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Product name: **Cancidas**
Procedure No. **EMEA/H/C/379/II/17**

SCIENTIFIC DISCUSSION

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1 Introduction

Caspofungin acetate is a semisynthetic lipopeptide compound of the echinocandin family and represents the first in a new class of antifungal agents (glucan synthesis inhibitors) that inhibits the synthesis of beta-1, 3-D-glucan, an essential component of the fungal cell wall. Cancidas was granted an EU Marketing Authorisation under exceptional circumstances on 24 October 2001, indicated in the treatment of invasive aspergillosis in adults, who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. The approved dosage is a single 70-mg loading dose on day 1, followed by 50 mg thereafter. Duration of treatment is not specified and is to be based upon the severity of the patient's underlying disease, recovery from immmunosuppression and clinical response. The Marketing Authorisation Holder (MAH) has committed to specific obligations and follow-up measures. Pursuant to article 13 (2) of Council Regulation (EEC) No 2309/93 and part 4G of the Annex to Council Directive 75/318/EEC, the MAH has agreed to provide, as requested by the CPMP, additional clinical data. These data will form the basis for a re-assessment of the benefit/risk ratio of Caspofungin MSD in the treatment of invasive aspergillosis.

A type II variation to extend the indication to include treatment of invasive candidiasis in non-neutropenic adult patients was granted an EU Marketing Authorisation 17 February 2003. The recommended dose regimen in these patients is a single 70-mg loading dose on day 1, followed by 50 mg thereafter. The duration of treatment is to be based upon the patient's clinical and microbiological response, but in general therapy should be continued for at least 14 days after the last positive culture.

Caspofungin has been given a marketing authorisation in the indication salvage treatment of invasive aspergillosis in the United States on 29 January 2001 and in more than 50 further countries. In addition caspofungin has been approved for invasive candidiasis in Korea and Brazil and for the primary treatment of oesophageal (EC) candidiasis (and, in some instances, oropharyngeal candidiasis [OPC]) in 5 countries in South America and the United States.

The present type II variation concerns an extension of the indications to include: "*Empirical therapy for presumed fungal infections in febrile neutropenic adult patients*" as requested by the MAH in September 2003. The recommended dose constitutes a single 70-mg loading dose on Day 1 followed by 50 mg thereafter. Duration of empirical therapy should be based on the patient's clinical response. Therapy should be continued until resolution of neutropenia. Patients diagnosed with a fungal infection should be treated for a minimum of 14 days treatment should be continued for at least 7 days after both neutropenia and clinical symptoms resolved.

2 Clinical assessment

2.1 Introduction

Invasive fungal infections are an important cause of morbidity and mortality in patients with neutropenia following chemotherapy for cancer, and Candida and Aspergillus species are the most commonly identified pathogens. Fever, without signs of localized infection, is the typical clinical presentation. Early, definitive diagnosis is difficult; therefore, empirical administration of antifungal agents has become the standard of care for neutropenic patients who remain febrile despite empirical antibacterial therapy. Conventional amphotericin B has been shown to reduce the frequency of proven fungal infections in febrile neutropenic hosts, but its use has been limited due to toxicity. A recent study of patients with persistent fever and neutropenia demonstrated that empirical therapy with AmBisome was as effective as conventional amphotericin B and associated with fewer breakthrough fungal infections, less infusion-related toxicity, and less nephrotoxicity. Nonetheless, infusion-related toxicity and nephrotoxicity still occurred in 17 to 19% of patients receiving AmBisome.
Caspofungin is the first in a new class of antifungals, the echinocandins. Caspofungin inhibits the synthesis of b-1, 3-D-glucan, an essential component of the cell wall of many pathogenic fungi, including Candida and Aspergillus spp. Caspofungin has been approved for the treatment of invasive

aspergillosis in patients who are refractory to or intolerant of other therapies and for the treatment of invasive candidiasis.
In view of its favourable efficacy and safety profile in documented fungal infections, caspofungin may represent an effective and well-tolerated agent as empirical therapy in patients with persistent febrile neutropenia.

2.2 Pharmacokinetics

There was one pharmacokinetics report associated with this dossier. It is a population PK/PD analysis performed on data obtained in **122** patients (out of 152) treated empirically with caspofungin in the Phase III Study 026. All doses were administered as 1-hr, constant-rate, intravenous infusions. The maximum duration of empirical treatment was 28 days.

Plasma samples were analyzed with a validated HPLC method using fluorescence detection. The limit of quantification was 125 ng/ml. End-of-infusion (C_{1hr}) and trough (C_{24hr}) samplings were performed. The PK parameters were the time-averaged C_{1hr} and C_{24hr} over two different time periods, namely Days 3 to 14 in analyses assessing effects on caspofungin PK, and Day 3 to the end of IV therapy in analyses assessing the effects of caspofungin PK on outcome. Statistical analysis was adequate. A relatively large number of concentration values were excluded due to inappropriate sampling times; furthermore, 34 pairs of trough and peak samples were assumed to include a switching error.

The following conclusions follow the lines of the previously characterised caspofungin PK profile:

- Neither end-of-infusion (C_{1hr}) nor trough (C_{24hr}) concentrations predict treatment outcome, not even in subgroup analyses (low-risk vs high-risk patients, and prior antifungal prophylaxis vs no prophylaxis).
- With the possible exception of nausea, the occurrence of clinical AE's and/or laboratory abnormalities does not appear to be increased by higher caspofungin plasma concentrations within the range of PK parameters examined.
- Weight is a significant covariate for C_{24hr} but not for C_{1hr}. However, the effect of weight is modest within the 50 to 90-kg range of body weights; the current recommendation to increase the daily dose from 50 to 70 mg in patients weighing more than 80 kg may remain.
- On average, C_{1hr} and C_{24hr} were increased 23% and 31%, respectively, in women relative to men. This does not warrant any dose adjustment based on gender.
- Older patients on average have modestly higher C_{24hr} concentrations than younger patients, but no dose adjustment is necessary based on age.
- Race, renal status, and serum albumin levels are not significant determinants of caspofungin PK.
- In general, the drug-interaction screening did not unravel any concomitant medication that would be likely to alter caspofungin PK.
- Both C_{1hr} and C_{24hr} concentrations are modestly reduced in empirical therapy patients relative to healthy subjects. This is similar to the observation made in invasive candidiasis patients and does not warrant further comments.

Therefore, PK parameters from this Phase III Study 026 are compared to those in previously studied healthy subjects (16 from Protocol 021 and 13 from Protocol 030 with the same dosage regimen of caspofungin).

2.3 Clinical efficacy

The efficacy data to support the extension of indication of caspofungin to empirical therapy of presumed fungal infections in febrile, neutropenic patients, originate from a Phase III study, Protocol 026: A Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of MK-0991 Versus Amphotericin B Liposome for Injection as Empirical Therapy in Patients With Persistent Fever and Neutropenia.

2.3.1 Summary of methods of the study Protocol 026

This is a double-blind and in-house blind, randomized, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin versus AmBisome in the treatment of persistent fever and neutropenia. Patients were stratified at study entry to either a high-risk stratum or a low-risk stratum. Patients at high risk had undergone allogeneic hematopoietic stem cell transplantation or received chemotherapy for a relapse of acute leukemia. All others were assigned to the low-risk stratum. Patients were also stratified by whether or not they had received prophylactic antifungal therapy during their chemotherapy regimen

Study period:	Jan 2000- Aug 2002, 116 study sites (over 40 study sites within the EU)
Participants:	Men and women 16 years and older, who had received chemotherapy for leukemia, lymphoma, or other cancers or had undergone bone marrow or peripheral-blood stem-cell transplantation, AND had an absolute neutrophil count <500/mm3 for at least 96 hours and had received at least 96 hours of parenteral systemic antibacterial therapy preceding randomization and fever >38.0°C at randomisation were enrolled.
Study design:	Phase III: Double blind (and in-house blind), randomised comparative (non-inferiority) study, including 1123 patients; 1 hr IV caspofungin 50 mg/day (after a loading dose 70mg day 1) (n=556) + 2 hrs IV placebo (multivitamin complex) versus 1 hr IV placebo (saline) + 2 hrs IV AmBisome 3 mg/kg (n=539). Dose increases to either 70mg/day caspofungin or AmBisome 5mg/kg/day were allowed if lack of efficacy. Stratification by two parameters: a) by risk category; high-risk stratum (allogenic HSCT and/or relapse of acute leukemia) and low risk stratum (all others) b) by prior antifungal prophylaxis Treatment duration: a) Patients without fungal infection: treatment until resolution of neutropenia (ANC ≥500) and for up to 72 hours. Maximum duration of empirical therapy: 28 days. b) Patients with documented fungal infection: recommended duration ≥14 days in total and at least 7 days after resolution of neutropenia and of symptoms. Max duration: 90 days
Committees:	Independent Committees were appointed: 1) to monitor the data and safety of the study (DSMB) and 2) to provide an assessment of the likelihood and outcome of fungal infections (Blinded Adjudication Committee BAC).
Study endpoints:	PRIMARY Favourable overall response (complete or partial) for the 5-part composition endpoint: 1. successful treatment on any baseline fungal infection, if present (BAC) 2. absence of breakthrough fungal infections up to 7 days post-therapy (BAC) 3. survival to 7 days post-therapy 4. absence of premature discontinuation due to drug-related toxicity or lack of efficacy 5. resolution of fever for at least 48 hours during the period of neutropenia SECONDARY 1. Assessment of each of the individual 5 components of the primary endpoint. 2. Proportion of patients who developed nephrotoxicity (primary safety analysis) 3. Proportion of patients with an infusion-related adverse event 4. Proportion of patients who discontinue therapy due to a drug-related AE 5. Proportion of patients reporting one or more drug-related adverse event TERTIARY 1. Proportion of patients requiring up-dosing of study drug due to inadequate response 2. Time to resolution of fever
Inclusion criteria:	Patients ≥16 years old and have: 1. Received chemotherapy for malignancy or undergone peripheral stem transplantation 2. An absolute neutrophil count <500/mm^3 for at least 96 hours 3. Received ≥96 hours of parenteral systemic antibacterial therapy preceding randomisation 4. Fever >38.0^{o}C at randomisation.
Exclusion criteria:	1. Documented invasive fungal infection at enrolment

	2. Inadequately managed bacterial infection 3. Platelet count, INR and LFTs exceeding specified thresholds 4. Requirement of cyclosporin A, rifampicin or concomitant systemic antifungal therapy 5. Received parenteral amphothericin B within 10 days prior to enrolment
Evaluation criteria	Primary objective: To compare, in patients with persistent fever and neutropenia, the proportion of patients in the caspofungin group with a successful treatment outcome to that of liposomal amphotericin B (AmBisome) (on all 5 study endpoints)
Safety evaluation:	The safety variables included the incidence of clinical and laboratory adverse experiences; nephrotoxicity, infusion-related events, laboratory tests outside predefined clinically significant limits (CSLAs) and patients who had study drug decreased because of toxicity.
Statistical methods:	The primary efficacy parameter was the proportion of patients who had a successful treatment outcome as defined in the primary objective. The secondary endpoints included assessment of each of the individual components of the primary endpoint. For each endpoint, the proportion and its 95% confidence interval (CI) was displayed and the difference in response rates between the 2 treatment groups was also displayed with its 95% CI (95.2% for the primary endpoint, using the adjusted alpha of 0.048 from the DSMB interim analysis plan). The CIs for the individual proportions were calculated using the normal approximation to the binomial distribution. The CI for the difference in response rates for the primary endpoint was calculated using the Cochran-Mantel-Haenszel adjustment for stratification.

The study was designed to test for noninferiority of caspofungin relative to Ambisome as empirical therapy in patients with persistent fever and neutropenia. The definition of noninferiority that was used for this study states that the 95.2% (two-sided) CI for the difference in response rates between the 2 treatment groups (calculated as caspofungin minus AmBisome) includes zero and the lower limit of the CI is not less than -10%.
The primary analysis was performed using the MITT population (at least 1 complete dose of therapy). The evaluable-patients analysis (at least 4 days of therapy and no protocol violations) provided supportive data to confirm the results of the MITT analysis.

As pointed out in the CPMP PtC (Point to Consider on the clinical evaluation of new agents for invasive fungal infections - CPMP/EWP/1343/01, dated 22 May 2003) there are some major problems with assessing the true efficacy in empiric therapy, since such an indication should be based solely on the successful treatment of any fungal infections documented from examination of specimens taken just before adding the antifungal agent. However, the confirmation of fungal infection from post-baseline specimens might only represent failure to treat an infection that was present, but not confirmed, before initiation of therapy, or albeit less likely, a failure of prophylaxis. Thus, the two possible roles of the drug cannot be differentiated. It is further stated in the CPMP PtC that a superiority trial would be the most appropriate for granting an indication that reflected the overall utility of the drug in this type of clinical situation. The MAH was therefore asked to justify the choice of a non-inferiority trial instead of a superiority trial. The response provided by the MAH was reasonable, even though a trial showing a difference would have been more convincing, for reasons stated in the CPMP PtC. At the time of the initiation of the caspofungin empirical therapy trial (1999), the prevailing approach for empirical antifungal therapy studies was the non-inferiority design using the delta of -10%. The CPMP PtC did not come into operation until recently, in November 2003. The P026 study was modelled after the earlier large randomised comparative trials in empirical therapy, including the one that led to the approval of AmBisome in this indication. Moreover, the MAH sought regulatory guidance from the FDA regarding the primary efficacy endpoint.

2.3.2 Results of the study Protocol 026.

- **Participant flow**

Of 1123 patients enrolled at 116 investigative sites, 1111 received at least one dose of study therapy and were included in the analysis of safety. Of the 1111 treated patients, **1095** were included in the MITT analysis; 8 patients in each treatment group were excluded. The most common reason for exclusion was absence of a temperature above 38°C at entry. There were **901** patients in the

evaluable-patients analysis; 210 patients (116 in the caspofungin group and 94 in the AmBisome group) were excluded. The most common reasons for exclusion from the evaluable-patients population were protocol violations that confounded assessment (12.6%) and inadequate study therapy (generally receipt of less than 4 days of study therapy; 5.1%). The most common protocol violation that resulted in exclusion from the evaluable-patients population was discontinuation of study therapy prior to resolution of neutropenia (without having met any failure endpoint at the time of discontinuation).

- **Baseline data**

Demographics and patient characteristics

The demographics and baseline patient characteristics of the 1111 treated patients are displayed in Table 1. The majority of patients enrolled in the study were men (56%) and White (89.5%). The mean ages of the caspofungin and AmBisome groups were 48.8 and 47.7 years, respectively.

The most common primary conditions reported in the study were acute myelogenous leukemia (AML; 64.0%), non-Hodgkin's lymphoma (NHL; 10.9%), and acute lymphocytic leukemia (ALL; 9.9%). Eighty-one patients (7.3%) had undergone allogeneic HSCT, and 165 (14.9%) had undergone autologous HSCT at some time prior to study entry. Most patients (73.4%) entered the study severely neutropenic with an absolute neutrophil count (ANC) less than 100 cells/microl.

Overall, 24.8% of the patients were in the high-risk category, and constituted 26.6% of the caspofungin and 22.9% of the AmBisome group. The numbers of patients categorized as high-risk due to allogeneic HSCT were similar in both treatment groups (6.6% of the caspofungin and 7.5% of the AmBisome group). A numerically larger proportion of patients in the caspofungin than the AmBisome group were considered high risk on the basis of relapsed acute leukemia (20.0% and 15.4%, respectively). The proportions of patients who received prior antifungal prophylaxis were similar in both treatment groups (56.2% of the caspofungin and 56.3% of the AmBisome group).

