CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-227

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #:	21-227
Applicant:	Merck & Co., Inc.
Name of Drug:	Cancidas™ (caspofungin acetate)
Documents Reviewed:	NDA Index and Summary sections (Vol. 1.1), Statistical sections (Vols. 8.1A, 8.8, and 8.10) dated July 28, 2000, and SAS datasets of the clinical efficacy and safety data.
Indications:	The treatment of invasive aspergillosis in patients who are refractory to, or intolerant of, other therapies.
Statistical Reviewer:	Cheryl Dixon, Ph.D. (HFD-725)
Medical Reviewer:	Dr. Eileen Navarro (HFD-590)

I. INTRODUCTION

Caspofungin, an echinocandin, is a member of a new class of compounds, the glucan synthesis inhibitors, that has been developed for the treatment of invasive and localized fungal infections. The ongoing clinical development program for caspofungin includes studies designed to evaluate the efficacy and safety of caspofungin in documented *Aspergillus* and *Candida* infections as well as in empiric therapy of neutropenic patients. This submission contains the results of the development program supporting the proposed invasive aspergillosis (IA) indication. The recommended dose for this indication is 50-mg caspofungin IV daily following a 70-mg loading dose on Day 1.

The efficacy of caspofungin in the treatment of aspergillosis was evaluated in a multicenter, non-comparative study in patients with documented disease who were refractory to or intolerant of other therapies (Protocol 019). A retrospective medical chart review of patients with invasive aspergillosis (the Historical Control Study, Protocol 028/029) was conducted to provide an approximate comparator group of patients with IA treated with standard antifungal therapy. Further supportive data were collected from patients with IA enrolled in the Compassionate Use Study (Protocol 024/025).

Reviewer's Comment: *The Compassionate Use Study only provided data on 3 patients with IA and will not be discussed in this review.*

The non-comparative *Aspergillus* study, Protocol 019, required well-documented IA using stringent diagnostic criteria. Only patients with definite extrapulmonary aspergillosis and definite or probable pulmonary aspergillosis were eligible. The

definitions of infection were modeled after the Mycoses Study Group (MSG) criteria. Patients were required to be refractory to or intolerant of other antifungal therapy. Refractory was defined as demonstrating progression of infection or failure to improve after a minimum of 7 days of therapeutic doses of effective antifungal therapy. Intolerance was defined as a doubling of creatinine or creatinine ≥ 2.5 mg/dL on standard therapy, or creatinine ≥ 2.5 mg/dL due to another preexisting condition, or other significant intolerance to amphotericin B or lipid formulations of amphotericin B.

The primary endpoint for the evaluation of IA was the overall clinical and radiographic response assessed at end of IV therapy. A favorable response was defined as either a complete response (resolution of all attributable clinical and radiographic findings of infection) or a partial response (clinically significant improvement in attributable clinical and radiographic findings). Documentation supporting significant improvement or resolution of attributable radiographic abnormalities was required for a patient to be classified as having had a favorable response. Patients were also evaluated for evidence of relapse (recurrence of infection after a favorable response at end of IV therapy) at a follow-up visit 4 weeks after discontinuation of IV therapy. Microbiologic outcomes were also assessed in patients for whom diagnosis was based on culture data.

Because of the complexities in determining the diagnosis of IA and assessing outcome after treatment, an independent Expert Panel reviewed the data on patients enrolled in Protocol 019. The panel was comprised of 3 mycologists noted to be international experts on aspergillosis. The Expert Panel was provided case report form data, and official reports of radiographs, relevant procedures, and autopsies, as appropriate. Based on the data provided, each member defined the diagnosis of infection, determined whether each patient was refractory to or intolerant of initial therapy, and determined the outcome after caspofungin therapy. The Expert Panel assigned patients who were considered both refractory and intolerant to initial therapy to the refractory category. Any disagreements were discussed and resolved at a face-to-face meeting with all three members present. In most cases, the final assessment of the Expert Panel also agreed with the investigator assessments. The Expert Panel's assessments are considered primary.

