

Background Document  
for  
Antiviral Drug Products Advisory Committee Meeting  
January 10, 2001

CANCIDAS™  
(Caspofungin acetate for intravenous injection)  
Merck Corporation  
NDA 21-227

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Special Pathogen and Immunologic Drug Products

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## I. Introduction

Merck Corporation has submitted a new drug application (NDA) for CANCIDAS™ (caspofungin acetate) for the indication of therapy for invasive aspergillosis (IA) in patients refractory to, or intolerant of, standard antifungal therapy. Caspofungin is the first member of a new class of antifungal drugs (echinocandins) submitted for approval as an antifungal agent. Caspofungin reduces the synthesis of  $\beta$  (1,3)-D-glucan, an essential structural cell wall component of fungi, whereas available antifungal agents including the polyenes, (such as amphotericin B) and the azoles, (such as itraconazole) are active against fungal cell membranes. The cell wall is a component of fungal cells that is not found in mammalian cells, and loss of cell wall glucan results in osmotic fragility of the fungal organism. The activity of the drug on the cell wall is accomplished indirectly, by non-competitive inhibition of a gene whose product is a cell membrane protein responsible for glucan synthesis.

The purpose of this document is to provide background information for the Antiviral Drug Products Advisory Committee meeting scheduled for January 10, 2001. The document is organized as follows:

1. A brief summary of CANCIDAS™ proposed labeling, microbiology, pharmacokinetics and animal model data.
2. Available therapies for IA; outcomes in historical controls.
3. Clinical data on the efficacy of CANCIDAS™ as therapy for refractory and intolerant IA
4. Safety of CANCIDAS™ in clinical studies of healthy subjects in the clinical pharmacology studies and in patients in the IA and Candida mucosal infections studies.

### **Proposed labeling of CANCIDAS™ :**

The proposed indication and usage, and dosage and administration sections of the product label for CANCIDAS™ for the treatment of IA reads as follows:

*Proposed indication and usage:*

"CANCIDAS™ is indicated for the treatment of IA in patients who are refractory to or intolerant of other therapies."

*Proposed dosage and administration:*

"A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily..... Although there is no information to demonstrate an increase in efficacy with higher doses, available safety data suggests that an increase in dose to 70 mg daily may be considered in patients without evidence of clinical response.....In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), after the initial 70-mg loading dose, CANCIDAS 35mg daily is recommended "

## II. CANCIDAS<sup>®</sup> Microbiology and Pharmacokinetics

### Microbiology

#### *Mechanism of action*

Caspofungin inhibits the activity of the enzyme glucan synthase from *Aspergillus fumigatus* with a 50% inhibitory concentration (IC<sub>50</sub>) value of 9.6 nM. The IC<sub>50</sub> values against *Candida albicans* and *Cryptococcus neoformans* were 0.6 nM and 2.5 :M, respectively. This enzyme is important in the synthesis of  $\beta$ -(1,3)-D-glucan from glucose. Glucan is an important constituent of the cell wall of many fungi. The proportion of this polysaccharide in the walls of different fungi varies which may explain the variable effect of the drug against various species. It is important to point out that even though caspofungin's ultimate activity is specific for a component of the fungal cell wall, this is accomplished by the drug's more immediate action on a cell membrane enzyme modulated by a FKS1 gene.

It is of note that incubation of *C. albicans* with cilofungin (an analogue of echinocandin) for 18 hours decreased the ergosterol content by 55 – 60 % and glucan content by >70% (Pfaller *et al.*, 1989). There was a minimal effect (4-13% reduction) on lanosterol. Chitin and manan content were increased. It is unclear whether the changes in chitin, mannan and ergosterol are a direct effect of cilofungin or a consequence of an alteration in glucan content leading to dysregulation

of carbohydrate synthesis that leads to changes in the integrity of the cell membrane. Whether caspofungin or other echinocandins will have a similar effect is unknown.

#### **Activity against *Aspergillus in vitro***

Caspofungin, like other echinocandins, does not show complete inhibition of growth against *Aspergillus* species. The minimum effective concentration (MEC) which altered the morphology of the hyphae of various species, varied from 0.06 to >2 :g/ml.

Staining with fluorescein dyes, which differentially penetrate the cell based on viability and non viability [5,6 carboxy fluorescein (CFDA) - a vital stain, and bis-(1,3-dibutylbarbituric acid) trimethane oxonol {DiBAC<sub>4</sub>(3)} - a non-vital stain, respectively], showed that caspofungin (0.3 :g/ml, for 6 hours) was lethal at the selective areas with active cell growth i.e., the apical tips of hyphae and areas of hyphal branching. In regions of less active growth the hyphae were viable. In comparison, amphotericin B at a concentration of 0.15 :g/ml resulted in an almost complete loss of viability of the organism. This difference is attributed to amphotericin B's disruption of membrane activity.

Standard broth dilution methods utilized for bacteria and yeasts are technically difficult to perform for filamentous fungi, therefore; *in vitro* susceptibility testing relies on a qualitative visual scale to quantitate growth inhibition. Using the NCCLS proposed method (M-38P), a substantial reduction in growth was used as an end-point. This was termed as MIC-2 (≡ 50% inhibition of growth) or MIC-80 (≡ 80% inhibition of growth). The *in vitro* susceptibility was measured in 5 different laboratories including the applicant's laboratory. The results of studies from 2 different laboratories are shown in Table 1. The MIC-2 and MIC-80 values shown in Table 1 show the variability in activity of caspofungin against different *Aspergillus* species.

The results of *in vitro* susceptibility of clinical isolates collected from patients enrolled in the study 019 are adequately described in the applicant's briefing package. Over 90 isolates [A. *fumigatus* (80), A. *flavus* (11), A. *niger* (4), and A. *terreus* (3)] were collected from 36 patients and tested for *in vitro* susceptibility.

It is of note that the *in vitro* activity of the drug varied with the medium, the concentration of the conidial suspension, and the incubation time. The usefulness of the MIC-2 or MIC-80 values in predicting clinical outcome has not been established.