Table 1: Baseline Patient Characteristics by Treatment Group (All Treated Patients)

	Caspofungin 70/50 mg ($N^{\dagger}$=564)		AmBisome 3.0 mg/kg ($N^{\dagger}$=547)		Total ($N^{\dagger}$=1111)	
	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)
Gender						
Male	325	(57.6)	297	(54.3)	622	(56.0)
Female	239	(42.4)	250	(45.7)	489	(44.0)
Race						
Asian	12	(2.1)	13	(2.4)	25	(2.3)
Black	21	(3.7)	19	(3.5)	40	(3.6)
Multi-racial	9	(1.6)	14	(2.6)	23	(2.1)
White	510	(90.4)	484	(88.5)	994	(89.5)
Other	12	(2.1)	17	(3.1)	29	(2.6)
Age (Years)						
17 and under	3	(0.5)	8	(1.5)	11	(1.0)
18 to 25	61	(10.8)	58	(10.6)	119	(10.7)
26 to 40	100	(17.7)	104	(19.0)	204	(18.4)
41 to 65	311	(55.1)	301	(55.0)	612	(55.1)
Over 65	89	(15.8)	76	(13.9)	165	(14.9)
Mean	48.8		47.7		48.3	
SD	15.8		15.6		15.8	
Median	51.0		49.0		50.0	
Range	17 to 83		16 to 83		16 to 83	
Primary Condition[§]						
Acute Leukemia						
Acute myelogenous leukemia	368	(65.2)	343	(62.7)	711	(64.0)
Acute lymphocytic leukemia	59	(10.5)	51	(9.3)	110	(9.9)
Acute leukemia (other)	3	(0.5)	3	(0.5)	6	(0.5)
Chronic Leukemia						
Chronic myelogenous	7	(1.2)	11	(2.0)	18	(1.6)

	Caspofungin 70/50 mg ($N^{\dagger}$=564)		AmBisome 3.0 mg/kg ($N^{\dagger}$=547)		Total ($N^{\dagger}$=1111)	
	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)
leukemia						
Chronic lymphocytic leukemia	8	(1.4)	4	(0.7)	12	(1.1)
Leukemia (other)	2	(0.4)	5	(0.9)	7	(0.6)
Lymphoma						
Hodgkin's lymphoma	14	(2.5)	11	(2.0)	25	(2.3)
Non-Hodgkin's lymphoma	59	(10.5)	62	(11.3)	121	(10.9)
Lymphoma (other)	2	(0.4)	2	(0.4)	4	(0.4)
Multiple myeloma	14	(2.5)	18	(3.3)	32	(2.9)
Myelodysplastic syndrome	10	(1.8)	15	(2.7)	25	(2.3)
Solid tumor	11	(2.0)	16	(2.9)	27	(2.4)
Other	7	(1.2)	6	(1.1)	13	(1.2)
Transplant Type[%]						
Allogeneic HSCT						
Bone marrow	29	(5.1)	26	(4.8)	55	(5.0)
Peripheral stem cell	10	(1.8)	16	(2.9)	26	(2.3)
Autologous HSCT						
Bone marrow	27	(4.8)	35	(6.4)	62	(5.6)
Peripheral stem cell	51	(9.0)	52	(9.5)	103	(9.3)
Neutropenic Status (cells/microliter)[¶]						
ANC <100	406	(72.0)	410	(75.0)	816	(73.4)
ANC <500	153	(27.1)	130	(23.8)	283	(25.5)
Risk Category						
High Risk	150	(26.6)	125	(22.9)	275	(24.8)
Allogeneic HSCT[#]	37	(6.6)	41	(7.5)	78	(7.0)
Chemotherapy for relapse of acute leukemia	113	(20.0)	84	(15.4)	197	(17.7)
Low Risk	414	(73.4)	422	(77.1)	836	(75.2)
Antifungal Prophylaxis Status						
Antifungal prophylaxis	317	(56.2)	308	(56.3)	625	(56.3)
No antifungal prophylaxis	247	(43.8)	239	(43.7)	486	(43.7)

[†] N = Number of patients in treatment group.
[‡] n = Number of patients in subgroup.
[§] Primary Condition Categories:
Acute leukemia (other) includes acute leukemia.
Leukemia (other) includes leukemia, lymphocytic leukemia, myelogenous leukemia.
Lymphoma (other) includes lymphoma.
Solid tumor includes Ewing's sarcoma, angiosarcoma, brain neoplasm, breast malignant neoplasm, germ cell neoplasm, ovarian malignant neoplasm, sarcoma, testicular malignant neoplasm, testicular neoplasm.
Other includes amyloidosis, aplastic anemia, blood dyscrasia, immunohemolytic anemia, macroglobulinemia, myelofibrosis, myeloproliferative disorder, progressive systemic sclerosis.
[%] Patients with more than one type of transplant are counted under each specific type of transplant.
[¶] The Neutropenic Status categories are mutually exclusive. The absolute neutrophil count (ANC) <500 category includes patients whose ANC is 100 to 499.
[#] Patients with allogeneic hematopoietic stem cell transplant (HSCT) and had received chemotherapy for relapse of acute leukemia are counted in the allogeneic HSCT row.

Duration of therapy

For the caspofungin group, the mean and median duration of therapy for all treated patients were 13 and 11 days, and for the AmBisome group 12.5 and 10 days, respectively. For both groups, the range was 1 to 90 days. The mean and median duration of therapy for high-risk patients were slightly greater than for low-risk patients in both treatment groups (respectively, 15.2 and 12.2 days for the caspofungin group and 14.5 and 12 days for the AmBisome group).

There was an option to increase the dose on Day 5 or later to 70 mg/day for caspofungin and 5 mg/kg/day for AmBisome. A similar number of patients in both treatment groups received study medication at the standard dose, as was the number of patients who had their dose increased due to

lack of efficacy (75 or 13.3% for caspofungin and 78 or 14.3% for AmBisome). The treatment groups were also similar with respect to the time that the dosage increase was implemented. Patients whose dose of study therapy was increased because of clinical deterioration had slightly lower response rates than those who continued to receive the standard dose in both treatment groups.
A total of 59 patients (30 in the caspofungin group and 29 in the AmBisome group) were treated for more than 28 days.

- **Outcomes and estimation**

Primary Composite Endpoint
To be considered a favorable overall response for this study, patients had to have a favorable response for all components of the composite endpoint.

Table 2: Proportion of Patients With a Favorable Overall Response and the Difference Between Treatment Groups Adjusted for Risk Category and Antifungal Prophylaxis Status
Modified Intention-to-Treat and Evaluable Patients Analyses

Favorable Overall Response	Caspofungin Estimated Response n[†] (%) (95% CI)	AmBisome Estimated Response n[†] (%) (95% CI)	Estimated Difference (95.2% CI)
MITT[‡] population	N[§]=556 190 **(33.9)** (30.0, 37.9)	N[§]=539 181 **(33.7)** (29.7, 37.7)	0.2 (-5.6, 6.0)
Evaluable population	N[§]=448 135 (30.1) (25.8, 34.3)	N[§]=453 140 (31.0) (26.7, 35.2)	-0.9 (-7.2, 5.4)

[†] n = number of patients with favorable response.
[‡] MITT = modified intention-to-treat.
[§] N = number of patients in the treatment group in the specified analysis population.

For the MITT population, the percentages of patients with a favorable overall response in the caspofungin and AmBisome groups, after adjustment for strata were 33.9% and 33.7%, respectively. The estimated difference in response rates between the 2 treatment groups (caspofungin minus AmBisome) was 0.2%, with a 95.2% CI of (-5.6, 6.0). The CI contains 0 and the lower limit (-5.6%) is above the prespecified limit of -10.0%, indicating that caspofungin is noninferior to AmBisome as empirical therapy in patients with persistent fever and neutropenia. The supportive analysis performed on the evaluable-patients population gives similar results.

It is important to examine the overall favorable response rates within each of the randomization strata (risk category and prophylaxis stratum) in the primary analysis population, because of their potential impact on the overall study outcome.
Table 3 displays the observed favorable overall response rates in the MITT population for the 2 treatment groups overall, by risk category, and by prophylaxis stratum. The observed (unadjusted for stratum) percentages of patients with favorable overall responses are 34.2% for caspofungin and 33.6% for AmBisome. The overall favorable response rates were somewhat higher for patients in the high- than the low-risk category for both treatment groups, and numerically were greatest in the high-risk patients who received caspofungin. Overall response rates were similar for both treatment groups whether or not antifungal prophylaxis was used. Results were similar for the MITT and the evaluable-patients populations.

Table 3: Summary of Overall Response and Individual Endpoints Overall, by Risk Category and Prophylaxis Stratum—Modified Intention-to-Treat Analysis

Population	Treatment Group	Endpoint					
		Overall Favorable Response	Successful Treatment of Baseline Infection[†]	Absence of Breakthrough Infection	Survival	Completed Therapy[‡]	Fever Resolution
Overall	Caspofungin	190/556	14/27	94.8	92.6	89.7	41.2
N=556	%[§]	(34.2)	(51.9)	(92.9, 96.6)	(90.5, 94.8)	(87.2, 92.3)	(37.1, 45.3)
	(95% CI)	(30.2, 38.1)	(33.0, 70.7)				
	AmBisome	181/539	7/27	95.5[¶]	89.2	85.5	41.4
N=539	%[§]	(33.6)	(25.9)	(93.8, 97.3)	(86.6, 91.9)	(82.6, 88.5)	(37.2, 45.5)
	(95% CI)	(29.6, 37.6)	(9.4, 42.5)				
High Risk	Caspofungin	63/146	3/8[%]	90.4	89.0	91.1	52.1
N=146	%[§]	(43.2)	(37.5)	(85.6, 95.2)	(84.0, 94.1)	(86.5, 95.7)	(44.0, 60.2)
	(95% CI)	(35.1, 51.2)					
	AmBisome	46/122	0/6[%]	93.4	85.2	85.2	50.0
N=122	%[§]	(37.7)	(0.0)	(89.1, 97.8)	(79.0, 91.5)	(79.0, 91.5)	(41.1, 58.9)
	(95% CI)	(29.1, 46.3)					
Low Risk	Caspofungin	127/410	11/19	96.3	93.9	89.3	37.3
N=410	%[§]	(31.0)	(57.9)	(94.5, 98.2)	(91.6, 96.2)	(86.3, 92.3)	(32.6, 42.0)
	(95% CI)	(26.5, 35.5)	(35.7, 80.1)				
	AmBisome	135/417	7/21	96.2[¶]	90.4	85.6	38.8
N=417	%[§]	(32.4)	(33.3)	(94.3, 98.0)	(87.6, 93.2)	(82.2, 89.0)	(34.2, 43.5)
	(95% CI)	(27.9, 36.9)	(13.2, 53.5)				
Prophylaxis	Caspofungin	105/313	6/13	95.2	92.0	90.4	39.6
N=313	%[§]	(33.5)	(46.2)	(92.8, 97.6)	(89.0, 95.0)	(87.2, 93.7)	(34.2, 45.0)
	(95% CI)	(28.3, 38.8)	(19.1, 73.3)				
	AmBisome	100/304	3/13	95.4[¶]	88.2	86.8	42.1
N=304	%[§]	(32.9)	(23.1)	(93.0, 97.8)	(84.5, 91.8)	(83.0, 90.6)	(36.6, 47.7)
	(95% CI)	(27.6, 38.2)	(0.2, 46.0)				
No Prophylaxis	Caspofungin	85/243	8/14	94.2	93.4	88.9	43.2
N=243	%[§]	(35.0)	(57.1)	(91.3, 97.2)	(90.3, 96.5)	(84.9, 92.8)	(37.0, 49.4)
	(95% CI)	(29.0, 41.0)	(31.2, 83.1)				
	AmBisome	81/235	4/14	95.7	90.6	83.8	40.4
N=235	%[§]	(34.5)	(28.6)	(93.2, 98.3)	(86.9, 94.4)	(79.1, 88.5)	(34.2, 46.7)
	(95% CI)	(28.4, 40.5)	(4.9, 52.2)				

N = number of modified intention-to-treat patients within each risk factor or substratum category by treatment group.
[†] For successful treatment of baseline infection endpoint, only patients with a baseline infection are included in this analysis.
[‡] Completed Therapy = completion of study therapy per protocol or discontinued therapy due to reason other than lack of efficacy or toxicity.
[§] Results by treatment group are displayed as % (Number of patients with a favorable response/number of patients in the analysis).
[%] When n <10, no CI is displayed.
[¶] Includes 1 additional patient determined by adjudication committee to have breakthrough fungal infection after frozen file.

- **Secondary Efficacy Results - Individual Components of Composite Endpoint**

Overview of Secondary Efficacy Endpoints

Table 4: Observed Proportion of Patients With a Favorable Response, Overall and By Endpoint
Modified Intention-to-Treat Analysis

Endpoint	Caspofungin 70/50 mg ($N^{\dagger}$=556) Observed Response m/n[‡] (%) (95% CI)	AmBisome 3.0 mg/kg ($N^{\dagger}$=539) Observed Response m/n[‡] (%) (95% CI)	Observed Difference % (95% CI)	p-value
Favorable Response (overall)	**190/556 (34.2) (30.2, 38.1)**	**181/539 (33.6) (29.6, 37.6)**	---	---
Successful treatment of baseline infection[§]	14/27 (51.9) (33.0, 70.7)	7/27 (25.9) (9.4, 42.5)	25.9 (0.9, 51.0)	0.043
Absence of breakthrough fungal infection	527/556 (94.8) (92.9, 96.6)	516/539 (95.7) (94.0, 97.4)	-0.8[§] (-3.3, 1.8)	0.556
Survival to 7-day follow-up	515/556 (92.6) (90.5, 94.8)	481/539 (89.2) (86.6, 91.9)	3.4 (0.0, 6.8)	0.051
Completed therapy or non-endpoint discontinuation	499/556 (89.7) (87.2, 92.3)	461/539 (85.5) (82.6, 88.5)	4.2 (0.3, 8.1)	0.034
Resolution of fever during neutropenia	229/556 (41.2) (37.1, 45.3)	223/539 (41.4) (37.2, 45.5)	-0.2 (-6.0, 5.6)	0.950

[†] N = Number of MITT patients in the treatment group.
[‡] m/n = Number of patients with a favorable response / Number of patients in the analysis.
[§] Only patients with a baseline infection are included in this analysis.

Overview of Baseline and Breakthrough Documented Infections

As already described, all cases of suspected fungal infection were reviewed by the Adjudication Committee, using blinded data. There were a total of 358 cases with suspected fungal infections reviewed by the Adjudication Committee. A total of **106** MITT patients had cases of documented (proven or probable) invasive fungal infections (53 with only baseline infection, 52 with only breakthrough infection, and 1 with both baseline and breakthrough infection). Three additional patients in the study had documented baseline infections, but were not included in the MITT population (incomplete dose of study therapy or did not meet the entry criterion for fever). Of the remaining patients 156 were considered to have a possible infection and 93 to have no fungal infection at all.

After locking of the clinical database, it was noted, during the preparation of narrative summaries, that 3 cases that should have been adjudicated were not, and one case previously adjudicated had important autopsy data that had been available but was missed in the earlier adjudication. These cases were sent to the adjudicators as blinded data in order to present the most complete and accurate adjudication dataset possible. However, the clean file was not altered because adjudication of these patients would have no impact on the primary study result: these patients failed other endpoints and were already failures for the primary analysis. Inclusion of these cases affects only the numbers and distribution of diagnoses for documented breakthrough infections in the AmBisome group; these were: 1 new case with breakthrough probable chronic disseminated candidiasis, and one change of diagnosis from breakthrough proven sinusitis to breakthrough proven disseminated fungal infection. The data on late-adjudicated cases, are included in the text and tables that follow. Inclusion of these data had no impact on the overall study analysis or its conclusions.

- **Successful Treatment of Baseline Infection**

Patients with baseline infections were enrolled into the study and included in the MITT analysis only if the likelihood of a fungal infection at the time of study entry was, at most, possible. Patients with known, documented invasive fungal infections were excluded. Therefore, those patients with baseline infections described below may have had possible infection present at study entry (or by Day 2), but the confirmatory information from tests or specimens obtained prior to or at entry, that led the Adjudicators to consider these probable or proven infections, did not become positive until after study entry.
The Adjudication Committee assessed the response to study therapy of all baseline invasive fungal infections. "Complete response" and "partial response" were considered favorable clinical outcomes.
Complete response was defined as resolution of all attributable signs, symptoms, and abnormalities detected by radiography, bronchoscopy, endoscopy, or other procedures, and negative cultures for fungal pathogens. A partial response was defined as clinically meaningful improvement in attributable symptoms and signs, as well as in attributable abnormalities detected by other procedures, as noted above.

As displayed in the Tables 3 and 4 the percentages of MITT patients who had successful treatment of their baseline fungal infections were **51.9%** in the caspofungin and **25.9%** in the AmBisome group. The difference in response rates between the 2 treatment groups (caspofungin minus AmBisome) was 25.9% with a 95% CI of (0.9, 51.0). Within each treatment group, the response rates were lower for patients in the high- than the low-risk category, as expected.

Demographics of Patients with Baseline Infections
There were 27 patients in each treatment group with baseline infections: 4.9% of the caspofungin and 5.0% of the AmBisome group. The baseline demographic characteristics of the 54 patients with baseline infections were generally similar between the 2 treatment groups.

Distribution of Baseline Infections, Overall, and by Stratum
The most common baseline infections were due to *Aspergillus* species (12 infections per group; the most common diagnosis was pneumonia) and *Candida* species (also 12 infections per group; the most common diagnosis was fungemia). The infection types were balanced between the 2 treatment groups. The remaining pathogens were *Dipodascus* (1), *Fusarium* (2), and *Mucor* (1) species, and mould NOS (not otherwise specified; 2).

