.2)
AIDS/ HIV		
AIDS	121 (40.3)	122 (40.5)
Non-AIDS but HIV +	28 (9.3)	32 (10.6)
Non-AIDS but presumed HIV +	73 (24.3)	77 (25.6)
Unknown HIV	56 (18.7)	50 (16.6)
HIV -	22 (7.3)	20 (6.6)
Endoscopy Grade (baseline)		
1	61 (20.3)	53 (17.6)
2	112 (37.3)	101 (33.6)
3	127 (42.3)	147 (48.8)
Odynophagia/Dysphagia		
Absent	7 (2.3)	8 (2.7)
Mild	60 (20.0)	50 (16.6)
Moderate	130 (43.3)	152 (50.5)
Severe	103 (34.3)	90 (29.9)
Missing	0	1 (0.3)
Retrosternal Pain		
Absent	61 (20.3)	69 (22.9)
Mild	68 (22.7)	70 (23.3)
Moderate	97 (32.3)	99 (32.9)
Severe	74 (24.7)	62 (20.6)
Missing	0	1 (0.3)

Baseline disease characteristics were similar between treatment groups. Between 77 and 79% of the patients experienced moderate to severe odynophagia/dysphagia, and between 54 and 57% of patients experienced moderate to severe retrosternal pain. Most patients had baseline endoscopies greater than Grade 1.

There were 229 *Candida* isolates in the anidulafungin group and 237 *Candida* isolates in the fluconazole group detected at baseline. The majority of patients had only 1 *Candida* isolate at baseline. Ten patients in the anidulafungin group and 14 patients in the fluconazole group had 2 *Candida* isolates detected. *Candida albicans*, the most common pathogen detected at baseline for both groups, was found in 212 (92.6%) anidulafungin patients and 213 (89.9%) fluconazole patients. *Candida glabrata* was found in 11 anidulafungin patients and 13 fluconazole patients. The remaining isolates, *C. krusei*, *C. lusitaniae*, *C. pelliculosa*, and *C. tropicalis*, occurred in 2 or fewer patients in each group.

3.1.3 Efficacy Results

Table 2 summarizes the results of the primary endpoint, endoscopic response at EOT for the clinically evaluable and ITT populations. For the clinically evaluable population, the endoscopic success (cured + improved) rate was 97.2% for anidulafungin and 98.8% for fluconazole. The difference in success rates (anidulafungin – fluconazole) was –1.6% and the lower limit of the 95% confidence interval about this difference is greater than the non-inferiority margin of –10%. The ITT results support the claim of non-inferiority of anidulafungin compared to fluconazole. It should be noted that there are more patients in the anidulafungin group that are considered improved than in the fluconazole group. When just the patients who were cured are considered, the lower bound of the difference in cure rates falls just outside the –10% needed to claim non-inferiority and the upper bound barely crosses zero. It should be noted that the upper bound of the exact confidence interval about the difference in cure rates would be just below zero (-0.2 clinically evaluable and -0.3 ITT). Thus, there are marginally significantly more cures on the fluconazole arm than on the anidulafungin arm (Fisher’s exact p-value=0.046 clinically evaluable and 0.042 ITT).

Table 2
Endoscopic Response at EOT

		Anidulafungin	Fluconazole	Difference (95% CI)
Clinically Evaluable		n=249	n=255	
	Success	242 (97.2)	252 (98.8)	-1.6 (-4.4, 1.2)
	Cured	219 (88.0)	238 (93.3)	-5.3 (-10.8, 0.2)
	Improved	23 (9.2)	14 (5.5)	
	Failure	7 (2.8)	3 (1.2)	
ITT		n=300	n=301	
	Success	260 (86.7)	265 (88.0)	-1.3 (-6.9, 4.3)
	Cured	230 (76.7)	251 (83.3)	-6.7 (-13.4, 0.0)
	Improved	30 (10.0)	14 (4.6)	
	Failure	8 (2.7)	5 (1.7)	
	Indeterminate	32 (10.7)	31 (10.3)	

Clinical response was a secondary endpoint. Table 3 summarizes the results for clinical response at EOT for the clinically evaluable and ITT populations. These results are similar to those seen for endoscopic response. The majority of the patients in the clinically evaluable population showed no signs of odynophagia/dysphagia or retrosternal pain at EOT. Only 1 anidulafungin patient and 5 fluconazole patients had mild odynophagia/dysphagia and 4

anidulafungin patients and 2 fluconazole patients had mild retrosternal pain at EOT. No patient in either treatment group had moderate or severe symptoms at EOT.