Table 1: *In vitro* susceptibility of *Aspergillus* species isolates to Caspofungin in 2 different laboratories<sup>‡</sup>

Species	Espinel-Ingroff, 2000 (MIC-2, ug/ml)				Arikan <i>et al.</i> , 1999 (MIC-80, ug/ml)		
	Range	(n)	MIC <sub>90</sub>	Geometric Mean	Range	(n)	Geometric Mean
<i>A. fumigatus</i>	0.12-4	(56)	0.5	0.25	0.25->16	(26)	0.7
<i>A. flavus</i>	0.06-2	(13)	0.2	0.2	0.25->16	(27)	2.7
<i>A. nigers</i>	0.06-0.5	(10)	0.2	0.14	0.25-1	(17)	0.4
<i>A. terreus</i>	0.06-0.2	(11)	0.2	0.12	0.5	(9)	0.5
<i>A. nidulans</i>	0.2-4	(13)	0.5	0.44	0.5-1	(3)*	0.6*

‡ NCCLS M-38P protocol using RPMI medium (24 hour read, 35°C. MIC in the Espinel-Ingroff study represent  $\geq$ 50% inhibition in growth (MIC-2) and in Arikan *et al* study  $\geq$ 80% inhibition of growth (MIC-80)

\*represent 48 and 72 hour values; no growth observed at 24 hours

### Activity against *Aspergillus in vivo*

The *in vivo* activity of MK-0991 against *Aspergillus* species (*A. fumigatus* and *A. flavus*) was measured in immunocompromised rodents.

Activity against *A. fumigatus* (strain MF5668) was measured in C'5 deficient, neutropenic, and pancytopenic mice. In a study done in pancytopenic rats, strain H11-20 was used for infection. Administration of caspofungin was initiated either at the time of challenge or 24 hours later. The activity was measured by following the survival rate. The results show that caspofungin was effective in improving the survival rate (for details see applicant's briefing package). The activity of caspofungin was comparable to amphotericin B.

The effect on mycological burden was measured in a single experiment conducted in mice rendered pancytopenic and immunosuppression maintained for 28 days. Treatment with caspofungin was initiated 24 hours post-infection for 7 days. Only kidney tissues were processed for measurement of mycological burden. Other organs were not tested. The results show that caspofungin was effective in reducing mycological burden (based on colony forming

units i.e., cfu and histological findings) on days 4, 15, and 28. The results of mycological burden on day 8 are less clear since one of untreated mice was negative for cfu but had histological evidence of infection in 2 of the 4 sections screened. Overall, the activity of caspofungin was comparable to amphotericin B.

Against *A. flavus* infection in C'5 deficient mice, caspofungin at a dose of 0.31 mg/kg/ day for 5 days was marginally more protective than amphotericin B. The effect of caspofungin on mycological burden in animals infected with *A. flavus* was not measured.

### **Pharmacokinetics**

Concentration-time profile analysis indicate that after administration of a single dose as a 1 hour infusion (at 20 mg and higher doses), the decline in caspofungin concentrations is triphasic. The third disposition (terminal elimination) phase may be due to slow release of drug from tissues. The disposition phase half-lives are 1-2 hours, 9-11 hours, and 40-50 hours for Alpha, Beta and Gamma phases, respectively.

The geometric mean values of caspofungin clearance for 5, 10, 20, 40, 70 and 100 mg doses were 10.36, 11.02, 10.77, 11.99, 9.85 and 12.43 mL/min, respectively.

### ***Absorption, Distribution, Metabolism and Excretion***

Caspofungin does not have a large distribution volume as the steady-state volume of distribution of caspofungin is 9.67 L. Caspofungin is extensively bound to albumin (~97%) and based on blood/plasma partitioning ratio of ~0.74, it is not taken up extensively by red blood cells.

The major metabolic pathways of caspofungin involve peptide hydrolysis and N-acetylation. Caspofungin degrades chemically to L-747969, a ring-opened peptide, which is the major component of extractable radioactivity in plasma seen at later time points (5 days after a single dose). L-747969 does not have antifungal activity and it is expected to form throughout the body.

*In vitro* incubation experiments suggest that 2 potentially reactive intermediates (M1 and M2) are formed during the degradation of caspofungin to L-747969, and that these form covalent adducts to protein. Low levels of irreversible binding to plasma proteins (3 to 7 pmol/mg protein) were seen *in vivo* during later time points (Days 5 to 20) in the clinical disposition study. Additional metabolism of caspofungin appears to involve the hydrolysis of this hexapeptide into its constitutive amino acids or their degradation products.

The metabolites M1 and M2 were identified as the synthetic amino acid, dihydroxyhomotyrosine, and its N-acetyl derivative, respectively. These metabolites were only seen in urine, indicating that the clearance of M1 and M2 is fast relative to the formation and/or release rate. It is unclear whether the polar hydrolysis metabolites M1 and M2 are formed directly from caspofungin or through L-747969 and/or the protein adducts. The metabolism of caspofungin is very slow. Caspofungin was the major component of radioactivity in plasma and urine at 24 to 30 hours postdose in the clinical disposition study, indicating that little biotransformation occurs during the first day or 2 postdose.

Caspofungin is excreted unchanged at low levels in urine (1.44% of dose). The appearance of low amounts of radioactivity in feces by the second day following administration, at which time radioactivity in plasma is largely intact drug, suggest that there may be a low rate of biliary excretion of unchanged drug as well. Renal clearance of caspofungin is very slow, averaging 0.15 mL/min and 0.16 mL/min on Day 14 of daily dosing at 70 mg.

A striking feature of the radioactivity recovery was that little excretion of drug-related material occurred during the first few days postdose and that the rate of recovery did not peak until 6 to 7 days postdose for both urine and feces. This finding is consistent with there being a series of slow disposition steps occurring prior to the major pathway(s) of excretion. The spontaneous degradation of caspofungin to L-747969, as well as the formation of M1 and M2, are slow processes that may contribute to the delayed recovery of radioactivity. Extensive binding of L-747969 to liver tissues may also slow its release from liver or further biotransformation. The impact of this binding on safety was not significant.

After administration of a [ $^3\text{H}$ ]-labeled 70 mg of caspofungin dose, over a collection period of 27 days, approximately 75% of the radiolabeled dose (34 % in feces and 41 % in urine) was recovered.

*Special Populations:*

Clinical pharmacokinetic studies were carried out in special populations to define the influence of several factors, including the following:

*Age –*

The geometric mean clearance of caspofungin in elderly is 9.48 mL/min as compared to 12.48 mL/min in young subjects. The geometric mean ratio of clearance in healthy elderly men when compared to healthy young men is 0.76 and the 90% CI for this ratio is 0.64 to 0.90. The decrease seen in clearance in the elderly as compared to young subjects is considered small (a reduction in the point estimate of about 25%). There would be no need to reduce caspofungin dose in the elderly.