With respect to risk-category, the distribution of infections was reasonably balanced in the 2 treatment groups, except that high-risk patients in the caspofungin group had a slightly higher proportion of *Aspergillus* baseline infections (6/146 or 4.1%) than low-risk patients (6/410 or 1.5%). For AmBisome there were similar proportions of *Aspergillus* baseline infection in the 2 risk categories (2/122 [1.6%] in the high-risk and 10/417 [2.4%] in the low-risk).

The distribution of infections by use of prior prophylaxis was balanced overall between the 2 treatment groups. The use of prophylaxis, however, was associated with lower overall rates of baseline infections due to *Candida* species (both treatment groups combined: 5/617 [0.8%] in patients with prior prophylaxis and 19/478 [4.0%] without prophylaxis). These findings are expected, in view of the frequent use of fluconazole prophylaxis in this study population.

The number of baseline infections due to Candida species in this study was as high as the number of baseline infections due to Aspergillus species (24 infections of each). This is somewhat surprising when considering the frequent use of fluconazole prophylaxis, which should reduce the number of Candida infections. However, the number of Candida infections is indeed much lower in patients who received antifungal prophylaxis than in those who did not.
Concerning the use of prophylaxis this use seems to be quite different according to the center involved and the investigator in charge: indeed, 37.7% of high risk patients did not receive any prophylaxis at all, whereas 54.4% of low risk patients did receive prophylaxis. This difference in "clinical practice" has to be taken into consideration when looking at the prophylaxis strata, meaning that it is very difficult to draw conclusions based upon the occurrence of prior prophylaxis.

Microbiology of Baseline Pathogens

There were 25 yeast pathogens and 30 mould pathogens (including the *Fusarium* sp. described in the footnote) identified either microbiologically or histologically as causing baseline infections by the Adjudication Committee; MIC data were available in 25/55 or 45.5% of total baseline pathogens.

The MIC distribution was examined for 15 unique pathogenic isolates tested from patients with baseline yeast infections. Most baseline yeast isolates were *Candida* species and had MICs to caspofungin ≤1 µg/ml. There were 2 isolates with caspofungin MIC >8 µg/ml: 1 *C. parapsilosis* that trailed and 1 *D. capitatus*, and 1 *C. krusei* had an MIC of 2µg/ml. All yeast isolates had MICs to amphotericin B ≤1.0 µg/ml.

The MIC distribution was examined for 10 unique pathogenic isolates from patients with baseline mould infections. Most baseline mould isolates were *Aspergillus* species. All mould isolates had MICs to caspofungin ≤0.5 µg/ml. Most mould isolates had MICs to amphotericin B ≤1 µg/ml; however, there were 3 isolates with higher MICs to amphotericin B: 1 *A. candidus* had an MIC of 2, another *A. candidus* had an MIC of 4, and 1 *A. terreus* had an MIC of 4 µg/ml.

Response to Treatment for Specific Baseline Infections

Response rates were higher in the caspofungin group for both baseline infections caused by *Candida* and *Aspergillus* species (see Table 5) and the difference was most pronounced for *Aspergillus* infections (overall) with rates of 41.7% for the caspofungin group and 8.3% for the AmBisome group. Results were similar in the MITT and evaluable-patients populations.

Table 5: Response to Treatment of Adjudicated Baseline Invasive Fungal Infections by Diagnosis
Modified Intention-to-Treat Patients

Baseline Invasive Fungal Infections[‡]	Caspofungin 70/50 mg (N[†]=556) Total n/m[§]	Caspofungin 70/50 mg (N[†]=556) Total %	AmBisome 3.0 mg/kg (N[†]=539) Total n/m[§]	AmBisome 3.0 mg/kg (N[†]=539) Total %
***Aspergillus* species (Total)**	**5/12**	**41.7**	**1/12**	**8.3**
Disseminated fungal infection	0/0	0.0	0/2	0.0
Paronychia	0/0	0.0	1/1	100.0
Pneumonia	3/9[%]	33.3	0/7	0.0
Sinusitis	2/3	66.7	0/2	0.0
***Candida* species (Total)**	**8/12**	**66.7**	**5/12**	**41.7**
Chronic disseminated candidiasis	1/2	50.0	0/0	0.0
Disseminated fungal infection	0/2	0.0	0/1	0.0
Empyema	0/0	0.0	0/1	0.0
Fungemia	7/8	87.5	5/9	55.6
Pneumonia	0/0	0.0	0/1	0.0
***Dipodascus* species (Total)**	**0/1**	**0.0**	**0/0**	**0.0**
Fungemia	0/1	0.0	0/0	0.0
***Fusarium* (Total)**	**0/0**	**0.0**	**1/2**	**50.0**
Disseminated fungal infection	0/0	0.0	0/1	0.0
Sinusitis	0/0	0.0	1/1	100.0
Mould (NOS) (Total)	**1/1**	**100.0**	**0/1**	**0.0**
Disseminated fungal infection	1/1	100.0	0/0	0.0
Pneumonia	0/0	0.0	0/1	0.0
***Mucor* species (Total)**	**0/1**	**0.0**	**0/0**	**0.0**
Hepatic mucormycosis	0/1	0.0	0/0	0.0

[†] N = Number of modified intention-to-treat patients in treatment group.
[‡] All adjudicated diagnoses and assessments.
[§] n/m = Number of patients with this category of infection and a favorable response/ umber of patients with this category of infection. Favorable response is defined as an Adjudication Committee assessment of complete or partial response.
[%] One patient included in this count had a mixed infection of *Aspergillus fumigatus* and *Fusarium* with an unfavorable response. The outcome for *Fusarium* is not shown in this table.

Of the favorable responses, partial responses were seen more often in infections caused by *Aspergillus* species, (frequently manifesting as pneumonia), whereas complete responses were more often seen with *Candida* infections (frequently manifesting as candidemias). Of the 14 successful responses in the caspofungin group, 6 were partial and 8 were complete (1 complete and 4 partial responses caused by *Aspergillus sp,* and 6 complete and 2 partial responses caused by *Candida sp.)*. Of the 7 successful responses in the Ambisome group, 3 were partial (2 *Candida sp.* and 1 *Fusarium sp.)* and 4 were complete (3 *Candida sp.* and 1 *Aspergillus sp).* A complete response for candidemias, documented by repeat blood cultures, was more readily achieved than a complete response for pneumonias, because of the typical lag times in resolution of associated radiographic abnormalities. The small numbers of isolates from individual species and limited availability of MIC data preclude an analysis of outcome by MIC.

Per Pathogen Outcomes for Baseline Infections

The clinical response by pathogen in MITT patients is displayed in Table 6. The proportions of patients in the caspofungin and AmBisome treatment groups that had favorable clinical responses to baseline *Aspergillus* pathogens were 46.2 and 7.7%, respectively, and to baseline *Candida* pathogens, they were 63.6 and 41.7%, respectively. These results are similar to those observed in the response to treatment for specific baseline infections (see Table 5) with this difference that for one patient in each treatment group, there were 2 unique baseline isolates of an *Aspergillus* species associated with pneumonia (*A. candidus* in the caspofungin group and *A. flavus* in the AmBisome group), and that one case of probable chronic disseminated candidiasis, in the absence of culture or histopathologic confirmation of *Candida* species, was considered to be "presumed *Candida* species" and thus not counted in the per pathogen displays.

The response rate of Ambisome for treating baseline fungal infections is unexpectedly very low (25.9%) when comparing this to results from other studies, e.g. Ambisome versus voriconazole (Walsh TJ et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002; 346:225-34.). Although it is acknowledged that the number of baseline infections is small, this seems to be mainly due to an abnormally low response rate for baseline infections caused by Aspergillus species. It is not understood what the exact reason for this could be. When looking at Table 6 it seems that 5 Aspergillus species in the Ambisome group were not further identified (versus 4 in the caspofungin group).

The scarcity of data directly related to Aspergillus infections in previously performed empirical studies is acknowledged. Data from studies with documented infections are indeed difficult to compare with the current empirical study data, due to the differences in study design, in applied definitions and in other criteria. This also applies to the historical control study, which is an entirely different study with another design and another patient population. Furthermore, there seems to be a discrepancy between microbiological data as provided in Table 6 for the AmBisome group and data provided in the originally submitted documentation. Indeed, the single A. terreus infection in the AmBisome group is not mentioned here and similarly only 3 instead of 4 A. flavus infections are documented. Instead 1 unknown mould and 1 Aspergillus-like mould are mentioned here as causative organisms. The apparent discrepancy between Table 6 submitted by the MAH in December 2003 and the original documentation submitted in September 2003 can be explained by the conventions used to present the data. In tables that displayed diagnosis of the invasive fungal infection, but not specific pathogen names, the diagnoses were grouped according to the Adjudication Committee's determination of the causative pathogen, and were displayed according to the genus of the causative pathogen. In contrast, in listing tables and in per pathogen displays, the causative pathogens were identified by genus and species, if this information was available. Therefore, even if it would have been useful to apply the same conventions at all times to prevent confusion, the discrepancy is here clarified.

Table 6: Clinical Response by Pathogen for Adjudicated Baseline Fungal Infections
Modified Intention-to-Treat Analysis

Pathogen	Caspofungin 70/50 mg ($N^{\dagger}$=556) m/n[‡]	%	AmBisome 3.0 mg/kg ($N^{\dagger}$=539) m/n[‡]	%	Total ($N^{\dagger}$=1095) m/n[‡]	%
***Aspergillus* species**	**6/13**	**(46.2)**	**1/13**	**(7.7)**	**7/26**	**(26.9)**
Aspergillus candidus	2/2	(100.0)	N/A[§]	N/A	2/2	(100.0)
Aspergillus flavus	2/2	(100.0)	1/5	(20.0)	3/7	(42.9)
Aspergillus fumigatus	0/5[%]	(0.0)	0/1	(0.0)	0/6	(0.0)
Aspergillus niger	N/A	N/A	0/1	(0.0)	0/1	(0.0)
Aspergillus terreus	N/A	N/A	0/1	(0.0)	0/1	(0.0)
Aspergillus species	2/4	(50.0)	0/5	(0.0)	2/9	(22.2)
***Candida* species**	**7/11**	**(63.6)**	**5/12**	**(41.7)**	**12/23**	**(52.2)**
Candida albicans	2/3	(66.7)	3/4	(75.0)	5/7	(71.4)
Candida glabrata	1/1	(100.0)	1/1	(100.0)	2/2	(100.0)
Candida krusei	0/1	(0.0)	1/3	(33.3)	1/4	(25.0)
Candida parapsilosis	1/1	(100.0)	0/1	(0.0)	1/2	(50.0)
Candida tropicalis	3/5	(60.0)	0/2	(0.0)	3/7	(42.9)
Candida species	N/A	N/A	0/1	(0.0)	0/1	(0.0)
***Dipodascus* species**	**0/1**	**(0.0)**	**N/A**	**N/A**	**0/1**	**(0.0)**
Dipodascus capitatus	0/1	(0.0)	N/A	N/A	0/1	(0.0)
***Fusarium* species**	**N/A**	**N/A**	**1/2**	**(50.0)**	**1/2**	**(50.0)**
Fusarium	N/A	N/A	1/2	(50.0)	1/2	(50.0)
***Mucor* species**	**0/1**	**(0.0)**	**N/A**	**N/A**	**0/1**	**(0.0)**
Mucor species	0/1	(0.0)	N/A	N/A	0/1	(0.0)

[†] N = Number of modified intention-to-treat patients in the treatment group.
[‡] m/n = Number of culture documented baseline isolates associated with favorable clinical response/total number of pathogens in patients with culture documented baseline infection.
[§] N/A = Not applicable (no patients with this particular pathogen).
[%] One patient included in this count had a mixed infection of *Aspergillus fumigatus* and *Fusarium* with an unfavorable response. The outcome for *Fusarium* is not shown in the table.

Baseline Fungemias

Of 15 baselines yeast MITT isolates tested, 12 were blood isolates. Thus, the MIC data available for blood isolates from patients in the MITT population resembled the overall MIC pattern for all yeast baseline pathogens. Yeasts caused all documented fungemias in this study.

Persistence of Baseline Infections

The persistence of baseline infections was examined by reviewing all documented baseline infections with an unfavorable outcome, as determined by the Adjudication Committee. A positive final on-therapy culture from a relevant site was considered persistence. Negative final on-therapy cultures were considered evidence of eradication. For disseminated infections, all relevant sites were reviewed and any positive final on-therapy culture from a relevant site was considered persistence. Posttherapy cultures, whether positive or negative, were not considered relevant here inasmuch as patients may have received alternative antifungal therapy, or could have relapsed.

In the caspofungin group, 2 of the 13 baseline infections with clinical failure were associated with documented microbiological persistence: One was a C. tropicalis disseminated fungal infection with positive blood culture at entry. Although repeat blood cultures were negative, the patient had a positive culture from skin biopsy on Day 6. This patient received 14 days of study therapy and was a clinical failure. The second was a case of Aspergillus fumigatus and Fusarium sp. pneumonia with sputum culture positive on Day –3 for A. fumigatus only, and subsequent sputum culture on Day 11

that was positive for both A. fumigatus and Fusarium sp. This patient received 19 days of therapy and was a clinical failure.
In the AmBisome group, 4 of the 20 baseline infections with clinical failure were associated with documented persistence. There were 3 cases of persistent candidemia (1 C. tropicalis, and 2 C. krusei) and one case of persistent Aspergillus niger in a disseminated fungal infection.

There were 27 patients with baseline infections in each treatment group. Apart from the persistence of infections as described above, the patients with documented baseline infections and unfavorable outcomes can be described as follows:

Among documented baseline infections in the MITT population, there were 13 unfavorable responses in the caspofungin group and 20 unfavorable responses in the AmBisome group. Most unfavorable responses were failures. The others were 2 indeterminate outcomes in the caspofungin group and 1 stable disease in the AmBisome group. The patient narrative summaries and adjudicators' assessments of the reason for an unfavorable clinical outcome were reviewed and selected patient characteristics and reasons for failure determined from this review are presented in a table (data not presented here).

Patients with unfavorable outcomes for baseline infections were a very high risk subset of patients; most were either high risk, or if low risk had acute leukemia (mostly AML), and entered with profound neutropenia. Most patients had multiple reasons for failure.
Of the 13 unfavorable responses in the caspofungin group, 5 were dose-increased for inadequate clinical response, 9 were prematurely discontinued due to lack of efficacy, 7 had persistent neutropenia, 10 had progressive signs or symptoms, 9 had progressive (or new) radiological abnormalities, 5 had a positive culture, including 2 with persistent baseline pathogen, 10 changed antifungal therapy, and 4 patients died.
For the 20 patients with unfavorable responses in the AmBisome group, 10 were dose-increased for inadequate clinical response, 5 were prematurely discontinued due to lack of efficacy, 13 had persistent neutropenia, 18 had progressive signs or symptoms, 14 had progressive (or new) radiological abnormalities, 12 had a positive culture, including 4 with persistent baseline pathogen, 8 changed antifungal therapy, and 10 patients died.

In the "baseline fungal infection" endpoint, there was an imbalance for persistent neutropenia (defined as ANC <500/µL at the end of study therapy) between treatment groups, which favours caspofungin.
Persistent neutropenia was commonly present in patients with an unfavorable treatment outcome (in 7 of the 13 caspofungin failures, 53.8 %, and in 13 of the 20 AmBisome failures, 65%), and only 1 of the 21 patients with favorable outcomes for both treatment groups. Although the two groups were well balanced at study entry, persistent neutropenia appeared somewhat more common in the AmBisome group (13/27, 48%, had persistent neutropenia in the AmBisome group vs. 7/27, 25.9%, in the caspofungin group), and this independent prognostic factor may have influenced the outcomes of baseline infections.

- **Absence of Breakthrough Infections**

Breakthrough infections were defined as probable and/or proven adjudicated infections with onset on or after Day 3 of study therapy and up to 7 days after completion of therapy.

The distinction between a baseline and a breakthrough infection was predefined, albeit very arbitrary, as based upon the given definitions (onset up to the second day of study therapy versus onset on or after the third day of study therapy). The adjudication committee decided if it was a baseline or breakthrough infection with date of onset as the date that a diagnostic test (e.g. a culture specimen) was obtained.

As displayed in Tables 3 and 4 the percentages of MITT patients without breakthrough infections were similar in both treatment groups (**94.8%** in the caspofungin and **95.5%** in the AmBisome group). The observed difference (caspofungin minus AmBisome) in response rates between the 2 treatment groups was -0.8% with a 95% CI of (-3.3, 1.8). Breakthrough infections were more common for patients in

the high-risk category in both treatment groups, as expected, but the rates of breakthrough infections appeared similar whether or not antifungal prophylaxis was used.

Demographics of Patients With Breakthrough Infections

In the MITT population there were 29 caspofungin patients and 24 AmBisome patients with breakthrough infections, when the late adjudication cases are included. The baseline demographic characteristics of these patient infections were generally similar.