Table 3
Clinical Response at EOT

		Anidulafungin	Fluconazole	Difference (95% CI)
Clinically Evaluable		n=249	n=255	
	Success	246 (98.8)	254 (99.6)	-0.8 (-2.8, 1.2)
	Cured	242	250	
	Improved	4	4	
	Failure	3 (1.2)	1 (0.4)	
ITT		n=300	n=301	
	Success	263 (87.7)	267 (88.7)	-1.0 (-6.5, 4.5)
	Cured	258	262	
	Improved	5	5	
	Failure	8 (2.7)	4 (1.3)	
	Indeterminate	29 (9.7)	30 (10.0)	

Mycological response was also a secondary endpoint. The per-patient mycological outcomes for the mycologically evaluable population are summarized in Table 4. Both treatment groups had high rates of mycological success at EOT. Though not prespecified, non-inferiority of anidulafungin to fluconazole would not be satisfied assuming a margin of 10%.

Table 3
Per-patient Mycological Response at EOT
Mycologically Evaluable Population

	Anidulafungin (n=180)	Fluconazole (n=186)	Difference (95% CI)
Success	156 (86.7)	169 (90.9)	-4.2 (-11.2, 2.8)
Proven eradication	152	156	
Presumed eradication	3	4	
Colonization	1	9	
Failure	24 (13.3)	17 (9.1)	
Proven persistence	23	12	
Presumed persistence	0	0	
Superinfection	1	5	

In addition to the EOT assessments, assessments were made at a 2 week follow-up visit. The remainder of this review will focus on the clinically evaluable population. The results of the ITT population are similar (not presented). Table 4 summarizes the endoscopic response at follow-up for the clinically evaluable population.

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Table 4
Endoscopic Response at Follow-up
Clinically Evaluable Population

	Anidulafungin n=249	Fluconazole n=255
Sustained Success	94	172
Relapse	132	55
Indeterminate	16	25
Failure	7	3

Reviewer's Comment: Note that these numbers are different than those presented by the Applicant in the VER002-4 Study report. First, the Applicant also defined a clinically evaluable analysis at follow-up population. Secondly, the Applicant assessed response at follow-up compared to baseline instead of EOT which assesses relapse.

Endoscopic response at follow-up was looked at in multiple ways. The first was success at follow-up. As seen in Table 5, the endoscopic success rate at follow-up was 37.8% in the anidulafungin group and 67.5% in the fluconazole group. The difference between these rates was statistically significant indicating that anidulafungin has a lower success rate than fluconazole at follow-up. The rate of relapse was also assessed at follow-up. For those patients who were successes at EOT, 54.5% in the anidulafungin group and 21.8% in the fluconazole group relapsed at follow-up. Since there were more patients in the fluconazole group who were indeterminate at follow-up, a more conservative assessment was made by looking at those who relapsed or were indeterminate. In this case, 61.2% in the anidulafungin and 31.7% in the fluconazole groups relapsed or were indeterminate at follow-up. Regardless, statistically significantly more anidulafungin patients relapsed at follow-up.

Table 5
Endoscopic Success and Relapse Rates at Follow-up
Clinically Evaluable Population

	Anidulafungin	Fluconazole	Difference (95% CI)	p-value*
Success	94/249 (37.8)	172/255 (67.5)	-29.7 (-38.4, -21.0)	< 0.0001
Relapse	132/242 (54.5)	55/252 (21.8)	32.7 (24.2, 41.2)	<0.0001
Relapse or indeterminate	148/242 (61.2)	80/252 (31.7)	29.5 (20.7, 38.3)	<0.0001

*Fisher's Exact Test

In order to characterize the extent of relapse, the endoscopy grade at follow-up was compared to baseline. Recall that the majority of the patients had an endoscopy of Grade 0 at EOT, i.e. the patient was considered a cure. Table 6 summarizes the endoscopy grades at baseline and follow-up for the patients who relapsed. Of the 132 anidulafungin patients who relapsed, 56 had endoscopy grades at follow-up less severe than baseline, 61 had endoscopy grades that were the similar to baseline, and 15 had endoscopy grades worse than baseline. This is in comparison to 34, 17, and 4 of the 55 fluconazole patients who relapsed, respectively. Thus, more of the anidulafungin patients, 76 or 30.5%, relapsed back to their

baseline level or worse compared to 21 or 8.2% of the fluconazole patients. This difference is statistically significant (Fisher's exact p-value <0.0001).