*Renal impairment –*

The geometric mean clearance of caspofungin is 9.72 mL/min in mild renal insufficiency, 7.08 mL/min in moderate renal insufficiency, 6.24 mL/min in advanced renal insufficiency, and 7.17 mL/min in end-stage renal insufficiency as compared to 9.31 mL/min in the control group. The geometric mean ratio (90% CI) of caspofungin clearance in mild, moderate, advanced, and end-stage renal insufficiency subjects when compared to controls are: 1.04 (0.85, 1.28), 0.76 (0.62, 0.94), 0.67 (0.56, 0.80), 0.77 (0.65, 0.92), respectively.

The geometric mean ratio (90% CI) of caspofungin AUC values in mild, moderate, advanced, and end-stage renal insufficiency subjects when compared to controls are: 0.96 (0.78, 1.17), 1.31 (1.07, 1.62), 1.49 (1.24, 1.79), 1.30 (1.09, 1.56), respectively. Given the overlapping range of confidence intervals, the effect of renal impairment on caspofungin exposure is similar in subjects with moderate, advanced (severe) and end-stage renal impairment and clearance of caspofungin is approximately 30% less in these subjects

compared to the clearance values in the control group. Overall impact of this reduction in clearance is not expected to warrant a dosage adjustment in subjects with renal impairment.

*Hepatic impairment –*

The geometric mean clearance of caspofungin is 6.33 mL/min in subjects with mild hepatic insufficiency and 5.55 in subjects with moderate hepatic insufficiency as compared to controls, 9.77 mL/min.

The geometric mean ratio of caspofungin clearance in subjects with mild hepatic impairment when compared to controls is 0.65 and the 90% CI for this estimate is 0.55 to 0.76. The geometric mean ratio of caspofungin clearance in subjects with moderate hepatic impairment when compared to controls is 0.57 with a range of 0.49 to 0.66 for the 90% CI.

The geometric mean ratio of caspofungin AUC values in subjects with mild hepatic impairment when compared to controls is 1.55 and the 90% CI for this estimate is 1.32 to 1.86. The geometric mean ratio of AUC values of caspofungin in subjects with moderate hepatic impairment when compared to controls is 1.76 with a range of 1.51 to 2.06 for the 90% CI.

Dose adjustment is needed in the moderate hepatic insufficiency patients. The dosing recommendation is 35 mg daily after 70 mg loading dose. From the results obtained in the single dose study, dosage adjustment is also needed in the mild group. The sponsor is performing a multiple dose study in mild hepatic insufficiency patients to confirm results obtained in the single dose study. The preliminary results, geometric mean ratio and (90% CI) received so far from the multiple dose study in the mild hepatic insufficiency group compared to matched healthy control: AUC<sub>0-24</sub>, and C<sub>24</sub> are 1.19 (1.03, 1.37) and 1.42 (1.14, 1.77). These results are obtained on day 14 after receiving 70 mg loading dose and 50 mg dose daily. Based on these preliminary results dosage adjustment in mild hepatic insufficiency group is not needed.

The effect of hepatic insufficiency on single doses of caspofungin was evaluated in otherwise healthy adults with mild to moderate hepatic insufficiency and compared to control subjects with normal hepatic function. Substantial increases in AUC were noted in subjects with hepatic insufficiency, varying from 55% in subjects with mild to 76% in subjects with moderate hepatic insufficiency, compared to normal controls. A multiple dose study is being undertaken to better characterize the drug's kinetics in moderate hepatic insufficiency.

*Drug-Drug Interaction:*

The following drugs (CYP450 substrates/inhibitors) were studied with caspofungin:

Cyclosporine, Amphotericin B, FK-506 (tacrolimus), itraconazole, and mycophenolate.

Although cyclosporine  $C_{24}$  changed 2 fold, the increase in  $AUC_{0-24}$  was approximately 35%. This change was considered clinically insignificant, and therefore, no dosage adjustment is recommended.

For FK-506, the geometric mean ratio (90% CI) of  $AUC_{0-12}$ ,  $C_{max}$ , and  $C_{12}$  are 0.80 (0.72, 0.89), 0.84 (0.75, 0.95), and 0.75 (0.63, 0.86), respectively. This should not be of concern since tacrolimus trough concentrations are usually monitored.

No remarkable changes ( $\pm 20\%$ ) of the point estimate were observed for  $AUC_{0-24}$ ,  $C_1$ , and  $C_{24}$  when caspofungin was administered with amphotericin B, itraconazole, and mycophenolate. Therefore, dosage adjustment would not be necessary.

### III. Efficacy

#### Outcome of patients with invasive aspergillosis refractory to or intolerant of standard antifungal therapies.

Despite the documented increase in invasive aspergillosis (IA) in patients at risk, development of effective therapies and the evaluation of efficacy of such therapies for a relatively rare but highly fatal disease, remains a challenge. Desoxycholate Amphotericin B (dAmB), was approved in 1971 for the treatment of IA following review of efficacy in 50 patients assembled from the published literature. The efficacy rate of dAmB ranged from 41% when unevaluable patients were excluded from analysis, to 32%, when an outcome of failure was imputed for missing data.

Several agents are approved as therapies for IA in patients refractory to or intolerant of amphotericin B. These include four intravenous formulations from 2 drug classes: Itraconazole, an azole also available in oral formulation, and three liposomal amphotericin B products. In the new drug applications for these drugs submitted to the Agency, the efficacy of these agents was compared to standard therapy consisting of amphotericin B with or without flucytosine, either through a historical control study or concurrently treated controls (Table 2).

**Table 2: Outcomes of patients with IA refractory to or intolerant of desoxycholate amphotericin B in the NDAs of antifungal agents approved for salvage therapy**

Drug (Date Approved)	Design, Endpoint Outcome	Efficacy of dAMB	
		N	% SUCCESS
ITRACONAZOLE (1992)	concurrent / EOT / mortality	43	10
ABELCET (1995)	historical / EOT / clinical success	(91) <sup>+</sup>	23
AMPHOTEC (1996)	historical / EOT / clinical success	(60)	43
	concurrent / EOT / clinical success	37	33
AMBISOME (1997)	concurrent / EOT / clinical success	16	31

Legend: R = refractory to desoxycholate Amphotericin B  
 I = intolerant of desoxycholate Amphotericin B  
 dAmB = desoxycholate Amphotericin B  
 EOT = end of therapy

<sup>+</sup>Numbers in parenthesis refer to evaluable patients obtained from historical control studies.

Differences in study design, as well as review methodologies preclude a comparison of efficacy across these studies, but the information is presented to provide some perspective on the outcome of patients with aspergillosis who are refractory to or intolerant of standard therapy. In the itraconazole application, the historical control consisted of patients recruited through single patient treatment INDs who were to receive itraconazole but failed to do so for a variety of reasons. These patients excluded from the active treatment arm were considered to have more severe disease, with many patients dying before the investigational drug could be administered. For Abelcet® and Amphotec®, a historical control was compiled from a retrospective review of patients who were refractory to or intolerant of amphotericin B (presented in parenthesis in Table 2).