In order to provide a comparison of the results in the non-comparative *Aspergillus* study to standard antifungal therapy, a retrospective chart review (Protocol 028/029, Historical Control Study) was performed of patients with well-documented IA treated with standard antifungal therapy from 1995 to 1998. The objective of this predefined comparison was to demonstrate that caspofungin was at least as effective as standard therapy. In the Historical Control Study, effort was made to identify a population that closely resembled the patients enrolled in Protocol 019. Criteria for diagnosis and outcome were the same in both studies, and 4 out of 10 sites selected for Protocol 028/029 also participated in Protocol 019. In the Historical Control Study, potential cases of IA were initially identified through hospital discharge summaries; consultation records from pulmonary, oncology, or infectious disease units; microbiology laboratory

records; and pathology reports (including both biopsy and autopsy records). Patient charts were identified for abstraction if the patient met eligibility criteria, including diagnoses of definite IA from any site or probable pulmonary IA, and treatment with at least 7 days of therapeutic doses of standard antifungal therapy to mirror minimum eligibility criteria for Protocol 019. Data regarding the diagnosis of IA, underlying disease, doses and duration of standard antifungal therapy, and data supporting outcome after treatment were abstracted from hospital records. The investigator at each site reviewed the abstracted data and made an assessment of clinical status at Week 1 and assessed clinical response at the end of standard antifungal therapy. Diagnostic criteria for IA and definition of response were the same as those used in Protocol 019.

Reviewer's comment: *To ensure consistency with Protocol 019, an expert review of all abstracted cases in Protocol 028/029 was to be performed. The expert review for Protocol 028/029 consisted of one investigator who also enrolled subjects into the Historical Control Study. The results of the expert review were not submitted in the original submission and have not been reviewed by this reviewer.*

In the Historical Control Study, patients were assessed at the end of Week 1 of therapy; the first time patients would have been eligible to enroll in Protocol 019. Patients were considered refractory if the clinical assessment of their condition was worsened or not improved at the end of Week 1. Patients were categorized as intolerant if their creatinine value was ≥ 2.5 mg/dL at the end of Week 1 of therapy. In all, 229 patient charts were abstracted for the Historical Control. Fifteen patients were considered to be nonrefractory/nonintolerant (NR/NI) (assessed as improved and not intolerant at Week 1) and prospectively excluded from the comparison group, because they would not have been eligible for entry into Protocol 019. The remaining 214 patients comprised the refractory/intolerant (R/I) population, 8 of whom had an indeterminate end of treatment (EOT) outcome. These patients were excluded for the comparison to Protocol 019, leaving 206 patients in the R/I population, with EOT indeterminates excluded. These 206 patients were further broken down into the refractory population (R) that consisted of 188 patients and the intolerant only population (IO) which consisted of 5 patients. The additional 13 patients were considered indeterminate of refractory or intolerant status at Week 1.

II. EFFICACY EVALUATION

Protocol 019 enrolled 69 patients with IA, who were refractory to or intolerant of other therapy by March 31, 2000. Fifty-eight patients completed therapy by the data cutoff date of February 7, 2000 and were reviewed by the Expert Panel. The Expert Panel determined that 54 of the 58 patients met diagnostic criteria for IA, received at least one dose of caspofungin and had data on which to base an assessment of outcome. An additional 11 patients completed therapy and had data available by April 19, 2000. At the time of the original NDA submission, the Expert Panel had not reviewed the data for

these 11 patients. However, an October 16, 2000 response to FDA request for information included the Expert Panel assessment of these 11 patients. Nine of the 11 patients were included in the Expert Panel outcome analysis. Thus, the Expert Panel considered 63 of the 69 patients evaluable for efficacy.