Table 6
Endoscopy Grade at Baseline and Follow-up
Relapsed Clinically Evaluable Population

Baseline	Anidulafungin (n=132)			Fluconazole (n=55)		
	1	2	3	1	2	3
1	16	6	3	4	2	0
2	16	15	6	9	3	2
3	14	26	30	15	10	10

The results for clinical response at follow-up support those seen for endoscopic response at follow-up. As seen in Table 7, significantly fewer anidulafungin patients remained clinical successes at follow-up compared to fluconazole patients or significantly more anidulafungin patients suffered a clinical relapse.

Table 7
Clinical Success and Relapse Rates at Follow-up
Clinically Evaluable Population

	Anidulafungin	Fluconazole	Difference (95% CI)
Success	126/249 (50.6)	189/255 (74.1)	-23.5 (-32.1, -14.9)
Relapse	104/246 (42.3)	41/254 (16.1)	26.2 (18.1, 34.3)
Relapse or indeterminate	120/246 (48.8)	65/254 (25.6)	23.2 (14.6, 31.8)

Table 8 summarizes relapse data for each of the clinical symptoms, odynophagia/dysphagia and retrosternal pain. Even though fewer patients had relapse of clinical symptoms compared to endoscopic relapse, significantly more anidulafungin patients experienced relapse of a clinical symptom. As was seen with endoscopic relapses, many of the clinical symptom relapses were the same or worse than the baseline severity.

Table 8
Clinical Symptom Relapse at Follow-up
Clinically Evaluable Population

	Anidulafungin (n=249)	Fluconazole (n=255)	p-value
Odynophagia/Dysphagia			
Relapse of symptom	45	12	<0.0001
same or worse than baseline	22	7	
Retrosternal Pain			
Relapse of symptom	25	8	0.0019
same or worse than baseline	17	2	

Mycological response at follow-up is summarized in Table 9. As was seen with endoscopic response and clinical response at follow-up, significantly fewer anidulafungin patients were mycological successes at follow-up compared to fluconazole patients.

Table 9
Per-patient Mycological Response at Follow-up
Mycologically Evaluable Population

	Anidulafungin (n=180)	Fluconazole (n=186)	Difference (95% CI)
Success	75 (41.7)	122 (65.6)	-23.9 (-34.4, -13.4)
Proven eradication	72	116	
Presumed eradication	2	2	
Colonization	1	4	
Failure	105 (58.3)	64 (34.4)	
Proven persistence	10	6	
Presumed persistence	4	0	
Proven recurrence	66	34	
Presumed recurrence	1	0	
Superinfection	12	6	
Unable to determine	12	18	

One additional analysis was performed by looking at the number of patients who were considered endoscopic, clinical, and mycological successes. This analysis was performed on the Mycologically Evaluable population. At EOT, 86.1% (155/180) of anidulafungin patients and 89.8% (167/186) of fluconazole patients were endoscopic, clinical, and mycological successes. At FU, only 28.3% (51/180) of anidulafungin patients and 55.4% (103/186) of fluconazole patients were endoscopic, clinical, and mycological successes.

3.2 Evaluation of Safety

A total of 237 patients (79.0%) in the anidulafungin group and 226 patients (75.1%) in the fluconazole group had at least one adverse event. Serious adverse events were reported in 60 (20.0%) anidulafungin patients and 44 (14.6%) fluconazole patients. There were 43 deaths during the study, 20 patients (7.7%) from the anidulafungin group and 23 patients (6.6%) from the fluconazole group. Only one death was considered possibly related to study drug and that patient received anidulafungin.

For a detailed review of the safety data, please see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Since the response rates of the primary endpoint, endoscopic response at EOT, were high, subgroup analyses for this time point are uninformative. Therefore, subgroup analyses will be presented for endoscopic response at follow-up.

4.1 Gender, Race and Age

The following table summarizes the number of patients who were considered sustained endoscopic successes at follow-up for gender, race, and age. There are no significant

treatment by subgroup interactions. The results for the various subgroups support the overall results. Regardless of the subgroup, anidulafungin has fewer successes at follow-up compared to fluconazole.