Despite the availability of these alternate therapies, the outcome for IA remains poor. In addition, while currently approved as therapies for patients refractory to or intolerant of dAmB, these agents are currently suggested as alternative for initial therapy by a number of authorities.

In this NDA, Merck compares the efficacy of caspofungin from a non-comparative open label study of patients with documented IA to a historical control derived from a retrospective review of charts in cases seen in a four-year period immediately preceding the open label studies. To ensure the comparability of the caspofungin treated cases to the historical controls, the same criteria were utilized to define cases and to assess outcome in the open label and the historical control studies. Nevertheless, some important differences between the open label and historical control studies bear pointing out:

1. Data source: The principal investigators prospectively identified cases by integrating clinical, radiologic and microbiological information in the open label studies. In the historical control, microbiology (including autopsy cultures) was an important method of case finding. Fifty-five percent of 87 patients with pulmonary aspergillosis and 61% of 42 patients with disseminated aspergillosis were identified by autopsy cultures in the historical control study. Furthermore, for 8 cases previously identified and treated as IA, only the last record of hospitalization was abstracted for inclusion. Additionally at one investigator site in the historical control study, 282 patients were not screened for possible inclusion because the patients had less than 2 positive cultures for *Aspergillus*

- spp.* On the other hand, 12 (17%) patients in the prospective open label study were considered for inclusion without a positive culture if an investigational test (galactomannan ELISA or PCR) were positive.
2. Case definitions: The historical control population was originally intended to reflect outcome in patients who would have been eligible for salvage therapy, by predetermined criteria for refractory infection or intolerance of therapy applied in the caspofungin open label study. Nevertheless, the conventions of drug use in IA made it difficult to define salvage therapy in the historical control population and no distinction was made between "primary and salvage therapy" in the applicant's analysis of the historical control study
  3. Demographics: To assure that the compared populations were analogous in terms of intensity of therapy for underlying disease, cases in the historical control were recruited backwards following first case enrolled in the prospective, open label study (Protocol 019). However, only four of the 20 sites that recruited cases in the open label study participated in assembling the historical control. In addition, most cases in the historical control were domestic, whereas nearly half the cases in the open label study were from international sites and differences in medical care between these sites and between domestic and international centers may be important in determining patient outcomes.
  4. Outcome assessment: The cases in the open label non-comparative study were reviewed by an independent expert panel, whereas the historical control cases were not reviewed by the expert panel at the time that the applicant submitted the NDA.

**Applicant efficacy analysis of CANCIDAS™ as salvage therapy in invasive aspergillosis refractory to or intolerant of standard antifungal therapy.**

Study 019 is a non-comparative, international trial of caspofungin in patients refractory to or intolerant of all available antifungal therapies. The efficacy of CANCIDAS™ is compared to the efficacy of all currently available antifungals in Study 028, a historical control study of patients refractory to or intolerant of seven days of standard antifungal therapy.

In Study 019, 69 patients were enrolled from US and non-US sites to receive the proposed label dose of 70 mg of CANCIDAS™ on Day 1, followed by 50 mg of CANCIDAS™ daily. These patients had been prospectively identified as either refractory to, or intolerant of 7 days treatment

with available antifungal therapy, and fulfilled the Mycoses Study Group criteria for proven/probable pulmonary aspergillosis or definite disseminated aspergillosis. In the historical control study (Study 028), 229 patients refractory or intolerant to antifungal therapies for IA fulfilled the same diagnostic and inclusion criteria.

The demographic and baseline characteristics of the patients in the 019 and historical control are comparable (Table 1 of the Appendix). The majority of patients in the historical controls was from US sites, and was refractory to antifungal therapy. A greater proportion of patients in the historical control study had definite infections and more disseminated infections.

The expert panel end-of-therapy response rates for CANCIDAS™ in Study 019 and the applicant's end-of-therapy response rates to available antifungal therapies in the historical control are shown in Table 3. The expert panel consisted of three members of the Mycoses Study Group who are internationally acknowledged experts in Mycology. The expert panel reviewed case report form data, radiographic, cultural and autopsy and pathology reports, in separately applying the criteria for disease definition, determining response to primary treatment as either refractory to or intolerant of standard therapy, and determining outcome of caspofungin treatment at end of treatment. Any discrepancies between the three panel members were resolved at face to face meetings with a review of case detail and relevant radiographs. A majority decision (2/3) determined the panel's final decision.

**TABLE 3: CLINICAL EFFICACY RATES FOR STUDY 019  
AS PER THE EXPERT PANEL / FDA ANALYSES  
COMPARED TO OUTCOMES IN THE HISTORICAL CONTROLS (STUDY 028)**

Population	CANCIDAS™ (Protocol 019)						Historical Control			
	Expert Panel		FDA ITT		FDA CE		Applicant MITT		FDA Subset MITT <sup>¶</sup>	
	N	[%]	N	[%]	N	[%]	N	[%]	N	[%]
All patients	26/63	41.3	25/65	38.5	25/56	44.6	35/214	16.4	19/96	19.8
Refractory	15/44	34.1	19/54	35.3	19/45	42.2	27/193	14.0	16/90	17.7
Intolerant Only	7/10	70.0	6/12	50.0	6/11	54.0	3/5	60.0	2/2	100
Pulmonary	21/45	46.7	21/51*	41.2	21/46	45.7	32/160	20.0	17/76	22.4
All other sites	5/18	27.8	4/10 <sup>*</sup>	40.0	4/8	50.0	3/54	5.6	2/20	10.0

\*\*6 patients with pulmonary infection suspected to have CNS aspergillosis

\* 1 patient with scalp osteomyelitis developed brain abscesses that subsequently resolved with continued therapy

<sup>¶</sup> FDA subset of the MITT= patients in the applicant's MITT who were defined in the submitted database to be either refractory to (7 days) or intolerant of (before or at 7 days) any antifungal agent(s)

ITT- intent to treat

MITT - modified intent to treat

CE – clinically evaluable

**FDA efficacy analysis of CANCIDAS™ for the treatment of invasive aspergillosis refractory to or intolerant of standard therapies compared to salvage therapies in the historical control**

The Division evaluated the clinical efficacy in the caspofungin treatment study (Study 019) and the historical control study (Study 028). In Study 019, the Expert Panel population excluded all patients who had no data at the end of therapy on which to base a response. Additionally, patients who were subsequently identified to have an infection other than aspergillosis were also excluded from the expert panel assessment. The Division's rates for end of therapy clinical success in this population for Study 019 were comparable to the Expert panel assessment. Additionally, the Division performed two efficacy analyses in Study 019, to achieve the following objectives:

- 1) To determine the overall efficacy of CANCIDAS™ in patients who fulfill the clinical criteria of definite and probable IA at the time the decision to treat is made, excluding autopsy or culture information available subsequent to completion or discontinuation of therapy (efficacy analysis in the intent to treat population [ITT]).
- 2) To determine the efficacy of CANCIDAS™ in patients who receive at least 7 days of therapy, in the same manner that the historical control population was determined to be refractory to or intolerant of 7 days of antifungal therapy (efficacy analysis in the clinically evaluable population [CE]).