***Reviewer's Comment**: As noted above, the original submission only included the Expert Panel assessment of 54 patients. An investigator assessment of the additional 11 patients was summarized separately. For the purpose of evaluating efficacy, this review will focus on all 63 patients who were evaluated by the Expert Panel in Protocol 019. For the Historical Control, the primary population for comparison to Protocol 019 will be the refractory/intolerant (R/I) population, with the EOT indeterminates excluded (N=206).*

The results from Protocol 019 are compared to the results of the R/I population, EOT indeterminates excluded, in Protocol 028/029. The comparison is presented in tabular displays of the baseline characteristics of the patients in each study, efficacy results overall, and clinically relevant disease and patients characteristics.

Table 1 summarizes the demographic and baseline characteristics for the patients in each study. The patients treated with caspofungin and those treated with standard therapy were generally similar with respect to gender, race, and age. There was a difference in the distribution of subjects enrolled by geographic region. In Protocol 019, the patients were almost evenly split between the US (46%) and Europe (54%). However, in the Historical Control, the majority of the patients (89%) were enrolled from the US. The majority of patients (approximately 70%) in each study had pulmonary aspergillosis. Hematologic malignancy was the most common underlying disease. At baseline, the proportion of patients who were neutropenic and the proportion of patients receiving high doses of corticosteroids were similar. Patients in both studies received amphotericin B, lipid formulations of amphotericin B, itraconazole, or multiple agents as prior or standard therapy. The distribution of the specific drugs differs in the two studies. Patients in Protocol 019 received multiple drug regimens more often than patients in the Historical Control (44% vs. 16%). Patients in the Historical Control most commonly received lipid formulations of amphotericin B and amphotericin B as their primary therapy. When breaking the multiple drug regimens into the individual drug categories, almost 60% of all patients received amphotericin B as part of their treatment regimen. More patients in Protocol 019 received Ambisome and itraconazole as part of their treatment regimen compared to patients in the Historical Control (Ambisome- 33.3% vs. 5.3% and itraconazole- 61.9% vs. 45.6%). The majority of patients in both studies were considered refractory to their initial therapy.

Table 1

Patient Demographic and Baseline Characteristics

Patient Characteristic	Protocol 019 (n=63)	Historical Control (n=206)
Gender n (%)		
Female	21 (33.3)	98 (47.6)
Male	42 (66.7)	108 (52.4)
Race n (%)		
Caucasian	59 (93.7)	172 (83.5)
Hispanic	3 (4.8)	16 (7.8)
Black	1 (1.6)	10 (4.9)
Other	-	8 (3.9)
Age mean (SD)	46.5 (14.5)	48.3 (13.2)
Min, Max	15, 69	19, 77
Study Site n (%)		
US	29 (46.0)	183 (88.8)
Europe	34 (54.0)	23 (11.2)
Site of Infection n (%)		
Pulmonary, probable	18 (28.6)	75 (36.4)
Pulmonary, definite	27 (42.9)	79 (38.3)
Disseminated	13 (20.6)	41 (19.9)
Sinus	3 (4.8)	6 (2.9)
Central nervous system	1 (1.6)	2 (1.0)
Skin	-	3 (1.5)
Pulmonary/Sinus	1 (1.6)	-
Underlying Disease n(%)		
Hematologic malignancy	41 (65.1)	144 (69.9)
Organ transplant	8 (12.7)	32 (15.5)
Solid tumor	3 (4.8)	10 (4.9)
Other risk factors	8 (12.7)	20 (9.7)
None	3 (4.8)	-
Neutropenic Status n(%)		
ANC < 500	14 (22.2)	57 (27.7)
ANC ≥ 500	49 (77.8)	149 (72.3)
Corticosteroid Use n (%)		
< 20 mg/day	40 (63.5)	132 (64.1)
≥ 20 mg/day	23 (36.5)	74 (35.9)
Prior/Standard Therapy n (%)		
Amphotericin B	14 (22.2)	67 (32.5)
Abelcet	6 (9.5)	69 (33.5)
Ambisome	5 (7.9)	6 (2.9)
Amphotec	-	7 (3.4)
Itraconazole	9 (14.3)	24 (11.7)
[redacted]		-
Multiple	28 (44.4)	33 (16.0)
Response to Prior Therapy n (%)		
Refractory only	36 (57.1)	188 (91.3)
Refractory and Intolerant	17 (27.0)	-
Intolerant only	10 (15.9)	5 (2.4)