Table 10
Subgroup Analyses Endoscopic Success at Follow-up
Clinically Evaluable Population

	Treatment Group	
	Anidulafungin	Fluconazole
Gender		
Male	41/110 (37.3)	81/120 (67.5)
Female	53/139 (38.1)	91/135 (67.4)
Age		
< 30	13/58 (22.4)	36/60 (60.0)
30-39	36/100 (36.0)	66/99 (66.7)
40-49	26/58 (44.8)	43/62 (69.4)
≥ 50	19/33 (57.6)	27/34 (79.4)
Race		
Asian	7/35 (20.0)	18/40 (45.0)
Black	36/120 (30.0)	78/114 (68.4)
White	15/37 (40.5)	25/37 (67.6)
Other	36/57 (63.1)	51/64 (79.7)

Considering only the anidulafungin patients, a logistic model was fit containing the factors above to determine if there were certain patients who may explain the lower success rates at follow-up. In this model, race and age were found to be significant predictors of sustained endoscopic success at follow-up. Increasing age increases the chance for a sustained success. Looking at age categorically shows that patients <30 have the least chance for success compared to patients ≥ 50 but patients 30-39 and 40-49 are not much different from patients ≥ 50 in their chance for success. When considering race, Asian patients have a decreased chance for success compared to White patients, Black patients are no different from White patients, and patients of Other race have an increased chance for success compared to White patients.

4.2 Other Special/Subgroup Populations

Two additional subgroups were considered: baseline endoscopy score and AIDS/HIV status. Table 11 summarizes the results of sustained endoscopic success at follow-up for these subgroups. Again, regardless of subgroup, anidulafungin has fewer sustained endoscopic successes at follow-up than fluconazole. Patients with baseline endoscopies of grade 3 have the lowest rate of sustained endoscopic success at follow-up. Also, HIV positive patients have lower sustained success rates than HIV negative patients do. It can be presumed that the patients with unknown HIV status are likely HIV negative since the response rate for this group is closer to the response rate for HIV negative patients than HIV positive patients.

Table 11
Endoscopic Success at Follow-up by AIDS/HIV Status and Baseline Endoscopy Grade
Clinically Evaluable Population

	Treatment Group	
	Anidulafungin	Fluconazole
AIDS/ HIV		
AIDS	25/99 (25.3)	62/100 (62.0)
Non-AIDS but HIV +	7/24 (29.2)	16/28 (57.1)
Non-AIDS but presumed HIV +	18/58 (31.0)	37/65 (56.9)
Unknown HIV	30/49 (61.2)	42/44 (95.5)
HIV -	14/19 (73.7)	15/18 (83.3)
Endoscopy Grade (baseline)		
1	22/50 (44.0)	32/44 (72.7)
2	43/91 (47.3)	65/87 (74.7)
3	29/108 (26.9)	75/124 (60.5)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Following the completion of Study VER002-4, but prior to unblinding study results, the bioanalytical facility that was testing plasma samples for anidulafungin revealed that there were no detectable levels of anidulafungin in approximately 75% of the samples from subjects who were randomized to receive anidulafungin. Further investigation of this problem determined that an error occurred at the contractor responsible for preparing the patient treatment kits. This error resulted in a 1:1 reversal of the assignment of the kits to Arm A or Arm B received by approximately 70% of patients. Kits labeled A were to contain anidulafungin and placebo to fluconazole and kits labeled B were to contain fluconazole and placebo to anidulafungin. The 1:1 reversal of kit assignment started September 27, 2001 and continued to the end of the study. This error did not affect kits sent to Argentina that used a separate randomization table or kits sent to the remaining study centers from the time of study start up to September 26, 2001.

Prior to unblinding the study, the Applicant was able to reconstruct a corrected patient treatment assignment table. This treatment assignment table was used for all analyses performed in this review. Even though the incident had no effect on the conduct of the study in terms of blinding and randomization of treatments, the effect if any on the conclusions drawn from the study had this error not been detected were investigated. This was done by analyzing the data using the original treatment assignment and performing a re-randomization test.

If the kit assignment problem had not been detected and the original treatment assignment table was used, the endoscopy success rates at EOT for the clinically evaluable population would have been 98.4% for anidulafungin and 97.6% for fluconazole. The 95% confidence interval about the 0.8% difference in these rates is (-2.0, 3.6). At follow-up, the sustained success rates would have been 56.1% for anidulafungin and 49.4% for fluconazole. The 95% confidence interval about the 6.7% difference in rates is (-2.4, 15.8). Thus, at EOT, the same conclusions would have been drawn i.e.; anidulafungin is non-inferior to fluconazole.

However, the statistically inferior difference of anidulafungin compared to fluconazole at follow-up would not have been concluded.

In addition, a re-randomization test was performed. This test was performed by randomly assigning the clinically evaluable patients to the two treatment groups. The distribution of the difference in sustained endoscopic success rates was computed based on 50,000 simulations of the study. The probability of seeing results as extreme as or more so than that observed was less than $1/50,000=0.00002$. The 2.5th and 97.5th percentiles of the re-randomization distribution added to the observed difference represent the ends of the 95% confidence interval around the observed difference. For sustained endoscopic success at follow-up, this confidence interval is (-38.8, -20.5). This result is in accordance with the analysis reported in Table 5.