The Division excluded indeterminates ( $n = 2$ ) at the end-of-therapy analysis to parallel the expert panel analysis in Study 019. Finally, the Division compared the efficacy in the ITT and CE populations to applicant's outcomes in the historical control population (Table 3). Caspofungin achieved clinical success rates between 38.5% to 50% in the ITT and between 44.6% and 54% in the CE analysis. The comparable rate in the applicant's analysis was 41% based on the expert panel assessment. There were no successes in the persistently neutropenic patients.

In an attempt to determine the efficacy of currently available salvage therapies, the applicant's historical control database was reviewed to characterize the antifungal agents employed as initial treatment of IA, and the category assessment of refractory or intolerant at least 7 days of treatment. The Division assembled a population requiring salvage therapy, analogous to that in

the open label study by excluding patients who received one antifungal or multiple concurrent antifungals without significant modifications throughout their treatment. The remaining 96 cases could be considered as patients who received treatment modifications for invasive aspergillosis refractory to or intolerant of the initial treatment.

Efficacy analyses in this population was then carried out, using the efficacy determined by the investigator as the default outcome. The overall outcome in the Division subpopulation of patients refractory to or intolerant of standard treatment did not differ from the overall outcomes in the applicant's historical control MITT population. There were no successes in the persistently neutropenic patients.

The most important information obtained from the historical control is a description of the contemporary use of available antifungal therapies in patients suspected to have IA, in the centers with the largest cumulative experience with treating these cases. Most patients in the historical control were treated with a multiplicity of antifungal drugs, concurrently or in sequence, with a mean 3.86 modifications to drug, dose and route of therapy over the course of therapy, which on the average lasted about 30 days. While intolerance was the reason for a significant number of these treatment modifications, the predominant reason for a treatment change was attributed to refractory disease. All of the available drugs were utilized as primary therapy, whether or not they are so labeled. In addition, no distinction can be made regarding their prophylactic or therapeutic use, particularly in the solid organ transplant recipient. Furthermore, their use in combination is the norm rather than the exception, with the oral formulation of itraconazole often employed as a single agent for suppression of the disease at the time of hospital discharge. When employed as such, it becomes very difficult to retrospectively define a discrete course of therapy and even more difficult to ascribe outcome to a specific antifungal agent.

While it can be argued that these adjustment therapies reflect the challenge in treating severely ill patients requiring salvage therapy, it is equally probable that the changes reflect the lack of certitude about the optimum therapeutic approach to a disease for which no antifungal drug has

consistently affected a cure, and for which immune reconstitution and surgical extirpation play equally important roles.

### **Efficacy of CANCIDAS™ in patients with invasive aspergillosis involving the central nervous system**

In protocol 019, definition of extrapulmonary involvement was based on histopathologic evidence of infection, possibly underestimating the degree of central nervous system (CNS) involvement. Nevertheless, in Study 019, six patients were considered to have possible CNS aspergillosis on entry into study. Two of these patients responded to caspofungin. The first was a 66 year old diabetic female (#366) diagnosed with *Aspergillus versicolor* skull osteomyelitis following a penetrating skull injury. She developed renal insufficiency following 520 mg of amphotericin B. A CT scan of the head at the start of caspofungin therapy showed a brain abscess that resolved following 27 days of caspofungin therapy. The second patient (# 251) was a 53 year old male with a successful renal transplant who was being treated for pulmonary aspergillosis with caspofungin following clinical failure of 36 days of liposomal amphotericin B. A head MRI done 10 days into treatment with caspofungin revealed bilateral brain abscesses that resolved after an additional 48 days of treatment. These two patients with successful outcomes at end of therapy had received significant prior therapy with amphotericin, and were less significantly immunocompromised compared to the patients who failed therapy.

Two patients were identified on autopsy to have central nervous system involvement, whereas this was clinically unsuspected when the patient was enrolled into the study (Table 4). The overall efficacy of caspofungin in patients with proven or suspected CNS infection is 25%.

Table 4: Central nervous system involvement in patients with IA

Patient #	Initial Diagnosis	Final Diagnosis	Outcome at end of therapy
018	definite pulmonary (possible CNS)*	disseminated w/CNS	failure
191	probable pulmonary, possible CNS		failure
251	probable pulmonary, possible CNS		partial response
366	skull osteomyelitis, possible CNS		complete response
426	probable pulmonary, possible CNS		failure
427	probable pulmonary, possible CNS		failure
506	probable pulmonary, possible CNS	disseminated#	failure
507	probable pulmonary (possible CNS) <sup>+</sup>	disseminated w/CNS	failure

\*clinically evident on day 16 of caspofungin

<sup>+</sup> clinically evident on day 58 of treatment

# brain excluded from autopsy

### Summary of CANCIDAS™ Efficacy in Invasive Aspergillosis

In the clinical studies of IA in patients refractory to or intolerant of IA, caspofungin achieved clinical success rates between 35.8% (refractory) to 70% (intolerant) in the expert panel's analytic population, to between 38.5% to 50% in the Division's ITT and between 44.6% and 54% in the Division's CE analytic populations. The efficacy rates for refractory patients were lower compared to the efficacy in patients who were only intolerant to standard drug therapy. Six of 8 of patients with possible CNS involvement and all persistently neutropenic patients failed. The success rates in the historical control study population were between 14.4 to 17%.

#### **IV. Safety of CANCIDAS™ in clinical studies of healthy subjects in the clinical pharmacology studies and in patients in the Invasive Aspergillosis and Candida mucosal infections studies.**

Caspofungin is a water soluble semisynthetic antifungal product active against a novel fungal target,  $\beta$  (1,3)-D-glucan. It is not related to any currently approved antifungal agents. Findings in preclinical studies in animals were notable for histamine release-like reactions, eosinophilia, and frequent elevations of transaminases. Most abnormalities were deemed to be mild in severity. In humans, the drug was studied over a variety of doses and durations in both healthy subjects and ill patients.