The percentage of patients with a favorable clinical response was higher in the caspofungin group from Protocol 019 than the Historical Control group (41.3% vs. 17.0%, respectively). The results are summarized in Table 2. For patients who were refractory, the success rates were 35.8% and 14.4%, respectively. Intolerant patients, who were the minority of patients in both studies, did relatively well in both studies.

Table 2
Clinical and Radiographic Response at End of Antifungal Therapy

	Protocol 019	Historical Control
Overall Favorable Response Rate, n (%)	26/63 (41.3)	35/206 (17.0)
(95% CI)	(28.3, 54.2)	(11.6, 22.4)
Response to Prior Therapy		
Refractory	19/53 (35.8)	27/188 (14.4)
Intolerant	7/10 (70.0)	3/5 (60.0)

The following table summarizes patient outcomes by potential clinically relevant predictors of outcome, namely site of infection, underlying disease, neutropenia at baseline, and high-dose corticosteroid use at baseline. In all categories, patients with caspofungin had higher favorable response rates than those patients treated with standard therapy in the Historical Control.

Table 3
Clinical and Radiographic Response at End of Antifungal Therapy
By Various Baseline Factors

	Protocol 019 n/N (%)	Historical Control n/N (%)
Infection Site		
Pulmonary	21/45 (46.7)	32/154 (20.8)
Extrapulmonary	5/18 (27.8)	3/52 (5.8)
Underlying Disease		
Hematologic malignancy	15/41 (36.6)	19/144 (13.2)
Organ transplant	3/8 (37.5)	9/32 (28.1)
Solid tumor	3/3 (100)	2/10 (20.0)
Other/none	5/11 (45.5)	5/20 (25.0)
Neutropenic Status		
Neutropenic	2/14 (14.3)	4/57 (7.0)
Nonneutropenic	24/49 (49.0)	31/149 (20.8)
Corticosetroid Use		
< 20 mg/day	18/40 (45.0)	27/132 (20.5)
≥ 20 mg/day	8/23 (34.8)	8/74 (10.8)

Reviewer's Comment: *In addition to the tabular comparison of the two studies, the applicant also conducted a more formal quantitative comparison of the results of Protocol 019 and the Historical Control Study using logistic regression. The logistic regression also adjusted for potential imbalance in identified prognostic factors and*

outcomes were compared after adjustment. The factors that the sponsor used to adjust the model seemed to be relatively balanced between two studies. Since the comparability of Protocol 019 and the Historical Control is questioned (see discussion below), conducting the logistic regression is not deemed appropriate and will not be discussed further.

During the review of this submission, questions regarding the actual comparability of these two studies arose. In order to answer some of our concerns regarding the use of historical controls and the comparability of Protocol 019 and the Historical Control Study, an epidemiological consult was requested from OPDRA. For a complete discussion of these issues, please refer to the consult memo written by Judy Staffa, Ph.D., R.Ph.

As documented in the medical literature, the use of historical controls can lead to false conclusions of a positive treatment effect due to a number of potential biases making the groups non-comparable. The remainder of this review will discuss the sources of potential bias associated with historical control studies as seen in this NDA submission. The major biases associated with historical controls can be grouped into three types: information bias, bias from secular trends in diagnosis and treatment, and selection bias. Each type of bias will be reviewed separately, highlighting the issues of most concern.