Distribution Of Breakthrough Infections Overall and by Stratum

There were 30 breakthrough infections in 29 patients in the caspofungin group, and 25 breakthrough infections in the 24 AmBisome patients. *Candida* species were the most common pathogens (chronic disseminated candidiasis [14] and fungemia [12] were the most common diagnoses). The second most common pathogens were *Aspergillus* species (pneumonia was the most common diagnosis [12]).

Table 7: Summary of adjudicated breakthrough infections
Modified Intention-to-Treat Patients

	Caspofungin (N=556)		Ambisome (N=539)	
Total Patients w/BTI	29		24	
Aspergillus spp.	10		9	
Disseminated FI		3		1
Pneumonia		6		6
Sinusitis		0		2
Facial		1		0
Candida spp.	16		15	
CDC		7		8
Disseminated FI		3		1
Fungemia		6		6
Other	4		1	
Fungemia		1		0
Disseminated FI		2		1
Pneumonia		1		0

Overall, by pathogen, the types of breakthrough infections were balanced between the 2 treatment groups. However, there were more breakthrough infections caused by species other than *Candida* or *Aspergillus* in the caspofungin than the AmBisome group (4/30 versus 1/25, respectively): these were caused by *Basidiomycetes* (1), *Zygomycetes* (2) and *Fusarium* (1) in the caspofungin group, and by a not further specified mould in the Ambisome group. Across pathogens, there were numerically more cases of disseminated fungal infection in the caspofungin than the AmBisome group (8 versus 3).

Breakthrough infection occurred more often in high-risk patients in both treatment groups (15/146 [10.3%] of caspofungin and 9/122 [7.4%] of AmBisome patients) than low-risk patients (15/410 [3.7%] and 16/417 [3.8%], respectively). Also there was a higher proportion of *Aspergillus* breakthrough infections in high-risk patients in both treatment groups (7/146 [4.8%] and 7/122 [5.7%], respectively) than low-risk patients (3/410 [0.7%] and 2/417 [0.5%], respectively).
The overall distribution of breakthrough infections was generally similar between the 2 treatment groups whether or not prophylaxis was used.

Microbiology of Breakthrough Pathogens

The organisms causing breakthrough infections were primarily *Candida* and *Aspergillus* species, but also included several less common yeast and mould pathogens. There were 32 yeast pathogens (including the *C. glabrata* in the footnote) and 24 mould pathogens identified either microbiologically or histologically as causing breakthrough infections by the Adjudication Committee; MIC data were available in 27/56 or 48.2% of total breakthrough pathogens.

Of the 17 unique yeast breakthrough isolates tested in the MITT population, 15 were blood isolates and 14 were *Candida* species.
There were 5 yeast isolates in the caspofungin arm and 2 from the AmBisome arm (1 C. *parapsilosis* and 1 C. *guilliermondii*, both trailers) with caspofungin MICs >8 μg/ml. In the caspofungin group, 3 of the 5 isolates with MICs >8 μg/ml in RPMI were trailing isolates (all C. *parapsilosis*) and one was a non-*Candida* isolate, *T. beigelii.* Trailing in RPMI medium has been consistently seen for some *Candida* species, especially C. *parapsilosis* and C. *guillermondii.* This *in vitro* phenomenon is not seen in other media and has not been associated with reduced susceptibility to caspofungin. The significance of caspofungin MICs for T. *beigelii* is unclear since there are no standardized testing methods for any anti-fungal agent against the non-*Candida* yeasts.
One breakthrough *Candida* isolate, *Candida albicans*, had a clear endpoint of MIC >8 μg/ml in RPMI. This isolate came from a patient with a breakthrough disseminated *Candida* infection involving multiple sites and blood. This patient had 4 separate *Candida albicans* isolates all determined to be of common origin by DNA and CA3 fingerprinting analyses: an oropharyngeal isolate, a blood isolate, a tissue isolate from lung biopsy and a tissue isolate from liver biopsy. Additional evaluation included MIC testing, FKS1 gene sequence analysis, assays of glucan synthase activity, and *in vivo* activity in the mouse TOKA disseminated candidiasis model. The liver and mouth isolates were considered fully susceptible to caspofungin by all methods. The lung and blood isolates, however, showed elevated MIC values both in RPMI (>128 μg/ml) and AM3 (>16 μg/ml) medium, had FKS single amino acid substitution at position 645, and reduced inhibition of glucan synthesis based on increased IC_{50} values. In the animal model, caspofungin showed efficacy against the blood but not the lung isolate. For the lung isolate, an ED_{90} value could not be calculated, although there was a significant reduction of C. *albicans* colony forming units (CFU) in kidneys of mice at doses ranging from 12 to 20 mg/kg/day, compared to infected, untreated controls.

All 10 unique mould breakthrough isolates from both treatment arms, most of which were *Aspergillus* species, had caspofungin MICs ≤0.5 μg/ml and amphotericin B MICs of ≤1 μg/ml. There was 1 *A. flavus* isolate with an amphotericin B MIC of 2 μg/ml.

Timing of Breakthrough Infections
Most breakthrough fungal infections in both treatment groups occurred while the patients were still receiving study therapy (only 4 of 30 cases for caspofungin and 5 of 25 for AmBisome occurred within 7 days after the end of study therapy).

Additional Information Regarding Documented Infections
- *Discordance Between Adjudication Committee and Investigator Assessments of Documented Infection*
Discordance between the Adjudication Committee and the investigators was common regarding the adjudicated probable and proven fungal infections but was generally not of clinical significance; most of the discordance was due to the different terminology used to describe the same pathogenic process. The Adjudication Committee, which was unaware of the investigators' assessments regarding treatment outcome, was generally more conservative than the investigators and assigned more unfavorable treatment outcomes.

Mortality in Patients with Documented Infections
Because mortality rates are substantial in this at-risk patient population, due to fungal and other infections, as well as underlying malignancy and its noninfectious complications, it is important to examine mortality from a variety of perspectives. This study examined mortality using three different prespecified approaches. This section presents mortality data in patients with documented fungal infections, with consideration of overall mortality and mortality potentially attributable to the fungal infection (e.g. death caused by or occurring in the presence of active fungal infection).
The other prespecified approaches to mortality were survival to 7 days posttherapy for the MITT population, as a component of the primary endpoint (see point 3 below) and a review of mortality for all treated patients in the Safety section.

Overall mortality rates in the MITT population due to or in the setting of active fungal infection are summarized separately for patients with baseline and breakthrough infections in Table 8 below.

Table 8: Mortality Rates in Patients with Documented Infections, Overall and in Setting of Active Fungal Infection—Modified Intention-to-Treat Analysis

Mortality Rates	Caspofungin 70/50 mg ($N^{\dagger}$=556)		AmBisome 3 mg/kg ($N^{\dagger}$=539)	
	Baseline Infection m/n[‡] (%)	Breakthrough Infection m/n[§] (%)	Baseline Infection m/n[‡] (%)	Breakthrough Infection m/n[§] (%)
Overall Deaths[‡]	3/27 (11.1)	10/29 (34.5)	12/27 (44.4)	10/24 (41.7)[%]
Deaths In Setting of Active Fungal Infection[§]	3/27 (11.1)	10/29 (34.5)	10/27 (37.0)	10/24 (41.7)[%]

[†] N= Number of modified intention-to-treat patients in treatment group.
[‡] m/n= Number of patients who died/Number of patients with documented infection type.
[§] m/n= Number of patients who died in the presence of active fungal infection/ Number of patients with documented infection type.
[%] Includes one patient adjudicated after frozen file.

- Mortality in Patients With Documented Baseline Infection

The mortality rate in patients with a baseline infection was substantially lower in the caspofungin than the AmBisome group (3 deaths [11.1%] versus 12 deaths [44.4%]) ($p<0.01$). The excess mortality in the AmBisome group appeared primarily to be associated with bacterial or fungal infections or nonspecific sepsis syndromes. Investigators made a determination about the relationship of the adverse experiences to death. The Adjudication Committee determined independently the presence of invasive fungal infections, but did not specifically assess whether a fungal infection contributed to the patient's death. However, a review of the narratives of the 15 deaths among 54 patients with baseline infections shows that 13 (86.7%) of these 15 deaths were either due to fungal infections or occurred in the setting of active fungal infection: 3 of 27 patients (11.1%) in the caspofungin group and 10 of 27 (37.0%) in the AmBisome group, thus yielding mortality rates in the setting of active fungal infection of **11.1%** and **37.0%**, respectively. These results are also consistent with the higher rate of successful treatment outcome for baseline infections in the caspofungin group. The Adjudication Committee assessed the treatment outcome of the baseline infection as failures in each of the 13 patients who died. In the remaining 2 cases, the deaths were due to noninfectious causes, and the Adjudication Committee's determination of treatment outcome for the baseline infection was favorable.

- Mortality in Patients With Documented Breakthrough Infection

During the study period, the mortality rate in patients with breakthrough infections was similar for the 2 treatment groups: 10 deaths **(34.5%)** in the caspofungin group and 10 deaths **(41.7%)** in the AmBisome group. The most common fatal adverse experiences were in the Body as a Whole system; usually related to a bacterial or fungal infection or a nonspecific sepsis syndrome. There was one additional fatal adverse experience in the caspofungin group reported in the poststudy period (more than 14 days after the end of study therapy) as a fatal fungal infection. Thus there were 11/29 or **37.9%** deaths in the setting of breakthrough infections in the caspofungin group. All 21 deaths (11 in the caspofungin group and 10 in the AmBisome group) were either due to a fungal infection or occurred in the presence of active fungal infection.

- Breakthrough Infections Identified After the 7-day Posttreatment Follow-Up Visit

All suspected fungal infections were adjudicated, but the analysis of breakthrough infections was limited to those that occurred and were documented by the 7-day posttherapy visit, as defined and required by the protocol. Evidence for breakthrough infections identified after the 7-day posttreatment follow-up visit was not required by protocol and was not uniformly available; however, in some cases, these data were reported by the investigator and all such information was provided to the Adjudication Committee. Any breakthrough infections identified from data obtained only after the 7-day posttherapy follow-up visit were documented by the Adjudication Committee. Although described in the study report, they were not counted in the primary analysis. There were 5 "post-7-day" breakthrough infections in the caspofungin group, and 6 in the AmBisome group. Of the 11 patients with "post-7-day" breakthrough infections, 3 patients died (or had a fatal adverse experience) during

the study (during 2 week posttreatment follow-up period): 2 in the caspofungin group and 1 in the AmBisome group. Based upon available data, the overall numbers of "post-7-day" breakthrough infections appeared similar between the treatment groups, with similar distribution of specific diagnoses, pathogens, and mortality.

- *Adjudicated Possible Invasive Fungal Infections*

The Adjudication Committee assessed all the same variables with respect to possible infections as for the documented infections, although, as prespecified, possible invasive fungal infections were not included in any of the formal study analyses. However, when possible infections were included according to the same conventions as documented infections, the conclusions of the primary study analysis remain unchanged for both the MITT and evaluable-patients populations.

The company was asked to prove its assertion that inclusion of "possible" invasive fungal infections in the primary analysis would not alter the main study conclusion. As specified in the protocol only documented infections (i.e. proven or probable infections) were considered for analysis. Concerning the possible breakthrough infections, the majority of patients (56/57) had pneumonias. Only 3 out of the 57 patients had microbiological data of which only one fulfilled the microbiological criteria for IFI as defined by the EORTC/MSG. Although the criteria of diagnosis of possible IFI were sufficient for initiating antifungal therapy, a post-hoc examination by the expert panel based upon all data available up to 7 days post-therapy could not demonstrate more definitive data, which is reassuring. Although it can be agreed that the occurrence of possible infections should be regarded with a high level of uncertainty, and that in the setting of an empirical therapy trial in febrile neutropenic patients, analysis of documented invasive fungal infections should be limited to the probable and proven categories, the higher numbers of possible breakthrough infections in the caspofungin group vs AmBisome group (38 vs 19) raises some concern.

- **Survival to 7-Day Follow-Up**

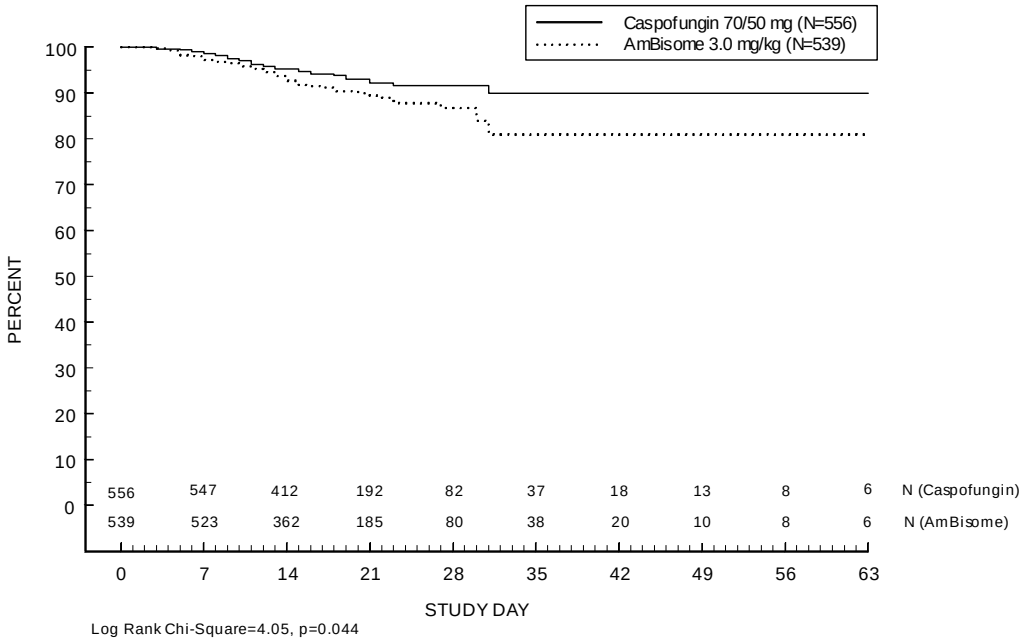
Four patients in the caspofungin group and five in the AmBisome group were lost to follow-up within 7 days after the completion of therapy and are therefore counted as failures for the survival endpoint. As shown in the Tables 3 and 4 the percentages of patients who survived for at least 7 days after completion of therapy were **92.6%** for caspofungin and **89.2%** for AmBisome. The observed difference (caspofungin minus AmBisome) in response rates between the 2 treatment groups was 3.4% with a 95% CI of (0.0, 6.8). The rate of survival to 7 days posttherapy was lower in high- than low-risk patients within each treatment group, as would be expected. For the evaluable-patients analysis, patients who were lost to follow-up earlier than 7 days after the completion of therapy are excluded from the analysis of the survival endpoint. Results were similar for the evaluable-patients population (survival rate 92.6% for caspofungin and 90.1% for AmBisome).

Kaplan-Meier Estimates of Survival Time

Kaplan-Meier estimates of the time to death for each of the treatment groups were calculated in order to reflect the probability of surviving beyond a given day through 7 days posttherapy (see Figure 1). It should be noted that most patients completed study treatment by 28 days and were followed only 7 days longer for the survival endpoint, or up to 35 days. Consequently, the population becomes much smaller after Day 35. The log-rank chi-square statistic was significant (p=0.044), indicating that there is a difference between the treatment groups with respect to time to death. A consistently higher proportion of caspofungin than AmBisome patients survived, and the difference was most pronounced after Study Day 28. The Kaplan-Meier estimates for survival to 7 days posttherapy was repeated for the evaluable-patients population, however, the log-rank chi-square statistic was not significant (p=0.192).

Kaplan-Meier estimates and curves were also calculated in order to assess the effect of the risk category on survival time. The log-rank chi-square statistic was significant (p=0.032), indicating that there is a difference among the 4 treatment group and risk category combinations with respect to time to death: there was a shorter survival time for high-risk patients in the AmBisome than the caspofungin group, and for low-risk patients in either treatment group.

Figure 1: Proportion of Patients Who Survived up to 7 days Post-Therapy by Treatment Group (Kaplan-Meier Curves) - Modified Intention-to-Treat Analysis



Deaths Reported During Treatment and Follow-up Period

In the analysis of the primary endpoint, patients lost to follow-up before 7 days post-therapy were considered failures. The percentages of patients who actually died during study therapy or the 7-day posttherapy follow-up period were numerically lower for caspofungin (**6.7%**, 37/556) than for AmBisome (**9.8%**, 53/539). Most of the deaths in both groups occurred during the 7-day posttreatment follow-up period. The treatment groups were generally balanced with respect to the most common fatal adverse experiences, which were related to various infections (fungal and non-fungal), hematologic malignancies, and respiratory illnesses. Cardiovascular fatal adverse experiences were slightly more frequent in the AmBisome group (10 [1.8%] for caspofungin and 19 [3.5%] for AmBisome). Fatal hepatobiliary system adverse experiences were noted in 2 caspofungin patients (0.4%) but not in the AmBisome group; neither was considered drug related. Similar adverse experiences led to death in both treatment groups and reflected the serious underlying diseases and complications expected in such a sick study population.