##### **Pharmacological Studies**

Pharmacological studies were performed on healthy volunteers, as well as special populations, some of whom had stable underlying illness and no confounding factors. Duration of drug exposures ranged from single doses to 21 days, administered under controlled conditions.

Studies in patients with fungal infections involved longer durations of drug exposure in a population on multiple concomitant medications and with multiple confounding background illnesses.

##### *Extent of exposures in the Clinical Pharmacology and Clinical Studies*

Of 612 patients who received single or multiple doses, 274 were healthy adults in the clinical pharmacology studies and 338 were patients with fungal infections. Eighty-one patients (32.8%) in the clinical pharmacology studies received the proposed label dose of 50 mg, whereas 157 (57.3 %) received doses higher than the proposed dose (generally 70 mg). Of the patients that received the highest dose strata, 75 (47.8%), received a single dose. This information is summarized in the following table:

Table 5: Summary of Caspofungin acetate in Clinical Pharmacology Studies

	Caspofungin Acetate			Total Number of Subjects Dosed With		
	<50mg	50mg	>50 mg	Caspofungin acetate	Amphotericin 0.5 mg/kg	Fluconazole 200 mg/d
Pharmacological	36	81	157	274	-	-
Clinical	34	233	71	338	89	93

Periods of treatment ranged from single dose [47 patients (17%)] to 162 days. Most patients received 7 – 10 days.

*Clinical and Laboratory Safety in the Clinical Pharmacology studies:*

The most frequent adverse events attributable to caspofungin in these healthy patients were mild to moderate infusion related adverse events and headaches. In subjects who received caspofungin acetate with itraconazole, a higher incidence of rash was noted in comparison to subjects who received caspofungin acetate alone.

Symptoms consistent with histamine release were noted in 5 patients (1.8%). This symptom complex could consist of dermatologic reactions (such as flushing, erythema, wheals, or rash), facial edema, respiratory symptoms (wheezing, or bronchoconstriction), and gastrointestinal symptoms (nausea, abdominal pain, or diarrhea), as illustrated by the following cases:

Patient 016 facial edema, swollen lips and wheezing

Patient 430 nausea, headache, pruritus, maculopapular rash, tachycardia, nasopharyngeal congestion and hypertrophy

The most frequent laboratory adverse event was an elevation of liver function tests. This appeared to be dose related, occasionally associated with an increase in the serum bilirubin, and exacerbated by cyclosporin co-administration. Although infrequent, increases in serum

creatinine to 1.5 times (range 1.0-1.5) baseline occurred even when caspofungin was administered alone. The adverse events reported are summarized in the following table:

**Table 6: Deaths, Serious Adverse Events and Treatment Discontinuations Due to AEs:  
Clinical Pharmacology Studies**

	All Caspofungin N=274		All Comparators N=38	
		n(%)		n(%)
<b>Death</b>				
From All Causes	0		0	
Due to Adverse Events	0		0	
<b>With any adverse event</b>	127	(46.4)	23	(60.5)
<i>drug related</i>	68	(24.8)	14	(36.8)
<i>serious</i>	6	(2.2*)	0	
<i>serious drug related</i>	0	0		
<b>Serious Adverse Events by dose*</b>				
<50 mg	1	(0.4)	-	
50 mg	2	(0.7)	-	
>50 mg	3	(1.1)	-	
<b>Discontinued from All Other Causes</b>	14	(5.2)	2	(5.3)
<i>Voluntary withdrawal</i>	1	(0.4)		
<i>Trial terminated?</i>	8	(2.9)		
<i>Lost to follow-up</i>	3	(1.1)		
<i>Protocol Deviation</i>	1	(0.4)		
<i>Administrative (IV access)</i>	1	(0.4)		
<b>Discontinued due to AE</b>	5	(1.8)*	0	
<i>due to a DRAE by dose*</i>				
<50 mg	1	(0.4)	-	
50 mg	1	(0.4)	-	
>50 mg	3	(1.1)	-	
<i>due to serious AE</i>	2	(0.7)	0	
<i>due to serious DRAE</i>	0		0	
<b>DRAE by body system</b>				
<i>Body as a whole</i>	26	(9.5)	5	(13.2)
<i>Cardiovascular</i>	27	(9.8)	6	(15.8)
<i>Nervous system</i>	25	(9.1)	11	(28.9)
<i>Digestive</i>	13	(4.7)	6	(15.8)
<i>Skin</i>	14	(5.1)	8	(21.1)

	<i>All Caspofungin</i> N=274		<i>All Comparators</i> N=38	
	n	(%)	n	(%)
<i>Respiratory</i>	2	(0.7)	2	(5.3)
<i>Urogenital</i>	1	(0.4)	2	(5.3)
<i>Metabolic</i>	1	(0.4)	0	

*DRAE = Drug-related adverse event*

*\*1 case each of trauma, cellulitis, pulmonary edema, cholelithiasis and pancreatitis, dyspnea and ascites, deep venous thrombosis; none were drug-related*

**Liver function abnormalities:**

An increase in liver enzymes was the most common laboratory adverse experiences observed, and are summarized in the following table.

**Table 7: Liver function abnormalities: Clinical Pharmacology Studies**

	Total		Caspofungin alone		Caspofungin plus other drugs*	
	Number	(%)	Number	(%)	Number	(%)
Number of subjects						
With one or more AE	14/243	5.1				
< 50 mg	0/36	0	0/28	0	0/8	0
50 mg	1/81	1.23	1/47	2.1	0/34	0
70 mg	13/156	8.33	5/115	4.3	8/41	19.5
ALT increase	11/273	4.0				
< 50 mg	0/36	.	0/28	0	0/8	0
50 mg	1/81	1.23	1/47	2.1	0/34	0
70 mg	10/156	6.4	2/115	1.7	8/41	19.5
AST increase	8/273	2.9				
< 50 mg	0/36	0	0/28	0	0/8	0
50 mg	1/81	1.23	1/47	2.1	0/34	0
70 mg	6/156	3.85	2/115	1.7	4/41	9.7
Bilirubin increase	9/273	3.29				
< 50 mg	0/36	0	2/28	7.1	0/8	0
50 mg	1/81	1.23	1/47	2.1	4/34	11.8
70 mg	6/156	3.85	2/115	1.7	0/41	0

\*Includes tacrolimus, cyclosporin, amphotericin B, itraconazole.