Most often, information is more accurate and complete for the current treated group than for a historical control group. This better information could lead to an apparent treatment effect that in actuality is due to differences in the quality of information available. For this submission, the assessment of outcome was not as rigorous with the Historical Control Study, due to the lower quality of available information. For example, the data was obtained retrospectively from medical records rather than prospectively from patient exams and information in concomitant medications and underlying disease (potential confounders) were not completely abstracted or available from medical records. Furthermore, the expert assessments varied greatly between the two studies.

The difference in calendar time between the experience of the current treated group and that of historical controls can also make observed differences difficult to interpret. Changes in other factors unrelated to the treatment of interest that occur over time could produce effects that are falsely attributed to the studied treatment. The Historical Control group for this submission was abstracted from patients diagnosed during the 3 years prior to and including the year Protocol 019 began enrollment. During this time, the historical control observed success rate increases each year from 12.1% in 1995 to 20.6% in 1998. These results are summarized in Table 4.

Table 4
Historical Control Success Rates
By Year of Enrollment

	1995	1996	1997	1998
	12.1%	12.5%	18.6%	20.6%
Total N=206	n=33	n=40	n=70	n=63

An improved ability over time to manage the underlying disease of these patients, possibly due to newly available treatments from 1995 to 2000 in transplantation and oncology, could also point to an explanation for some of the differences seen in the two groups.

Selection bias occurs when certain types of patients are selected into the treatment group but not into the control group, or vice versa. As discussed previously, there were differences in the distribution of US patients and European patients between studies. In addition to the difference in distribution, there were differences in the success rates by geographic region as summarized in Table 5. The European patients appear to have had a higher success rate than the US patients in Protocol 019. However, the reverse is true for the Historical Control though the number of European subjects is small.

Table 5
Clinical and Radiographic Response at End of Antifungal Therapy
By Geographic Region

	Protocol 019	**Historical Control**
US	10/29 (34.5)	32/183 (17.5)
Europe	16/34 (47.1)	3/23 (13.0)

Table 6 summarizes the duration of prior/standard therapy, the duration of caspofungin therapy for patients enrolled in Protocol 019, and the total duration of treatment for the current aspergillosis infection. Patients in Protocol 019 were on their prior therapy longer than the Historical Control group was on their total therapy. This can be seen in the difference in the means, 49.8 days for the caspofungin group versus 29.2 days for the Historical Control group. The largest percentage of patients received 0 to 25 days of prior/standard therapy. Patients in Protocol 019 then went on to receive an average of 36.3 days of caspofungin therapy extending their total duration of therapy (prior therapy plus caspofungin therapy) to an average of 86.1 days. The largest difference in total therapy is accounted for during the first three weeks of total duration. It is known that patients who receive short courses of therapy are less likely to respond. On the other hand, there is the possibility that less aggressive therapy may have been pursued for severely ill patients. Therefore, Protocol 019 potentially enrolled subjects who were less ill than patients enrolled into the Historical Control. Taking all of these factors into consideration, the Historical Control group may be more comparable to the population of patients eligible to enroll into Protocol 019 rather than to the group of patients at the end of caspofungin therapy.

Table 6
Duration of Therapy

	Protocol 019	Historical Control
Duration of Prior/Standard Therapy, days		
0-25	29 (46.0)	132 (64.1)
26-50	18 (28.6)	44 (21.4)
51-75	6 (9.5)	15 (7.3)
76-100	4 (6.3)	6 (2.9)
> 100	6 (9.5)	9 (4.4)
Mean (sd)	49.8 (75.6)	29.2 (27.7)
Median	29	20
Min, Max	2, 520	7, 142
Duration of Cancidas Therapy, days		
0-25	29 (46.0)	
26-50	19 (30.2)	
51-75	8 (12.7)	N/A
76-100	3 (4.8)	
> 100	4 (6.3)	
Mean (sd)	36.3 (35.0)	
Median	28	
Min, Max	1, 162	
Duration of Total Therapy, days		
0-25	10 (15.9)	132 (64.1)
26-50	18 (28.6)	44 (21.4)
51-75	9 (14.3)	15 (7.3)
76-100	8 (12.7)	6 (2.9)
> 100	18 (28.6)	9 (4.4)
Mean (sd)	86.1 (87.1)	29.2 (27.7)
Median	57	20
Min, Max	9, 527	7, 142