Overall, 90 (8.2%) MITT patients died, 37 in the caspofungin group and 53 in the AmBisome group. Few patients died during study therapy; the majority of fatal events (79/90; 88%) occurred during the 7-day follow-up. Autopsy was performed in 21 (23%) cases. Of these 10 had documented IFI (5 in each treatment group), according to the adjudicators and IFI was confirmed in all cases at autopsy. In the other 11 cases, 2 with possible pneumonia and 9 with non-fungal deaths (not considered to have IFI by Adjudicators), no invasive fungal infection could be detected at autopsy. Fatal adverse events in the remaining cases included e.g. cardiovascular events, respiratory illnesses and sepsis/multiple organ failure reflecting the serious underlying disease and complications that could be expected in this study population. Data suggest that most patients (other than those discussed above with documented IFI) died due to non-fungal causes.

The MAH was asked to investigate if there was indeed an increase in creatinine levels in those patients who died and to analyse if these levels could be a reason for the difference in survival seen between both treatment groups. As expected, an increase in creatinine in patients with already pre-existing renal impairment was indeed a clear predictor of increased mortality. As clearly demonstrated in this analysis, the outcome of a baseline infection as well as the presence of persistent neutropenia are important prognostic factors for survival. The survival endpoint as presented in the application file had to be re-analysed due to the existing imbalance in persistent neutropenia in the patients with a baseline

infection. Taking these data into consideration, the survival advantage for caspofungin appears at least doubtful.

- **Absence of Premature Discontinuation Due to Toxicity of Lack of Efficacy**

The study endpoint defined discontinuations due to either toxicity or lack of efficacy as failure for the MITT analysis. In contrast, patients who discontinued therapy for reasons other than study drug-related toxicity or lack of efficacy were, like patients who completed therapy, considered as successes. Patients who prematurely discontinued therapy due to lack of efficacy had either suspected fungal infection generally requiring a change of antifungal therapy or persistent fever without a suspected fungal infection.

As shown in the Tables 3 and 4 the rates of absence of premature discontinuation for toxicity or lack of efficacy were consistently higher in the caspofungin group, overall (**89.7%** for caspofungin versus **85.5%** for AmBisome) and for both high- and low-risk categories and with or without use of antifungal prophylaxis. Results for the evaluable-patients population were generally similar (88.2% for caspofungin and 83.4% for AmBisome, respectively).

Reason for Premature Discontinuation

More than one reason for discontinuation was possible; however, only one reason was identified by the investigator for assessment of this endpoint. The specific reasons for endpoint discontinuations are summarized in Table 9 below.

Table 9: Summary of Premature Discontinuations Modified Intention-to-Treat Analysis

	Caspofungin 70/50 mg ($N^{\dagger}$=556)		AmBisome 3 mg/kg ($N^{\dagger}$=539)	
Discontinued Due to:	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)
Lack of efficacy	**30**	**(5.4)**	**34**	**(6.3)**
Persistent fever	6	(1.1)	9	(1.7)
Suspected fungal infection	24	(4.5)	25	(4.6)
Toxicity (drug-related adverse experience)	**27**	**(4.9)**	**44**	**(8.2)**
Clinical	24	(4.3)	35	(6.5)
Laboratory	3	(0.5)	13	(2.4)

† N= Number of modified intention-to-treat patients in treatment group.
‡ n= Number of patients with specific reason for premature discontinuation.

Lack of Efficacy

Lack of efficacy could have been due either to suspected fungal infection or to persistent fever without specific evidence to suggest fungal infection. As shown above similar proportions of patients in both treatment groups discontinued for each of the lack of efficacy reasons.

All discontinuations due to lack of efficacy were reviewed. If any evidence of fungal infection was present, then the case was adjudicated. In contrast to other analyses in this submission, possible invasive fungal infections in the Adjudicators' assessment were included with probable or proven infections in order to permit an adequate comparison with the investigators' clinical management of the patients. For all 49 discontinuations due to suspected fungal infection, the Adjudication Committee agreed that there was at least a possible fungal infection (either baseline and breakthrough infection). Of baseline infections, all but 2 were considered by the Adjudication Committee to have unfavorable treatment outcomes, thus showing fundamental agreement between the investigators' and the Adjudication Committee's decisions regarding possible and documented infection.

Toxicity

Caspofungin had generally lower rates of discontinuation due to drug-related adverse experiences (4.9% for caspofungin and 8.2% for AmBisome). Relatively few patients prematurely discontinued therapy due to drug-related clinical adverse experiences. Nine patients in the caspofungin group were

discontinued due to drug-related adverse experiences of the skin and skin appendages, and 1 case was a serious rash; all patients recovered. Five patients in the caspofungin group were discontinued due to drug-related adverse experiences in the hepatobiliary system or hyperbilirubinemia; one of the adverse experiences was considered serious. Of these 5 patients 4 patients had underlying hepatic dysfunction. The hepatobiliary adverse experience generally occurred in the setting of other concomitant organ dysfunction or allergic reaction, with no particular pattern to the biochemical abnormalities noted. The biochemical abnormalities that occurred during therapy were relatively mild in 2 cases, and in 2 of 3 other cases with marked abnormalities, this appeared to be an isolated event. The adverse experience resolved in 2 cases. With regard to the 3 cases with hepatobiliary adverse experiences that did not resolve, 14-day follow-up information was available only in 1 case; the other 2 patients died of other causes within 4 days after discontinuation of therapy and therefore resolution could not be assessed.
Very few patients discontinued therapy due to drug-related laboratory adverse experiences (3 versus 13 cases in the caspofungin and the AmBisome group, respectively). Laboratory drug-related adverse experiences leading to discontinuation were primarily related to liver function tests (ALT, AST, alkaline phosphatase, and total or direct hyperbilirubinemia) or to increased serum creatinine. In each test category, there were fewer discontinuations in the caspofungin than the AmBisome group.

- **Resolution of Fever During Neutropenia**

Fever resolution was defined as a maximum oral temperature (or its equivalent, using noninfusion-related temperatures) of <38 degrees Celsius for at least 48 consecutive hours during the period of neutropenia (ANC <500/µL). As shown in the Tables 3 and 4 similar percentages of patients experienced fever resolution during neutropenia: **41.2%** in the caspofungin and **41.4%** in the AmBisome group. The observed difference (caspofungin minus AmBisome) in response rates between the 2 treatment groups was -0.2% with a 95% CI of (-6.0, 5.6). This endpoint had the lowest success rate of all the individual components of the composite primary endpoint. Unexpectedly, there was a higher rate of fever resolution in the high-risk category for both treatment groups (50 to 52.1% for high-risk patients; 37.3 to 38.9% for low-risk patients). A detailed exploration was undertaken of the durations of fever, neutropenia, and fever during neutropenia, with an emphasis on differences related to risk category rather than treatment group.

Time to Resolution of Fever During Study Therapy
Kaplan-Meier estimates were computed for the proportion of MITT patients with persistent fever during study therapy. The log-rank chi-square statistic was not significant (p=0.834), indicating that there is no difference between the treatment groups with respect to time to resolution of fever. By Day 7 of study therapy, ~50% of the patients in each treatment group had resolution of fever.
Kaplan-Meier estimates were also used to display the time to resolution of fever by the 4 treatment and risk category groups for MITT patients. The log-rank chi-square statistic was not significant (p=0.402), indicating that there is no difference among the 4 treatment and risk category groups with respect to time to resolution of fever.

Time to Resolution of Neutropenia During Study Therapy
Kaplan-Meier estimates were calculated for the time to resolution of neutropenia. In the MITT analysis, the log-rank chi-square statistic was not significant (p=0.732), indicating no difference between the treatment groups with respect to time to resolution of neutropenia. By Day 8 of study therapy, ~50% of the patients in each treatment group had resolution of neutropenia during study therapy.
For the MITT analysis, Kaplan-Meier estimates were also computed for the time to resolution of neutropenia for the 4 treatment group and risk category subgroups. The median times to resolution of neutropenia for the low-risk groups (8 days for both treatment groups) were lower than those observed in the high-risk groups (11 and 12 days for the caspofungin and AmBisome groups, respectively). The log-rank chi-square statistic was highly significant (p<0.001), indicating a difference among the 4 treatment groups and risk category combinations groups with respect to time to resolution of neutropenia. Low-risk patients had a shorter duration of neutropenia (by 3 to 4 days) than high-risk patients in both treatment groups. However, for each risk category, caspofungin and AmBisome had similar response rates for this endpoint.

Time to Resolution of Fever During Neutropenia

The log-rank chi-square statistic was not significant (p=0.258), indicating no difference between the treatment groups with respect to time to resolution of fever during neutropenia. By Day 10 of study therapy, ~50% of the patients in each treatment group had resolution of fever during neutropenia, compared with Day 7 in the analysis for resolution of fever irrespective of neutropenia. Kaplan-Meier estimates for the time to resolution of fever during neutropenia for the MITT analysis were also calculated for the 4 treatment groups and risk category groups. No significant difference was observed (p=0.075) among the 4 treatment group and risk category combinations.

However, as the duration of neutropenia was markedly different between the risk categories for both treatment groups, additional Kaplan-Meier calculations were performed to examine the effect of risk category alone. The log-rank chi-square statistic was significant (p=0.021), indicating a difference between the risk categories with respect to time to resolution of fever during neutropenia. Unexpectedly, the proportion of patients with persistent fever during neutropenia was consistently higher in the low-risk than the high-risk stratum, a fact explained by the censoring of data from patients whose neutropenia had resolved before 48 hours without fever could be demonstrated. Since the low-risk patients had shorter durations of neutropenia, they were censored from this analysis to a greater extent than high-risk patients. Such patients are thus considered failures for both the fever resolution and the overall endpoint.

Exploratory Analyses Based on Variations of the Resolution of Fever Endpoint

Fever is a nonspecific finding in the neutropenic patient and can be caused by a variety of infectious and noninfectious problems, including viral and bacterial as well as fungal infections, the underlying primary malignancy, or it can be a complication of therapy. A number of exploratory analyses were performed in which fever resolution was either substantively modified from the definition used in the primary analysis or was excluded entirely from the composite primary analysis. For consistency, handling of all other endpoints was unchanged in these analyses.

For the primary analysis, fever resolution was defined as having a maximum oral temperature of $<38^{o}$ C for at least 48 consecutive hours during neutropenia. The primary analysis was repeated in an exploratory manner using variations of the definition of fever resolution as follows: (1) resolution of fever for 24 hours prior to the resolution of neutropenia, (2) resolution of fever at the 7-day posttherapy follow-up visit, and (3) exclusion of fever resolution from the composite endpoint. These definitions can be considered progressively less conservative than that used for the primary analysis because (1) the shortening of the required duration without fever from 48 to 24 hours during neutropenia should be more readily and frequently achieved, (2) the "afebrile at 7-day follow-up" endpoint is independent of neutropenia, and also because the temperature recorded is a single measurement and not the maximum temperature over a 24-hour period, and (3) exclusion of fever resolution simply disregards the temperature data.

Table 10 summarizes the observed rates of overall favorable responses and for fever resolution according to each of the 4 definitions.

It is apparent that the overall favorable response rates and the fever resolution rates increase substantially with progressively less conservative definitions of fever resolution. It should be noted that all other endpoint responses (e.g., those for documented infection, survival, and discontinuation of therapy) were handled identically to the primary analysis, and so these other individual endpoint responses are unchanged. Overall response rates are increased most dramatically when fever resolution is excluded entirely, and reflects a composite outcome that consists solely of endpoints of documented infection, survival, and premature discontinuation of therapy.

Table 10: Summary of Observed Responses by Fever Resolution Definition
Modified Intention-to-Treat Analysis

	Caspofungin 70/50 mg ($N^{\dagger}$=556)	AmBisome 3 mg/kg ($N^{\dagger}$=539)

Definition of Fever Resolution	Overall Favorable Response m/n[‡] (%) (95% CI)	Fever Resolution m/n[§] (%) (95% CI)	Overall Favorable Response m/n[‡] (%) (95% CI)	Fever Resolution m/n[§] (%) (95% CI)
Afebrile 48 hrs during neutropenia	190/556 (34.2) (30.2, 38.1)	229/556 (41.2) (37.1, 45.3)	181/539 (33.6) (29.6, 37.6)	223/539 (41.4) (37.2, 45.5)
Afebrile 24 hrs during neutropenia	287/556 (51.6) (47.5, 55.8)	344/556 (61.9) (57.8, 65.9)	257/539 (47.7) (43.5, 51.9)	328/539 (60.9) (56.7, 65.0)
Afebrile at 7-day follow-up	308/556 (55.4) (51.3, 59.5)	350/556 (62.9) (58.9, 67.0)	289/539 (53.6) (49.4, 57.8)	335/539 (62.2) (58.1, 66.2)
Fever resolution excluded	454/556 (81.7) (78.4, 84.9)	---	403/539 (74.8) (71.1, 78.4)	---

[†] N = Number of modified intention-to-treat (MITT) patients in the treatment group.
[‡] m/n = Number of patients with overall favorable response/ Number of MITT patients in treatment group.
[§] m/n = Number of patients with resolution of fever/number of MITT patients in treatment group.

Overall response with fever resolution for 24 hours during neutropenia

The primary analysis was repeated after fever resolution was redefined as having a maximum oral temperature of <38° C for at least 24 consecutive hours during the period of neutropenia. It was expected that requirement of a shorter period without fever would increase the response rate in low-risk patients whose short durations of neutropenia would not permit a demonstration of 48 hours without fever despite favorable responses for all other endpoints. It was confirmed that the difference in fever resolution rates between risk categories is much smaller than that observed with the 48 hour afebrile endpoint used in the primary analysis (see Figure 2).

Overall response with fever resolution at the 7-day follow-up visit

The primary analysis was repeated after fever resolution was redefined as having a maximum oral temperature (or its equivalent) of <38° C at the 7-day posttherapy follow-up visit in order to evaluate outcome when temperature was not linked to neutropenia. Similarly, these results confirm the expectation that the difference in fever resolution rates between risk categories is eliminated with the 7-day posttherapy endpoint (see Figure 2).

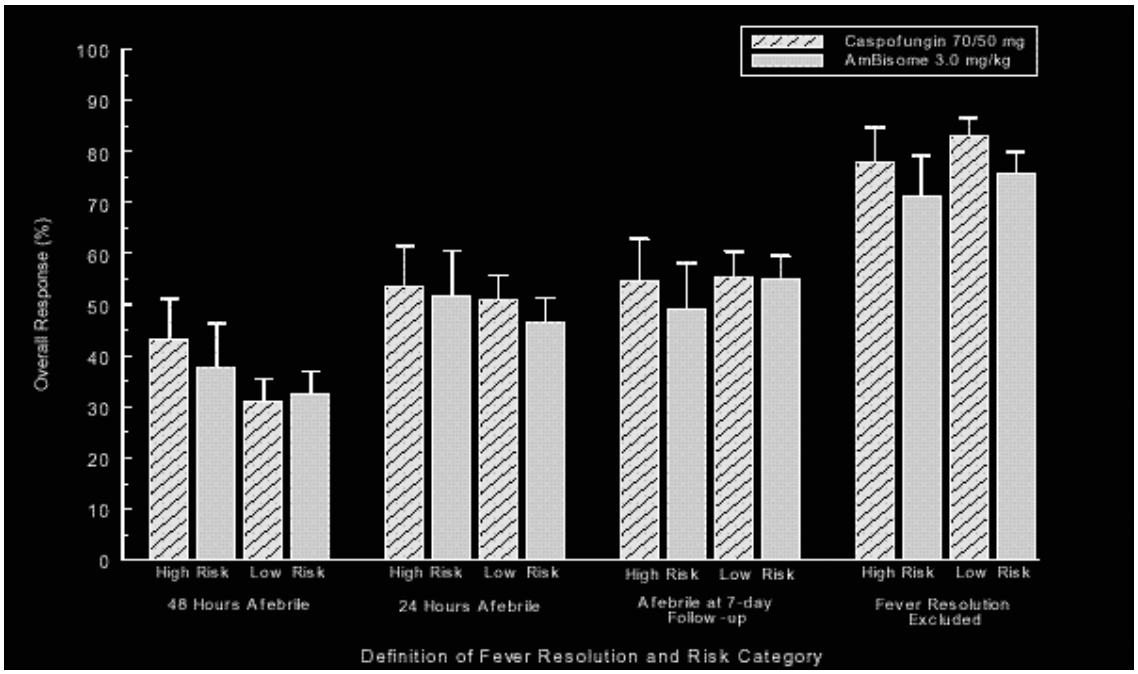
Overall response excluding the resolution of fever endpoint

This analysis demonstrates that overall response rates increase markedly for both treatment groups, and that low-risk patients have higher overall response rates (by at least 4%) than high-risk patients, as would be expected, when fever resolution is excluded from the endpoint and efficacy is based upon documented invasive fungal infections, survival, and completion of therapy (see Figure 2).