At the dose and durations administered, these increases did not exceed a 4-fold increase over the upper limit of normal (ULN), and were generally reversible following discontinuation of the drug. Concomitant administration of caspofungin acetate with cyclosporin A was associated with a pronounced increase in ALT and/or AST compared to when the drug is used alone. The liver enzyme and bilirubin elevations appear to be dose related, although the numbers of patients in the dose categories are small.

#### *Other events*

Six patients had serious adverse events that were not considered to be drug related. Mild to moderate infusion related adverse events (pruritus, erythema, induration and pain) and frequent headaches also occurred. As previously noted, increases in creatinine to up to 1.5 times baseline were seen in 5 of 156 patients.

#### **Safety in Protocol 019: Non-Comparative Clinical Studies on Invasive Aspergillosis:**

Of the 69 patients enrolled in the study, 42 (60.9%) had exposures longer than the 14 day course for patients in the mucosal candidiasis studies.

Clinical adverse events were frequent (93.1%) and often considered serious (75.9%), although the incidence of drug-related clinical adverse experiences was 13.8%.

- 1) Drug related adverse events developed in eight patients. These included headaches(1), nausea(2), fever(2), flushing(2) and rash(1). Flushing was a distinctive drug related adverse event in two patients. One patient was a 45 year-old female who experienced flushing (“sensation of warmth”) accompanied by a rash, stomatitis and peribuccal exanthema starting on Day 3 through 6 of caspofungin acetate therapy. These symptoms resolved on continued caspofungin acetate therapy with no associated eosinophilia, or increased liver function tests.
- 2) Serious adverse events: Only one serious clinical adverse event was drug related, that of a 38 year old patient post allogeneic bone marrow transplant for multiple myeloma who developed pulmonary infiltrates, for which the investigator discontinued therapy. None of

the other serious adverse events, including deaths, edema/swelling, or hypotension were drug related.

- 3) Treatment discontinuations: Twenty-three patients (39.7%) discontinued therapy due to an adverse event, all serious and generally attributed to the underlying disease, or worsening of invasive aspergillosis.
- 4) Deaths: 53.4% of the patients died, none of which were attributed to caspofungin.
- 5) Two patients developed flushing, and erythema, possibly consistent with a histamine-mediated reaction. Rashes were seen in 12 additional patients without any other feature compatible with a histamine reaction.

### **Laboratory Adverse Events in Protocol 019**

- 1) Serious drug related laboratory adverse events was reported in a 23-year-old man who underwent an allogeneic bone marrow transplant for Hodgkin's disease and disseminated aspergillosis, refractory to AmBisome™. The patient was noted to have a serum calcium of 11 mg/dL (baseline, 9 mg/dL); on Day 28. Four days later, the calcium had risen to 12.8 mg/dL for which he was treated with pamidronate. The hypercalcemia was initially considered to be due to underlying lymphoma or aspergillosis of the spine. On follow-up, hypercalcemia did not recur despite worsening aspergillosis and a bone marrow biopsy that failed to demonstrate relapsed lymphoma. The patient was not on any medications that could have caused hypercalcemia, which at this time was considered to be probably related to caspofungin acetate because of resolution following drug discontinuation.

An increase in urine protein (3/51 patients; 5.9%) and an increase in tacrolimus levels (2/17 patients; 11.8%) were the only other drug related adverse events. There were no drug-related deaths.

- 2) Liver function abnormalities were the most common laboratory adverse experiences (15%) among the patient population, with increased serum alkaline phosphatase in 21.1% and increased AST in 14.8%. Two of 57 patients (3.5%) had 5-fold change over baseline in any one liver enzyme value whereas 15/57 (26.3%) had a 2.5-fold change over the upper limit of normal in any one liver enzyme value. Only 2 of these patients with increased liver function

tests had a concomitant raised bilirubin. The investigators attributed all of these elevations in liver enzymes to the patients' underlying disease.

- 3) Forty patients in Study 019 had elevated baseline creatinine or a history of renal insufficiency. One of these patients discontinued therapy due to a progressive rise in BUN and creatinine. Twelve patients developed renal insufficiency in Protocol 019. Only 2 of these occurred in patients without prior renal insufficiency. The first patient (described above) developed renal failure with hypercalcemia, whereas the other, a 42-year old Caucasian female developed renal insufficiency on follow-up, off drug.
- 4) Two patients developed elevated tacrolimus levels and were considered possibly drug-related laboratory adverse experiences although these patients were receiving a number of concomitant medications that often alter tacrolimus levels.
- 5) Possible histamine and other dermatologic reactions: Sixteen patients had elevations of eosinophils over baseline. Four (25%) of these patients (patient nos. 16, 57, 62 and 446) had a dermatologic adverse event consisting of either pruritus, rash or erythema and flushing. On the other hand, 11 other patients had a rash or erythema or pruritus, but no elevation in eosinophils (patient nos. 61, 63, 102, 157, 297, 326, 327, 328, 411, 412, 486).

The dose employed in most of these patients was similar to that utilized in the mucosal Candida studies. However, given the severe underlying diseases predisposing to aspergillosis and the longer duration of treatment for this infection, the adverse event rates from this study are higher than those reported for the patients with mucosal Candidiasis.

### **Supportive Safety Information**

Controlled Clinical Studies for Candida Infections (Protocols 003, 004, 020)

Four hundred fifty five patients with mucosal Candida infections received caspofungin acetate. None of the patients that received caspofungin experienced a serious drug-related clinical adverse event. The incidence of drug-related clinical adverse experiences was generally similar among the caspofungin acetate patients that received either 35 mg, 50 mg or 70 mg doses (45.1 to 55.4%). Discontinuations due to drug related adverse events were infrequent (6/445 or 1.3%). No deaths in these studies were attributed to drug.

By contrast, control patients treated with amphotericin B group experienced serious drug-related clinical adverse experiences in 4% and serious drug-related clinical adverse experiences leading to discontinuation of therapy in 2.2%. Among fluconazole treated patients serious adverse events were reported in 1.1 %.

The following table summarizes the incidence of selected clinical adverse experiences (incidence >3% for at least one treatment dose; deemed to be drug-related) in the clinical studies with Candida infections that employed a comparator.