Based on the 2 analyses above, it is reasonable to say that the results at the end of therapy are robust to the treatment kit assignment problem, while the results at follow-up are very much against anidulafungin.

As part of the plan to determine the cause of the kit assignment problem, it was agreed that all plasma samples would be analyzed for anidulafungin regardless of treatment assignment and selected samples would be analyzed for fluconazole. All samples taken from patients assigned to a particular drug contained that drug. However, some unexpected drug concentrations were found in a few samples. Twenty-nine patients had at least 1 plasma sample with both drugs. Seven of these patients had quantifiable concentrations of both drugs in all plasma samples. Fifty-two percent of the patients with anomalous drug concentrations were from Site 019 (15 of 29). Of the remaining 14 patients, 5 were from site 010, 3 were from site 012 and the last 5 were from 5 different sites.

Since there was a concern about the validity of the data from Site 019, the Division decided to reanalyze the data excluding this site. Site 019 enrolled 24 anidulafungin patients and 23 fluconazole patients. Of these patients, 18 anidulafungin patients and 19 fluconazole patients were clinically evaluable. Table 12 summarizes the endoscopy results excluding Site 019. These results are consistent with the results for the entire study. Therefore, further analyses excluding Site 019 were not performed.

Table 12
Endoscopy Results Excluding Site 019

	Anidulafungin	Fluconazole	Difference (95% CI)
Clinically Evaluable	n=231	n=236	
Success @ EOT	225 (97.4)	233 (98.7)	-1.3 (-4.2, 1.6)
Sustained Success @ FU	90 (39.0)	163 (69.1)	-30.1 (-39.1, -21.1)
ITT	n=276	n=278	
Success @ EOT	241 (87.3)	245 (88.1)	-0.8 (-6.6, 5.0)
Sustained Success @ FU	101 (36.6)	169 (60.8)	-24.2 (-32.6, -15.8)

Although the Division believes that the Applicant has corrected the kit assignment problem and that with the exception of site 019, the problems with the plasma samples are most likely

due to random error, the Division of Scientific Investigations has stronger feelings regarding the data integrity. Additional analyses were performed by looking at the group of patients not affected by the treatment kit mix-up compared to the group of patients affected by the treatment kit mix-up and also by looking at the group of patients who had PK samples compared to those who did not have PK sampling. The results of these analyses (not shown) are robust, regardless of the group of patients. In all cases, the conclusions drawn are the same as those drawn for the overall study:

- At EOT, anidulafungin is non-inferior to fluconazole with respect to endoscopic success.
- At follow-up, anidulafungin is statistically inferior to fluconazole with respect to sustained endoscopic success.

Finally, there was concern about having only a single study to support a single indication NDA for a non-life threatening disease. Typically, the error rate associated with one Phase 3 study is 0.05 (two-sided) and with two Phase 3 studies is $0.00125=2*(0.05/2)^2$ (two-sided). If this conservative approach is taken for this study, the confidence interval about the difference in endoscopic success rates (see Table 2) for the clinically evaluable population would be (-6.0, 2.8). Non-inferiority of anidulafungin to fluconazole is maintained. Also, inferiority of anidulafungin at follow-up is still concluded. Therefore, this study is robust to provide enough evidence that might have been seen had 2 studies been performed.

5.2 Conclusions and Recommendations

In a single Phase 3 study of anidulafungin (100/50 mg) versus fluconazole (200/100 mg) in the treatment of esophageal candidiasis, anidulafungin was shown to be non-inferior to fluconazole at the end of therapy. However, by 2 weeks following EOT, significantly more patients who received anidulafungin relapsed compared to those patients who received fluconazole.

The dose of anidulafungin chosen for this Phase 3 study was based on a small dose ranging study that tested two doses (70/35 mg and 50/25 mg) that were lower than the dose used in this study. There is also preliminary evidence from a dose ranging study of invasive candidiasis that a higher dose (200/100 mg) may be needed for that indication. Due to the significant increase in relapse only two weeks following end of treatment, it is of concern as to whether the appropriate dose has been chosen for the treatment of esophageal candidiasis. It is therefore recommended that an additional dose ranging study be performed including the dose studied in this Phase 3 study and at least one higher dose. This study would investigate whether the amount of relapse can be improved upon with increased doses. It may also be useful to include a fluconazole arm to provide a positive control.

Also, for future studies in esophageal candidiasis, the appropriateness of the EOT assessment as a primary endpoint should be determined. At a minimum, the follow-up assessment should be considered a co-primary endpoint.

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