The data from this study suggest that patients with short durations of neutropenia may frequently fail the fever resolution endpoint but have favorable outcomes for other endpoint components. This explains the paradoxical observation that high-risk patients, in whom a longer period of neutropenia was demonstrated, in fact had higher rates of favorable overall responses (43.2% for caspofungin and 37.7% AmBisome) than low-risk category patients (31.0% for caspofungin and 32.4% for AmBisome) when the 48 hour-afebrile-during- neutropenia definition of fever resolution was used in the primary analysis (see Table 3). In fact, the high-risk patients in the primary analysis had substantially higher rates of fever resolution (52.1% for caspofungin and 50.0% for AmBisome) than low-risk patients (37.3% for caspofungin and 38.8% for AmBisome). Review of the primary analysis by risk category using variations of the fever resolution endpoint confirms the observation that low-risk patients have higher response rates than high-risk patients when the less conservative fever resolution definitions are used. This is most apparent when fever resolution is excluded entirely from the overall endpoint. The results of the analysis that excludes fever resolution indicate much higher overall response rates in both treatment groups, and also suggest that caspofungin may be superior to AmBisome as empirical therapy when fever resolution is excluded and only the other 4 secondary endpoints are considered: overall favourable response of 81.7% for caspofungin versus 74.7% for Ambisome when adjusted for strata (estimated difference in response rate 7.0% with a 95% CI of (1.9, 12.1)).

The difference in fever resolution between the high and low risk groups seems indeed to be the cause for the higher overall response rate seen in high risk patients, for the reasons explained above. This is confirmed when using the less conservative definitions for fever resolution. Nevertheless, although it is acknowledged that by extending the period without fever a number of patients in the low risk group would be excluded from the analysis due to rapid recovery of their neutropenia, the criterion of 48 hours without fever seems a minimum requirement for the fever resolution endpoint. Theoretically, fever resolution for 5 consecutive days during neutropenia would even be a better endpoint, although practically more difficult to realise. It is reassuring to see that response rates for caspofungin as compared to Ambisome remain similar, independently of the definitions used for fever resolution.

Figure 2: Variations of fever resolution endpoint – Overall response by risk category



- **Ancillary analyses**

The primary analysis of efficacy was repeated for demographic subpopulations based on gender, age (≤ or >65 years of age), and race (Caucasian versus non-Caucasian). Caspofungin seemed similarly efficacious in both males and females, in both older adult patients (>65 years) and those up to 65 years of age, and in Caucasians as well as non-Caucasian patients, although a limited number of patients over 65 years and of non-White patients were studied.

2.3.3 Clinical studies in special populations

No special studies were performed in patients with renal or hepatic impairment.
Children were not included in the empirical study and no specific data were obtained in children for this indication. Nevertheless, a paediatric study is planned to start in 2005, which will closely follow the design of the present adult study, but will be primarily a safety study.

2.3.4 Issue on dose increase of caspofungin to 70mg

The recommendation of a dose increase of caspofungin to 70 mg in case of inadequate clinical response cannot be endorsed due to lack of supportive data. A minimum requirement to support the recommendation of up-dosing is that a dose-response effect of higher doses of caspofungin should have been documented. It is worth recalling that caspofungin has been authorised for use in invasive

aspergillosis only under exceptional circumstances. In particular, there is an ongoing Specific Obligation (S.O.) to evaluate higher doses of caspofungin in invasive aspergillosis. This S.O. will not be fulfilled, since the aspergillosis study has been stopped. Instead, the MAH has included a wording on the 70mg dosage in the SPC.
Similarly, the MAH has withdrawn the request to increase the dose to 70 mg and has proposed deletion of the text regarding updosing to 70mg for empirical therapy.

The wording in section 4.2 of the SPC as proposed by the MAH is as follows*: "A single 70-mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter. Doses higher than 70 mg daily have not been adequately studied."* This new wording applies to the existing indications of Invasive Aspergillosis and Invasive Candidiasis as well as to the current variation II/17 for the empirical treatment indication.

2.3.5 Conclusion on clinical efficacy

The indication, as proposed by the MAH, " *Empirical therapy for presumed fungal infections in febrile, neutropaenic adult patients*, should be revised.
The requested indication is misleading since it implies that caspofungin will be useful regardless of the identity of any fungal pathogen, a fact which is not supported by the data provided. Therefore the CPMP decided to adopt an alternate wording, as follows: **"***Empirical therapy for presumed fungal infections (such as Candida and Aspergillus) in febrile, neutropaenic adult patients*". Together with this revised indication, a warning statement regarding uncommon yeasts and non-aspergillus moulds was added to section 4.4 of the SPC as follows: "*Limited data suggest that less common non-Candida yeasts and non-Aspergillus moulds are not covered by caspofungin. The efficacy of caspofungin against these fungal pathogens has not been established.*"

However, the current indication for invasive candidasis (IC) is inconsistent with the extension, since it includes only **non-neutropenic** patients. The number of neutropenic patients with IC who have received caspofungin has increased with the data from the empirical trial and now totals 26 patients (14 patients from the invasive candiasis trial (P014) trial and 12 patients from the current trial). In comparison with the 22 neutropenic patients who received AmBisome/amphotericin B in these trials, favourable response rates were slightly higher in the caspofungin group (15/26 (58%) vs 9/22 (41%)). Considering the great difficulties in recruiting a large number of neutropenic patients with documented IC, the CPMP is of the opinion that efficacy for caspofungin has been sufficiently demonstrated to delete the restriction of the IC indication to non-neutropenic patients.

2.4 Clinical safety

2.4.1 Supportive clinical data

- ***Background Summary***

Safety information on **876** individuals who received single or multiple doses of caspofungin has been submitted previously through the original and supplemental Marketing Applications in patients with invasive aspergillosis (N=72), oesophageal or oropharyngeal candidiasis (N=285), and invasive candidiasis (N=125). In addition, a total of 394 subjects received caspofungin in Phase I trials.

The following drug-related adverse experiences have been reported in at least 2% of patients with invasive aspergillosis or Candida infections: infused vein complications/ thrombophlebitis, fever, diarrhea, nausea, vomiting, headache, chills, increased ALT and AST, increased alkaline phosphatase, increased blood urea nitrogen (BUN), increased bilirubin, decreased serum albumin, decreased serum potassium, eosinophilia, decreased hemoglobin/hematocrit, decreased WBCs and decreased platelets. Possible allergic type reactions have been reported in clinical studies including isolated reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Cases of anaphylaxis during administration of caspofungin have also been reported.
The following serious adverse experiences have been reported in association with caspofungin in at least one patient in clinical studies: pulmonary infiltrates, venous thrombosis, hypercalcemia, rash, and thrombocytopenia.

- ***Safety data to support this variation***

The safety data to support the extension of indication of caspofungin to empirical therapy of presumed fungal infections in febrile, neutropenic patients, originate from a Phase III study, **Protocol 026**: A Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of MK-0991 Versus Amphotericin B Liposome for Injection as Empirical Therapy in Patients With Persistent Fever and Neutropenia.

1 <u>Patient exposure</u>

There were 1123 patients randomized in the study, of whom **1111** received at least one dose of active therapy (564 patients received caspofungin and 547 patients received AmBisome) and were included in the analysis of safety. The duration of study therapy for both treatment groups ranged from 1 to 90 days. The mean duration of study therapy in the caspofungin and AmBisome groups were 13.0 and 12.5 days, respectively.

Table 11 displays the descriptive statistics for duration of therapy (after Day 1) by treatment group and dose to define the exposure of patients to elevated doses of study therapy. Therapy on Day 1 was excluded from the analysis so that the 70-mg loading dose of caspofungin on Day 1 would not skew the results. The mean durations of the standard dose of study therapy were similar for the 2 treatment groups (10.4 and 10.3 days for caspofungin and AmBisome, respectively). Similar numbers of patients received the increased dose of study therapy after Day 1 (13.3% for caspofungin and 14.3% for AmBisome). In addition, the mean durations of study therapy at the increased dose were also similar for the 2 treatment groups (11.6 and 10.0 days for caspofungin and AmBisome, respectively).

<u>Table 11:</u> Descriptive Statistics for Duration of Therapy by Treatment Group and Dose

	Caspofungin 70/50 mg ($N^{\dagger}$=564)		AmBisome 3.0 mg/kg ($N^{\dagger}$=547)	
Days on Study Therapy[‡]	50 mg	70 mg	3 mg/kg	5 mg/kg
n[§]	558	81	526	89
Mean	10.4	11.6	10.3	10.0
Standard deviation	7.7	14.2	8.9	8.5
Median	9.0	7.0	8.0	7.0
Range	1 to 49	1 to 89	1 to 89	1 to 47

[†] N = Number of patients in the treatment group.
[‡] Excluding the first dose of study therapy.
[§] n = Number of patients who received at least 1 day of study therapy at the specified dose after Day 1.

2 <u>Adverse events</u>

As expected in seriously ill patients, clinical adverse experiences were common in this study: of the 1111 patients, 1039 (93.5%) reported at least 1 clinical adverse experience: 521 (92.4%) in the caspofungin group and 518 (94.7%) in the AmBisome group.

Drug-related clinical adverse experiences were significantly less common in the caspofungin than the AmBisome group ($p<0.001$). The proportion of patients in the caspofungin group who discontinued from therapy due to a serious drug-related clinical adverse experience was also significantly smaller than the corresponding proportion in the AmBisome group ($p=0.015$) (see Table 12).

Table 12: Clinical Adverse Experience Summary - Treatment and Follow-Up Phases

Number (%) of Patients:	Caspofungin 70/50 mg ($N^{\dagger}$=564) n[§]	(%)	AmBisome 3.0 mg/kg ($N^{\dagger}$=547) N[§]	(%)	Observed Difference[‡] (%)	95% CI	p-Value
With one or more adverse experiences	521	(92.4)	518	(94.7)	-2.3	(-5.2, 0.6)	0.116
With no adverse experience	43	(7.6)	29	(5.3)	--[%]	--[%]	--[%]
With drug-related adverse experiences[¶]	265	(47.0)	326	(59.6)	-12.6	(-18.4, -6.8)	<0.001
With serious adverse experiences	147	(26.1)	165	(30.2)	-4.1	(-9.4, 1.2)	0.128
With serious drug-related adverse experiences[¶]	9	(1.6)	16	(2.9)	-1.3	(-3.1, 0.4)	0.135
Who died	61	(10.8)	75	(13.7)	-2.9	(-6.8, 1.0)	0.141
Discontinued due to an adverse experience	78	(13.8)	83	(15.2)	-1.3	(-5.5, 2.8)	0.525
Discontinued due to a drug-related adverse experience[¶]	25	(4.4)	35	(6.4)	-2.0	(-4.6, 0.7)	0.147
Discontinued due to a serious adverse experience	39	(6.9)	49	(9.0)	-2.0	(-5.2, 1.1)	0.207
Discontinued due to a serious drug-related adverse experience[¶]	4	(0.7)	14	(2.6)	-1.9	(-3.3, -0.4)	0.015

[†] N = Number of patients in treatment group that received a dose of study therapy
[‡] Observed difference = Caspofungin 70/50 mg—AmBisome 3.0 mg/kg.
[§] n = Number of patients with a clinical adverse experience
[%] Observed difference is not displayed because patients with no adverse experience are the complement of patients with one or more adverse experiences.
[¶] Determined by the investigator to be possibly, probably, or definitely drug related.

Table 13: Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
Treatment and Follow-Up Phases

	Caspofungin 70/50 mg ($N^{\dagger}$=564)				AmBisome 3.0 mg/kg ($N^{\dagger}$=547)			
	Overall		Drug Related		Overall		Drug Related	
	n[‡]	(%)	n[‡]	(%)	n[‡]	(%)	n[‡]	(%)
Patients with one or more adverse experience	521	(92.4)	265	(47.0)	518	(94.7)	326	(59.6)
Patients with no adverse experience	43	(7.6)	299	(53.0)	29	(5.3)	221	(40.4)
Body as a Whole/Site Unspecified	**402**	**(71.3)**	**170**	**(30.1)**	**408**	**(74.6)**	**223**	**(40.8)**
Abdominal distention	26	(4.6)	2	(0.4)	22	(4.0)	5	(0.9)
Abdominal pain	61	(10.8)	8	(1.4)	69	(12.6)	13	(2.4)
Abdominal tenderness	13	(2.3)	1	(0.2)	13	(2.4)	2	(0.4)
Asthenia/fatigue	29	(5.1)	2	(0.4)	29	(5.3)	3	(0.5)
Bacteremia	42	(7.4)	1	(0.2)	35	(6.4)	0	(0.0)
Bacterial infection	6	(1.1)	0	(0.0)	11	(2.0)	0	(0.0)
Catheter site erythema	21	(3.7)	0	(0.0)	20	(3.7)	0	(0.0)
Catheter site pain	13	(2.3)	0	(0.0)	13	(2.4)	0	(0.0)
Chest pain	36	(6.4)	3	(0.5)	41	(7.5)	9	(1.6)
Chills	127	(22.5)	78	(13.8)	169	(30.9)	135	(24.7)
Diaphoresis	17	(3.0)	8	(1.4)	10	(1.8)	5	(0.9)
Dizziness	25	(4.4)	5	(0.9)	21	(3.8)	10	(1.8)
Edema	44	(7.8)	1	(0.2)	30	(5.5)	0	(0.0)
Facial edema	15	(2.7)	0	(0.0)	14	(2.6)	3	(0.5)
Fever	153	(27.1)	96	(17.0)	160	(29.3)	106	(19.4)
Fluid overload	29	(5.1)	4	(0.7)	32	(5.9)	3	(0.5)
Fluid retention	11	(2.0)	0	(0.0)	13	(2.4)	1	(0.2)
Flushing	13	(2.3)	10	(1.8)	30	(5.5)	23	(4.2)
Fungal infection	19	(3.4)	0	(0.0)	23	(4.2)	2	(0.4)
Fungemia	12	(2.1)	0	(0.0)	9	(1.6)	1	(0.2)
Lower extremity edema	47	(8.3)	5	(0.9)	55	(10.1)	4	(0.7)
Mass	12	(2.1)	1	(0.2)	5	(0.9)	0	(0.0)
Mucous membrane disorder	35	(6.2)	1	(0.2)	42	(7.7)	0	(0.0)
Pain	20	(3.5)	2	(0.4)	20	(3.7)	2	(0.4)
Perspiration	13	(2.3)	8	(1.4)	8	(1.5)	7	(1.3)