Table 8: Selected clinical adverse events

	<i>CANCIDAS</i> 50 mg (N=84) (percent)	<i>Fluconazole</i> 200 mg (N=93) (percent)	<i>CANCIDAS</i> 50 mg (N=80) (percent)	<i>CANCIDAS</i> 70 mg (N=65) (percent)	<i>Amphotericin B</i> 0.5 mg/kg (N=89) (percent)
<b><i>Body as a Whole</i></b>					
<i>Chills</i>	**	**	2.5	1.5	75.3
<i>Edema, facial</i>	**	**	0.0	3.1	0.0
<i>Fever</i>	3.6	1.1	21.3	26.2	69.7
<i>Flu-like illness</i>	**	**	0.0	3.1	0.0
<i>Malaise</i>	**	**	0.0	0.0	5.6
<i>Pain</i>	**	**	1.3	4.6	5.6
<b><i>Peripheral Vascular</i></b>					
<i>Phlebitis/thrombophlebitis</i>	23.8	17.2	12.5	15.4	22.5
<b><i>Digestive System</i></b>					
<i>Nausea</i>	6.0	6.5	2.5	3.1	21.3
<i>Vomiting</i>	1.2	3.2	1.3	3.1	13.5
<b><i>Musculoskeletal</i></b>					
<i>Myalgia</i>	**	**	0.0	3.1	2.2
<b><i>Nervous System &amp; Psychiatric</i></b>					
<i>Headache</i>	6.0	1.1	11.3	7.7	19.1

	<i>CANCIDAS</i>	<i>Fluconazole</i>	<i>CANCIDAS</i>	<i>CANCIDAS</i>	<i>Amphotericin B</i>
	<i>50 mg</i>	<i>200 mg</i>	<i>50 mg</i>	<i>70 mg</i>	<i>0.5 mg/kg</i>
	<i>(N=84)</i>	<i>(N=93)</i>	<i>(N=80)</i>	<i>(N=65)</i>	<i>(N=89)</i>
	<i>(percent)</i>	<i>(percent)</i>	<i>(percent)</i>	<i>(percent)</i>	<i>(percent)</i>
<i>Paresthesia</i>	**	**	1.3	3.1	1.1
<b><i>Respiratory System</i></b>					
<i>Tachypnea</i>	**	**	1.3	0.0	4.5
<b><i>Skin &amp; Skin Appendage</i></b>					
<i>Erythema</i>	**	**	1.3	1.5	7.9
<i>Rash</i>	**	**	1.3	4.6	3.4

Compared to Amphotericin B, there were less systemic infusional toxicities of fever and chills, and less local infusional adverse events (pain and phlebitis). On the other hand, flu-like illnesses, facial edema, and myalgia were more prominent with caspofungin compared to amphotericin B. Rashes were more frequently seen with caspofungin, and appeared to be more frequent in patients that received the 70 mg dose. Respiratory symptoms such as tachypnea or bronchitis (13 or 4.9%) were more frequently observed in the caspofungin treated patients compared to amphotericin B or fluconazole (bronchitis: 0 and 1 patient, respectively). These symptoms were generally mild, with no patients requiring hospitalization or treatment discontinuations.

Nineteen patients developed mucosal candidiasis (7.2%) in the caspofungin treated group compared to 2 in the amphotericin B (2.2%) and 3 (3.2%) in the fluconazole group.

The clinically significant laboratory abnormalities that distinguished caspofungin from amphotericin other than the anticipated renal and electrolyte abnormalities with the latter drug are the development of eosinophilia (3.1% for caspofungin, vs, 1.1% for amphotericin B). A mean increase in creatinine of 1.1 times baseline (range:1.0-2.51) was noted in patients who received caspofungin, compared to a mean increase of 2 times baseline (range:1.2-3.6) in patients who received amphotericin B.

**Summary of Safety of Caspofungin in Protocol 019**

Intravenous site irritation, elevation of serum transaminases and signs of histamine release were identified in preclinical studies. The transaminase elevations seen in the clinical studies were generally mild, and did not require treatment discontinuations. Co-administration of tacrolimus resulted in more frequent transaminase elevations, although the magnitude of those elevations did not appear to be significantly higher than the elevations in patients without tacrolimus.

Histamine release appeared to be related to rapidity of dose infusion in animals. When caspofungin was administered to patients, symptoms compatible with histamine release were noted. Eosinophilia rarely accompanied these symptoms.

In this population of severely ill patients on multiple concomitant therapies, only 10 patients had a drug related adverse event, consisting of 14.55 of all adverse events. This rate of caspofungin attributed adverse events is much less than the 48 % rate in the Candida comparative trials. Of the 28 patients who discontinued therapy due to an adverse event, most of these symptoms were due to progressive aspergillosis or end organ dysfunction.

Caspofungin acetate was generally tolerated in all patients enrolled in this protocol, no deaths were directly attributable to the drug, and only one serious drug related adverse event was felt to be drug-related. This database had the potential of demonstrating adverse event rates from longer treatment exposures but the confounding factors in the severely ill patient makes it difficult to obtain an accurate picture of the events attributable to the drug alone.

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APPENDIX - TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS ; STUDY 019 (CANCIDAS) VS STUDY 028 (HISTORICAL CONTROL)

Baseline Characteristic	Study 019¶		Historical Control	
	N	(%)	N	(%)
<b>Demographics:</b>				
Age (y)	47.4		48.2	
Sex female/male	23/46	33/67	107/122	47/53
<b>Study Site:</b>				
Domestic	29	46.1	199	87
International	34	53.9	30	13
<b>Extent of Infection:</b>				
Pulmonary, probable	18	28.5	87	38.0
Pulmonary, definite	27	42.8	86	37.6*
Extrapulmonary+	18	28.5	56	24.5**
<b>Response to prior Rx:</b>				
Refractory	36	57.1	193	84.3 #
Intolerant only	10	15.9	5	2.1
Refractory <b>and</b> intolerant	17	27.0	no analogous population#	
<b>Underlying Disease:</b>				
Hematologic malignancy	43	68.2	159	69.4
Bone marrow transplant	20	31.7	94	41.0
Organ transplant	9	14.2	35	15.3
Solid tumor	3	4.8	12	5.2
Other risk factors §	1	1.6	23	10.0
None	2	3.2	0	
ANC <500	16	25.4	59	25.8
<b>Type of prior treatment:</b>				
ABELCET	6	9.5	74	32.3
AMBISOME	5	7.9	6	2.6
AMPHOTEC			8	3.5
dAmB	14	30.2	79	34.5
Itraconazole	9	14.3	29	12.7
Voriconazole	1	1.6		
Multiple drugs	28	44.4	33	14.4
Mean duration (days)	47.7		29.5	

¶ in Study 019, 69 enrolled, 63 expert panel evaluable, in historical control, 229 enrolled, 214 evaluable, 15 cases non intolerant and non refractory excluded

+ includes single organ involvement outside of pulmonary

\*55% identified at autopsy \*\*61% identified at autopsy

# no distinction between refractory only and refractory and intolerant patients in the historical control, an additional 16 cases initially determined to be either refractory or intolerant later considered to be indeterminate at week one