Table 7 demonstrates the importance of the time on treatment to overall outcome. Even though there were differences in the distributions of duration of therapy for the current aspergillosis infection, the favorable response rate stratified by total duration of therapy does not differ between the two studies. The favorable response rate ranges from approximately 10% for 0-25 days on therapy to 67% for more than 100 days on therapy in both Protocol 019 and the Historical Control Study. Though an effective treatment may allow patients to remain on treatment longer, the fact that time on treatment is so highly predictive of outcome cannot be ignored especially given that patients treated with caspofungin were on their prior therapy longer than the Historical Controls were on their standard therapy.

Table 7
Clinical and Radiographic Response at End of Antifungal Therapy
By Total Duration of Therapy

Days	Protocol 019	Historical Control
0-25	1/10 (10.0)	9/132 (6.8)
26-50	5/18 (27.8)	10/44 (22.7)
51-75	4/9 (44.4)	7/15 (46.7)
76-100	4/8 (50.0)	3/6 (50.0)
> 100	12/18 (66.7)	6/9 (66.7)
Overall efficacy	26/63 (41.3)	35/206 (17.0)

Another example of selection bias is the differences in the exclusion criteria for the two studies. The exclusion criteria were more relaxed in the Historical Control Study. This may have allowed sicker patients into the historical control group whose outcomes would be worse. The most troublesome exclusion criteria is that patients who were not expected to survive at least 5 days were to be excluded from enrollment into Protocol 019. This criterion was not implemented in the Historical Control Study.

All of the biases discussed above could act to predispose the Historical Control group to have a lower success rate and the caspofungin treated group to have a higher success rate independent of treatment with caspofungin. These notable differences between Protocol 019 and the Historical Control Study may provide alternative explanations for at least part of the treatment effect seen. It is not clear that all of the treatment effect is due to treatment with caspofungin and it is difficult to quantify the potential effects of these biases. Therefore, the two study populations are not comparable from a statistical standpoint.

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III. SAFETY EVALUATION

In addition to Protocol 019, clinical pharmacology studies and additional comparative studies in Candida infections support the safety of caspofungin. The following table is a clinical adverse event summary from Protocol 019. For the detailed review of the safety data, please see the Medical Officer review written by Dr. Eileen Navarro.

Table 8
Clinical Adverse Event Summary

Number (%) of patients:	Caspofungin Acetate 50 mg[1] (N=69)
With one or more adverse experience	64 (92.8)
With no adverse experience	5 (7.2)
With drug-related adverse experience[2]	10 (14.5)
With serious adverse experiences	54 (78.3)
With serious drug related adverse experiences	1 (1.4)
Who dies	38 (55.1)
Discontinued therapy due to an adverse experience	27 (39.1)
Discontinued therapy due to a drug related adverse experience	1 (1.4)
Discontinued therapy due to a serious adverse experience	27 (39.1)
Discontinued therapy due to a serious drug related adverse experience	1 (1.4)

1 Patients received a loading dose of caspofungin acetate 70-mg on Day 1 and then received caspofungin acetate 50 mg for remainder of treatment period.
2 Considered by the investigator to be possibly, probably, or definitely drug related.

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Reviewer's Conclusions (which may be conveyed to the sponsor in the action letter)

The Historical Control Study is not comparable to Protocol 019. Therefore, the efficacy of Cancidas ™ (caspofungin acetate) for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies has not been demonstrated compared to a control. It is up to the reviewing medical division to determine whether the results of Protocol 019 alone are sufficient on which to determine the efficacy of this drug.

Cheryl Dixon, Ph.D.
Biostatistician, DOB III

Concur: Karen Higgins, Sc.D.
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cc:
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This review contains 12 pages.