	Caspofungin 70/50 mg ($N^{\dagger}$=564)				AmBisome 3.0 mg/kg ($N^{\dagger}$=547)			
	Overall		Drug Related		Overall		Drug Related	
	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)
Sepsis	13	(2.3)	0	(0.0)	16	(2.9)	0	(0.0)
Septic shock	8	(1.4)	0	(0.0)	14	(2.6)	0	(0.0)
Upper extremity edema	10	(1.8)	0	(0.0)	12	(2.2)	2	(0.4)
Cardiovascular System	**217**	**(38.5)**	**32**	**(5.7)**	**198**	**(36.2)**	**40**	**(7.3)**
Congestive heart failure	15	(2.7)	2	(0.4)	19	(3.5)	0	(0.0)
Ecchymosis	20	(3.5)	0	(0.0)	10	(1.8)	0	(0.0)
Hematoma	18	(3.2)	0	(0.0)	8	(1.5)	0	(0.0)
Hypertension	38	(6.7)	6	(1.1)	38	(6.9)	11	(2.0)
Hypotension	36	(6.4)	5	(0.9)	52	(9.5)	7	(1.3)
Petechia	25	(4.4)	0	(0.0)	19	(3.5)	0	(0.0)
Phlebitis	11	(2.0)	1	(0.2)	8	(1.5)	1	(0.2)
Pulmonary edema	21	(3.7)	0	(0.0)	20	(3.7)	2	(0.4)
Systolic murmur	11	(2.0)	0	(0.0)	11	(2.0)	0	(0.0)
Tachycardia	42	(7.4)	8	(1.4)	52	(9.5)	13	(2.4)
Vascular access complication	20	(3.5)	0	(0.0)	8	(1.5)	1	(0.2)
Digestive System	**269**	**(47.7)**	**56**	**(9.9)**	**286**	**(52.3)**	**103**	**(18.8)**
Constipation	26	(4.6)	1	(0.2)	21	(3.8)	3	(0.5)
Diarrhea	115	(20.4)	15	(2.7)	87	(15.9)	13	(2.4)
Dry mouth	11	(2.0)	2	(0.4)	12	(2.2)	3	(0.5)
Dysphagia	8	(1.4)	1	(0.2)	11	(2.0)	0	(0.0)
Epigastric discomfort	12	(2.1)	2	(0.4)	14	(2.6)	3	(0.5)
Gastrointestinal bleeding	5	(0.9)	0	(0.0)	15	(2.7)	0	(0.0)
Heartburn	11	(2.0)	1	(0.2)	9	(1.6)	4	(0.7)
Hemorrhoids	14	(2.5)	0	(0.0)	11	(2.0)	0	(0.0)
Nausea	64	(11.3)	20	(3.5)	109	(19.9)	62	(11.3)
Oral candidiasis	9	(1.6)	0	(0.0)	11	(2.0)	0	(0.0)
Vomiting	52	(9.2)	20	(3.5)	95	(17.4)	47	(8.6)
Eyes, Ears, Nose, and Throat	**142**	**(25.2)**	**15**	**(2.7)**	**152**	**(27.8)**	**13**	**(2.4)**
Epistaxis	28	(5.0)	1	(0.2)	40	(7.3)	0	(0.0)
Nasal congestion	4	(0.7)	0	(0.0)	17	(3.1)	2	(0.4)
Nasal secretion	11	(2.0)	0	(0.0)	11	(2.0)	0	(0.0)
Pharyngitis	22	(3.9)	3	(0.5)	8	(1.5)	0	(0.0)
Sinusitis	17	(3.0)	0	(0.0)	8	(1.5)	0	(0.0)
Hemic and Lymphatic System	**79**	**(14.0)**	**4**	**(0.7)**	**65**	**(11.9)**	**0**	**(0.0)**
Acute myelogenous leukemia	21	(3.7)	0	(0.0)	16	(2.9)	0	(0.0)
Coagulation disorder	13	(2.3)	2	(0.4)	7	(1.3)	0	(0.0)
Lymphadenopathy	12	(2.1)	0	(0.0)	2	(0.4)	0	(0.0)
Hepatobiliary System	**66**	**(11.7)**	**16**	**(2.8)**	**57**	**(10.4)**	**16**	**(2.9)**
Hepatic disorder	19	(3.4)	6	(1.1)	12	(2.2)	4	(0.7)
Jaundice	7	(1.2)	2	(0.4)	16	(2.9)	4	(0.7)
Immune System	**38**	**(6.7)**	**1**	**(0.2)**	**47**	**(8.6)**	**9**	**(1.6)**
Graft versus host disease	7	(1.2)	0	(0.0)	12	(2.2)	0	(0.0)
Transfusion reaction	21	(3.7)	0	(0.0)	20	(3.7)	0	(0.0)
Metabolism and Nutrition	**105**	**(18.6)**	**31**	**(5.5)**	**112**	**(20.5)**	**33**	**(6.0)**
Anorexia	14	(2.5)	0	(0.0)	12	(2.2)	2	(0.4)
Hyperglycemia	7	(1.2)	1	(0.2)	13	(2.4)	0	(0.0)
Hypokalemia	37	(6.6)	21	(3.7)	45	(8.2)	23	(4.2)
Weight loss	17	(3.0)	0	(0.0)	13	(2.4)	0	(0.0)
Musculoskeletal System	**105**	**(18.6)**	**6**	**(1.1)**	**112**	**(20.5)**	**26**	**(4.8)**
Back pain	24	(4.3)	4	(0.7)	40	(7.3)	15	(2.7)
Leg pain	20	(3.5)	2	(0.4)	12	(2.2)	1	(0.2)
Muscular weakness	16	(2.8)	0	(0.0)	12	(2.2)	2	(0.4)
Nervous System	**127**	**(22.5)**	**33**	**(5.9)**	**151**	**(27.6)**	**47**	**(8.6)**
Headache	59	(10.5)	24	(4.3)	66	(12.1)	31	(5.7)
Insomnia	22	(3.9)	0	(0.0)	28	(5.1)	0	(0.0)
Paresthesia	5	(0.9)	3	(0.5)	11	(2.0)	6	(1.1)
Tremor	12	(2.1)	4	(0.7)	15	(2.7)	6	(1.1)
Psychiatric Disorder	**91**	**(16.1)**	**6**	**(1.1)**	**88**	**(16.1)**	**12**	**(2.2)**
Anxiety	23	(4.1)	3	(0.5)	27	(4.9)	3	(0.5)
Confusion	29	(5.1)	1	(0.2)	30	(5.5)	6	(1.1)
Depression	21	(3.7)	0	(0.0)	18	(3.3)	0	(0.0)

	Caspofungin 70/50 mg ($N^{\dagger}$=564)				AmBisome 3.0 mg/kg ($N^{\dagger}$=547)			
	Overall		Drug Related		Overall		Drug Related	
	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)	$n^{\ddagger}$	(%)
Respiratory System	**269**	**(47.7)**	**24**	**(4.3)**	**261**	**(47.7)**	**51**	**(9.3)**
Breath sound abnormality	23	(4.1)	2	(0.4)	24	(4.4)	0	(0.0)
Cough	66	(11.7)	3	(0.5)	61	(11.2)	8	(1.5)
Dyspnea	56	(9.9)	11	(2.0)	55	(10.1)	23	(4.2)
Hemoptysis	9	(1.6)	0	(0.0)	19	(3.5)	1	(0.2)
Hypoxia	17	(3.0)	2	(0.4)	22	(4.0)	4	(0.7)
Pleural effusion	27	(4.8)	1	(0.2)	18	(3.3)	1	(0.2)
Pneumonia	81	(14.4)	1	(0.2)	65	(11.9)	1	(0.2)
Pulmonary infiltration	21	(3.7)	0	(0.0)	17	(3.1)	0	(0.0)
Rales	40	(7.1)	2	(0.4)	44	(8.0)	1	(0.2)
Respiratory condition	7	(1.2)	0	(0.0)	11	(2.0)	0	(0.0)
Respiratory failure	19	(3.4)	0	(0.0)	16	(2.9)	1	(0.2)
Respiratory insufficiency	16	(2.8)	0	(0.0)	13	(2.4)	0	(0.0)
Tachypnea	20	(3.5)	2	(0.4)	25	(4.6)	11	(2.0)
Wheezing	10	(1.8)	1	(0.2)	12	(2.2)	3	(0.5)
Skin and Skin Appendages	**234**	**(41.5)**	**54**	**(9.6)**	**212**	**(38.8)**	**48**	**(8.8)**
Alopecia	17	(3.0)	0	(0.0)	11	(2.0)	0	(0.0)
Catheter site infection	23	(4.1)	0	(0.0)	13	(2.4)	0	(0.0)
Exanthema	17	(3.0)	5	(0.9)	14	(2.6)	6	(1.1)
Herpes simplex	21	(3.7)	0	(0.0)	21	(3.8)	0	(0.0)
Pruritus	25	(4.4)	10	(1.8)	23	(4.2)	7	(1.3)
Rash	119	(21.1)	35	(6.2)	101	(18.5)	29	(5.3)
Skin erythema	36	(6.4)	5	(0.9)	28	(5.1)	6	(1.1)
Skin lesion	12	(2.1)	2	(0.4)	14	(2.6)	0	(0.0)
Urticaria	11	(2.0)	4	(0.7)	9	(1.6)	1	(0.2)
Urogenital System	**99**	**(17.6)**	**10**	**(1.8)**	**106**	**(19.4)**	**18**	**(3.3)**
Acute renal failure	4	(0.7)	3	(0.5)	11	(2.0)	6	(1.1)
Dysuria	11	(2.0)	1	(0.2)	11	(2.0)	0	(0.0)
Hematuria	14	(2.5)	0	(0.0)	17	(3.1)	1	(0.2)
Renal insufficiency	22	(3.9)	6	(1.1)	26	(4.8)	10	(1.8)
Urinary incontinence	9	(1.6)	1	(0.2)	12	(2.2)	0	(0.0)

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
†N = the number of patients in the treatment group.
‡n = the number of patients with the specific adverse experience.

The number (%) of patients with specific clinical adverse experiences, both overall and drug related and occurring at an incidence of at least 2% overall, is displayed by body system in Table 13 above.

The most frequently reported drug-related adverse experiences in the caspofungin group were consistent with those reported overall and included fever (17.0%), chills (13.8%), rash (6.2%), and headache (4.3%).
The most frequently reported drug-related clinical adverse experiences in the AmBisome group were chills (24.7%), fever (19.4%), nausea (11.3%), vomiting (8.6%), and headache (5.7%). The drug-related adverse experiences of chills, nausea, and vomiting were less common in the caspofungin than the AmBisome group ($p<0.05$).

3 Serious adverse events and deaths

Overall, 312 (28%) of the 1111 patients had at least one serious clinical adverse experience: 147 (26.1%) in the caspofungin group and 165 (30.2%) in the AmBisome group. The most common serious adverse experiences across treatment groups were pneumonia (4.2%), AML (3.0%), and respiratory failure (2.8%). There were 25 patients with serious clinical adverse experiences determined by the investigator to be possibly, probably, or definitely related to study therapy: 9 (1.6%) in the caspofungin group and 16 (2.9%) in the AmBisome group.
In the caspofungin group, 3 patients had serious drug-related adverse experiences of renal failure or insufficiency. Two patients with serious drug-related adverse experiences of rash recovered. The remaining cases were (1) an infusion-related hypersensitivity reaction (consisting of chills, rigors, chest tightness, and tachypnea lasting 15 minutes, followed 2 hours later by nausea and high fever, resolving over 3 hours after the infusion), (2) a case of progressive hyperbilirubinemia in the setting of metastatic disease of the lungs and liver, (3) congestive heart failure, hypokalemia, and extension of a

prior myocardial infarction in the setting of AML and underlying cardiovascular disease, and (4) bronchiolitis obliterans with organizing pneumonia noted on lung biopsy performed 3 days after completion of study therapy.
In the AmBisome group, 5 patients had serious drug-related adverse experiences in the respiratory system consisting of 3 adverse experiences of respiratory distress, 2 dyspnea, and 1 hypoxia, 3 patients had serious drug-related adverse experiences in the immune system (hypersensitivity reaction [3], anaphylaxis [1], and anaphylactic reaction [1]) and 3 patients had serious drug-related adverse experiences in the urogenital system (acute renal failure [2], and renal insufficiency [1]). The remaining cases were a hypokalemia, a ventricular fibrillation with cardiac arrest, a fungal infection and a Grand mal seizure.
There were 136 patients (12.2% of the 1111 patients receiving study drug) who died as a result of a fatal adverse experience that occurred during the course of the study: 61 (10.8%) in the caspofungin group and 75 (13.7%) in the AmBisome group. Only 3 patients had serious adverse experiences leading to death that were considered either possibly, probably or definitely drug-related by the investigator. One patient was treated with caspofungin but discontinued and subsequently expired due to renal insufficiency that was felt by the investigator to be possibly related to study drug therapy. The other 2 patients who died due to a drug-related serious adverse experience were in the AmBisome group: one experienced a cardiac arrest reported by the investigator as possibly related to study therapy, while the other died due to respiratory distress that was probably related to study therapy. The remaining deaths were due to complications of underlying diseases or infections, and the distribution of the different aetiologies was generally similar in the 2 treatment groups.

4 <u>Discontinuations due to AES</u>

There were 161 discontinuations from study therapy as a result of a clinical adverse experience, including 78 (13.8%) in the caspofungin group and 83 (15.2%) in the AmBisome group. The most frequently reported specific clinical adverse experiences leading to discontinuation of study therapy in the caspofungin group were rash (1.4%), fever (1.1%), and pneumonia (1.1%), and in the AmBisome group were AML (1.5%), fever (1.3%), pneumonia (1.1%), and fungal infection (1.1%).

Of the 161 discontinuations, 60 occurred because of a drug-related clinical adverse experience, including 25 (4.4%) in the caspofungin group and 35 (6.4%) in the AmBisome group.
In the caspofungin group ten patients discontinued due to drug-related adverse experiences of the skin and skin appendages (1 case was a serious rash; all patients recovered), and five patients were discontinued due to drug-related adverse experiences in the hepatobiliary system or hyperbilirubinemia (one of the adverse experiences was considered serious).
There were 35 discontinuations in the AmBisome group due to drug-related clinical adverse experiences: 4 because of hypersensitivity reactions, 3 anaphylaxis or anaphylactic-type reactions and 4 fevers.

Of the patients with a serious drug-related clinical adverse experience as described above, 4 patients in the caspofungin group discontinued treatment (the patient with the hypersensitivity reaction, the patient with the hyperbilirubinemia, one patient with renal insufficiency and one patient with rash). In the AmBisome group all except for 2 patients with a serious drug-related clinical adverse experience (one case of renal insufficiency and the patient with hypokalemia) discontinued treatment.

5 <u>Laboratory findings</u>

Of the 1111 patients, 627 (56.4%) reported at least 1 laboratory adverse experience: 302 (53.5%) in the caspofungin group and 325 (59.4%) in the AmBisome group. Laboratory adverse experiences were significantly less common in the caspofungin than the AmBisome group ($p=0.049$).
Other significant differences in favour of caspofungin included the following safety parameters: the proportion of patients with drug-related laboratory adverse experiences ($p<0.001$), the proportion of patients who discontinued from therapy due to a laboratory adverse experience ($p=0.026$), and the proportion of patients who discontinued from therapy due to a drug-related laboratory adverse experience ($p=0.010$) (see Table 14).

The number (%) of patients with specific laboratory adverse experiences, both overall and drug related, is displayed by test category in Table 15.

The most common drug-related laboratory adverse experiences in the caspofungin group were increased ALT (8.7%), hypokalemia (7.3%), increased alkaline phosphatase (7.0%), increased AST (7.0%), and total blood bilirubin increased (3.0%).
The most frequently reported drug-related laboratory adverse experiences in the AmBisome group were increased alkaline phosphatase (12.0%), hypokalemia (11.8%), increased ALT (8.9%), increased AST (7.6%), and increased serum creatinine (5.5%).
The drug-related adverse experiences of increased alkaline phosphatase, hypokalemia, and increased serum creatinine were less common in patients who received caspofungin than in patients who received AmBisome ($p<0.05$).

Table 14: Laboratory Adverse Experience Summary - Treatment and Follow-Up Phases

Number (%) of Patients:	Caspofungin 70/50 mg (N[†]=564) n[‡]	(%)	AmBisome 3.0 mg/kg (N[†]=547) n[‡]	(%)	Observed Difference[§] (%)	95% CI	p-Value
with at least one laboratory test postbaseline	564	(100.0)	547	(100.0)			
with one or more adverse experiences	302	(53.5)	325	(59.4)	-5.9	(-11.7, 0.0)	0.049
with no adverse experience	262	(46.5)	222	(40.6)	--[%]	--[%]	--[%]
with drug-related adverse experiences[¶]	127	(22.5)	175	(32.0)	-9.5	(-14.7, -4.3)	<0.001
with serious adverse experiences	2	(0.4)	5	(0.9)	-0.6	(-1.5, 0.4)	0.239
with serious drug-related adverse experiences[¶]	0	(0.0)	1	(0.2)	-0.2	(-0.5, 0.2)	0.310
who died	0	(0.0)	0	(0.0)	0.0	--[#]	--[#]
Discontinued due to an adverse experience	6	(1.1)	16	(2.9)	-1.9	(-3.5, -0.2)	0.026
Discontinued due to a drug-related adverse experience[¶]	3	(0.5)	13	(2.4)	-1.8	(-3.3, -0.4)	0.010
discontinued due to a serious adverse experience	1	(0.2)	3	(0.5)	-0.4	(-1.1, 0.3)	0.302
discontinued due to a serious drug-related adverse experience[¶]	0	(0.0)	1	(0.2)	-0.2	(-0.5, 0.2)	0.310

[†] N = Number of patients in treatment group.
[‡] n = Number of patients meeting criteria.
[§] Observed Difference = Caspofungin 70/50 mg—AmBisome 3.0 mg/kg.
[%] Observed difference is not displayed because patients with no adverse experience are the complement of patients with one or more adverse experiences.
[¶] Determined by the investigator to be possibly, probably, or definitely drug related.
[#] Confidence Interval (CI) cannot be calculated because no patients in the study had this event.

- Serious Laboratory Adverse Experiences
Two patients (0.4%) in the caspofungin group and 5 patients (0.9%) in the AmBisome group experienced a serious laboratory adverse experience. Neither of the 2 serious laboratory adverse experiences reported in the caspofungin group were determined to be drug related, but 1 of the 5 serious adverse experiences in the AmBisome group (increased total serum bilirubin) was determined to be drug related.

- Discontinuations Due to Laboratory Adverse Experiences
There were 22 patients overall who discontinued from study therapy due to a laboratory adverse experience: 6 (1.1%) in the caspofungin group and 16 (2.9%) in the AmBisome group. Of the 6 discontinuations in the caspofungin group, 3 were due to a drug-related adverse experience of hepatic dysfunction (increased AST, ALT and alkaline phosphatase [1], increased ALT only [1], and increased total and direct bilirubin only [1]). In the AmBisome group, there were 13 (2.4%) drug-related discontinuations: 9 due to abnormal liver function tests (increased bilirubin, increased alkaline phosphatase, increased ALT and AST), and 4 due to increased creatinine.

Table 15: Number (%) of Patients With Specific Laboratory Adverse Experiences. At Least 50 Patients With Laboratory Test and Overall Incidence ≥2.0% in One or More Treatment Groups by Laboratory Test Category—Treatment and Follow-Up Phases

	Caspofungin 70/50 mg ($N^{\dagger}$=564)				AmBisome 3.0 mg/kg ($N^{\dagger}$=547)			
	Overall		Drug-Related		Overall		Drug-Related	
	n/m[‡]	(%)	n/m[‡]	(%)	n/m[‡]	(%)	n/m[‡]	(%)
Patients with one or more adverse experience	302/564	(53.5)	127/564	(22.5)	325/547	(59.4)	175/547	(32.0)
Patients with no adverse experience	262/564	(46.5)	437/564	(77.5)	222/547	(40.6)	372/547	(68.0)
Blood Chemistry Test	**275/564**	**(48.8)**	**119/564**	**(21.1)**	**312/545**	**(57.2)**	**171/545**	**(31.4)**
Alanine aminotransferase increased	101/561	(18.0)	49/561	(8.7)	110/542	(20.3)	48/542	(8.9)
Alkaline phosphatase increased	82/559	(14.7)	39/559	(7.0)	125/540	(23.1)	65/540	(12.0)
Aspartate aminotransferase increased	80/561	(14.3)	39/561	(7.0)	95/541	(17.6)	41/541	(7.6)
Bicarbonate decreased	8/335	(2.4)	2/335	(0.6)	10/335	(3.0)	1/335	(0.3)
Bicarbonate increased	5/335	(1.5)	1/335	(0.3)	9/335	(2.7)	2/335	(0.6)
Blood carbon dioxide decreased	6/106	(5.7)	2/106	(1.9)	3/97	(3.1)	0/97	(0.0)
Blood carbon dioxide increased	4/106	(3.8)	0/106	(0.0)	1/97	(1.0)	0/97	(0.0)
Blood urea decreased	6/293	(2.0)	0/293	(0.0)	1/275	(0.4)	0/275	(0.0)
Blood urea increased	6/293	(2.0)	0/293	(0.0)	17/275	(6.2)	1/275	(0.4)
Blood urea nitrogen increased	16/257	(6.2)	5/257	(1.9)	27/255	(10.6)	8/255	(3.1)
Direct blood bilirubin increased	28/382	(7.3)	10/382	(2.6)	50/387	(12.9)	20/387	(5.2)
Hyperchloremia	10/527	(1.9)	1/527	(0.2)	14/506	(2.8)	1/506	(0.2)
Hypernatremia	10/563	(1.8)	3/563	(0.5)	15/544	(2.8)	1/544	(0.2)
Hyperphosphatemia	15/529	(2.8)	3/529	(0.6)	21/515	(4.1)	4/515	(0.8)
Hypocalcemia	26/557	(4.7)	7/557	(1.3)	35/535	(6.5)	6/535	(1.1)
Hypokalemia	85/563	(15.1)	41/563	(7.3)	123/544	(22.6)	64/544	(11.8)
Hypomagnesemia	40/515	(7.8)	12/515	(2.3)	49/497	(9.9)	13/497	(2.6)
Hyponatremia	12/563	(2.1)	1/563	(0.2)	18/544	(3.3)	1/544	(0.2)
Hypophosphatemia	32/529	(6.0)	7/529	(1.3)	36/515	(7.0)	10/515	(1.9)
Hypouricemia	13/530	(2.5)	2/530	(0.4)	11/510	(2.2)	0/510	(0.0)
Nonfasting blood glucose increased	36/557	(6.5)	3/557	(0.5)	46/541	(8.5)	3/541	(0.6)
Serum albumin decreased	41/550	(7.5)	0/550	(0.0)	41/533	(7.7)	0/533	(0.0)
Serum creatinine increased	19/563	(3.4)	7/563	(1.2)	62/545	(11.4)	30/545	(5.5)
Total blood bilirubin increased	58/563	(10.3)	17/563	(3.0)	74/543	(13.6)	28/543	(5.2)
Total serum protein decreased	26/556	(4.7)	0/556	(0.0)	29/538	(5.4)	1/538	(0.2)
Hematology Laboratory Test	**34/563**	**(6.0)**	**2/563**	**(0.4)**	**28/547**	**(5.1)**	**4/547**	**(0.7)**
Hemoglobin decreased	10/563	(1.8)	0/563	(0.0)	11/545	(2.0)	2/545	(0.4)
Platelets decreased	15/563	(2.7)	1/563	(0.2)	9/545	(1.7)	1/545	(0.2)
Hemostatic Function Test	**49/549**	**(8.9)**	**5/549**	**(0.9)**	**46/530**	**(8.7)**	**6/530**	**(1.1)**
International normalized ratio increased	18/546	(3.3)	2/546	(0.4)	19/528	(3.6)	1/528	(0.2)
Partial thromboplastin time increased	20/537	(3.7)	3/537	(0.6)	19/515	(3.7)	1/515	(0.2)
Prothrombin time increased	26/476	(5.5)	3/476	(0.6)	26/451	(5.8)	5/451	(1.1)
Urinalysis Test	**55/515**	**(10.7)**	**8/515**	**(1.6)**	**53/492**	**(10.8)**	**6/492**	**(1.2)**
Crystalluria	10/367	(2.7)	1/367	(0.3)	1/357	(0.3)	0/357	(0.0)
Erythrocyturia	17/510	(3.3)	1/510	(0.2)	18/485	(3.7)	0/485	(0.0)
Glycosuria	8/497	(1.6)	1/497	(0.2)	11/472	(2.3)	1/472	(0.2)
Hematuria	11/510	(2.2)	1/510	(0.2)	7/485	(1.4)	1/485	(0.2)
Leukocyturia	18/497	(3.6)	0/497	(0.0)	16/477	(3.4)	0/477	(0.0)
Proteinuria	22/498	(4.4)	2/498	(0.4)	22/474	(4.6)	2/474	(0.4)
Urinary epithelial cells increased	9/357	(2.5)	1/357	(0.3)	10/355	(2.8)	2/355	(0.6)

[†]N = the number of patients in the treatment group

[‡]n/m = number of patients with laboratory adverse experiences/number of patients for whom the laboratory test was recorded postbaseline.

Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

- Safety Analyses

Four safety hypotheses were predefined for this study. The primary safety analysis for this study was a comparison of the incidence of nephrotoxicity between the 2 treatment groups. The results of the 4 safety analyses are summarized in Table 16.

Table 16: Statistical Tests of Safety Endpoints

	Caspofungin 70/50 mg ($N^{\dagger}$=564) % (95% CI)	AmBisome 3.0 mg/kg ($N^{\dagger}$=547) % (95% CI)	Observed Difference[‡] (%) (95% CI)	p-Value
Nephrotoxicity	2.6[§] (1.2, 3.9)	11.5[§] (8.8, 14.2)	-8.9 (-12,-5.9)	<0.001
Infusion-related event	35.1	51.6	16.4 (-22.2, -10.7)	<0.001
Drug-related adverse experience	54.4	69.3	-14.9 (-20.5, -9.2)	<0.001
Discontinuation due to drug related adverse experience	5.0	8.0	-3.1 (-6.0, -0.2)	0.037

† N = Number of patients in treatment group.
‡ Observed difference = Caspofungin 70/50 mg—AmBisome 3.0 mg/kg
§ For analysis of nephrotoxicity, percent was calculated as m/n (Number of patients with nephrotoxicity/ Number of patients with serum creatinine data). For caspofungin, n= 547 and for AmBisome n = 522.

- Nephrotoxicity

Nephrotoxicity was predefined as a doubling of serum creatinine or an increase in creatinine by ≥1 mg/dL, if the creatinine was elevated at study entry. The analysis included all patients who met these criteria during study therapy, whether or not the elevations were considered to be adverse experiences. As predefined in the protocol, the analysis of nephrotoxicity was performed using the data from only those patients with a creatinine clearance >30 ml/min at baseline. The observed proportions of patients with nephrotoxicity were **2.6%** (14/547) for caspofungin and **11.5%** (60/522) for AmBisome. The difference in nephrotoxicity rates between the 2 treatment groups (caspofungin minus AmBisome) was -8.9%, with a 95% CI of (-12.0, -5.9). The CI lies completely below 0, indicating that caspofungin is superior to AmBisome with respect to the risk of nephrotoxicity.

- Infusion-Related Adverse Experiences

Infusion-related adverse experiences were recorded daily during intravenous study therapy. The proportions of patients who developed at least 1 infusion-related event were **35.1%** (198/564) and **51.6%** (282/547) in the caspofungin and AmBisome groups, respectively. The difference in proportions between the 2 treatment groups (caspofungin minus AmBisome) was -16.4%, with a 95% CI of (-22.2, -10.7) and an associated p-value <0.001, indicating that caspofungin is superior to AmBisome with respect to the occurrence of infusion-related events (mainly chills and fever). There were numerically fewer severe infusion-related events in the caspofungin group than in the AmBisome group (5.1% in the caspofungin group versus 8.6% in the AmBisome group).

- Drug-Related Clinical and Laboratory Adverse Experiences

Overall, 686 (61.7%) of the 1111 patients reported one or more clinical or laboratory adverse experiences determined by the investigator to be drug related: 307 (**54.4%**) in the caspofungin group and 379 (**69.3%**) in the AmBisome group. The difference between the 2 treatment groups (caspofungin minus AmBisome) was -14.9, with a 95% CI of (-20.5, -9.2) and an associated p-value <0.001, indicating that caspofungin is superior to AmBisome with respect to the occurrence of drug-related adverse experiences.

- Discontinuations Due to Drug-Related Clinical or Laboratory Adverse Experiences
Seventy-two (6.5%) of the 1111 patients discontinued therapy due to a clinical or laboratory adverse experience determined by the investigator to be drug related: 28 (**5.0%**) in the caspofungin group and 44 (**8.0%**) in the AmBisome group. The difference between the 2 treatment groups (caspofungin minus AmBisome) was -3.1, with a 95% CI of (-6.0, -0.2) and an associated p-value of 0.037, indicating that caspofungin is superior to AmBisome with respect to the occurrence of drug-related adverse experiences that result in discontinuation from therapy.

6 <u>Safety in special populations</u>
Adverse experience summaries were reviewed for patient subgroups based on age, gender, and race.
Of the 1111 patients enrolled in the study that received active therapy, 14.9% (165 patients) were >65 years of age. Not unexpectedly, patients in this age category in both treatment groups had higher incidences of serious clinical adverse experiences and death than those patients aged 65 years and younger (37.1% versus 24% in the caspofungin group and 40.8% versus 28.5% in the AmBisome group, respectively for serious clinical adverse experiences; 20.2% versus 9.1% in the caspofungin group and 23.7% versus 12.1% in the AmBisome group, respectively for deaths). However, given the relatively small number of elderly patients any actual differences due to patient age are difficult to assess.
Of the 1111 patients enrolled in the study that received active therapy, 622 patients were male and 489 were female. Overall, the clinical and laboratory adverse experience profile showed similar incidence of clinical adverse experiences in males and females in both treatment groups.
Overall, nearly 90% of patients (994/1111) were white. As a result, the clinical and laboratory adverse experience profile of patients who were white mirrors that of the overall study populations, and any apparent differences in the occurrence of adverse experiences in other races should be considered in context, given the small size of this population.

2.4.2 Post-marketing data

From 14-Dec-2000 through 15-Mar-2003, a total of 300 spontaneous and compassionate-use, named-patient, or temporary-use-authorization study reports were identified. Of these reports, 207 were spontaneous adverse experience reports received from healthcare providers and 120 (58%) were serious. The remaining 93 were compassionate-use, named-patient, or temporary-use-authorization study reports that were not part of Merck clinical trials of which 73 (78%) met the criteria for serious.
In the 120 spontaneous reports that had at least one serious adverse event, the most frequently reported serious adverse events were death NOS (10 reports), hypokalemia (9), increased alkaline phosphatase (8), increased AST (8), increased ALT (7), and multiorgan failure (7). In the 73 serious compassionate-use, named-patient, temporary-use-authorization study reports, the most frequently reported serious adverse experiences were death NOS (11), multiorgan failure (11), aspergillosis (6), septic shock (6) and increased alkaline phosphatase (4).

From 14-Dec-2000 through 15-Mar-2003, 95 reports of fatal outcomes were identified concerning patients who received caspofungin in the postmarketing environment, including 38 spontaneous reports and 57 compassionate-use, named-patient, or temporary-use-authorization study reports. In 22 reports, the causes of death were unknown and/or there was insufficient information, precluding a proper evaluation.
In the remaining 73 reports, the patients' deaths were most likely related to their serious underlying medical illnesses (e.g., aspergillosis, candidiasis, leukaemia, sepsis, and pneumonia).

Six spontaneous reports were identified which may be indicative of possible drug interactions with caspofungin. The reported interacting therapies included cyclosporine (2), gemtuzumab (1), ciprofloxacin and clindamycin (1), tacrolimus (1), and warfarin (1).
In 2 reports, limited information was received involving possible drug interactions with cyclosporine, precluding further evaluation, since no information was provided in either report regarding blood cyclosporine levels or dosing regimens of other concomitant therapies. In 2 clinical studies, cyclosporine (one 4-mg/kg dose or two 3-mg/kg doses) increased the area under the curve (AUC) of

caspofungin by ~35%, probably due to reduced uptake of caspofungin by the liver, while blood levels of cyclosporine remained unchanged.
One report concerned possible drug toxicity with caspofungin and gemtuzumab ozogamicin in a patient with preexisting leukemia, diabetes mellitus, and elevated AST and ALT. The patient received 1 day of therapy with gemtuzumab ozogamicin. Over the next 8 days, his condition deteriorated; he developed hepatic failure and hepatorenal syndrome. Therapy with caspofungin was started on the eighth day, and on the following day, he experienced a "significant" increase in liver enzymes. He died 2 days later from hepatic and respiratory failure. Hepatotoxicity, including severe hepatic veno-occlusive disease, has been reported in association with the use of gemtuzumab ozogamicin as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or hematopoietic stem-cell transplant.
The 3 remaining reports of potential drug interactions consisted of 1) a patient who developed bronchospasm, shortness of breath, chills, and back pain on the third day of infusion with caspofungin, which was attributed to a possible drug interaction between caspofungin, ciprofloxacin, and clindamycin, 2) a patient on therapy with tacrolimus 2 mg twice a day. When concomitant therapy with itraconazole and amphotericin B were switched to caspofungin, the patient developed decreased blood tacrolimus levels, and 3) a patient with an increased prothrombin time attributed to a possible drug interaction with warfarin and caspofungin. Concomitant therapy included fluconazole, which is known to increase the effect of warfarin. No information was provided in this report regarding the temporal relationship between the initiating of any medications and the patient's increased prothrombin time.

Hepatic Adverse Events

A total of 67 reports that may represent hepatic injury were identified in patients treated with caspofungin, of which 41 were spontaneous and 26 were from compassionate-use, named-patient, or temporary-use-authorization programs.
In 49 of the 67 reports, the patient had serious underlying medical conditions, pre-existing hepatic disease/elevations in liver function tests, and/or concomitant therapies that were associated with hepatotoxicity. In another 15 reports, there was insufficient information for a proper evaluation. Elevated liver enzymes (AST, ALT, and alkaline phosphatase), elevated direct and total bilirubin and rare cases of hepatic dysfunction are included in the "Side Effects" section of the current CCDS for caspofungin. All 67 reports were either consistent with the current CCDS for caspofungin and/or were reported as not related to therapy with caspofungin.

Renal Adverse Events

A total of 22 reports representing possible renal dysfunction were identified in patients treated with caspofungin (14 reports were from the marketed environment, and 8 occurred in patients who received caspofungin from compassionate-use, named-patient, or temporary-use-authorization programs).

In 19 of the 22 reports, the patients received concomitant medications known to be associated with nephrotoxicity, including tobramycin, tacrolimus, ciprofloxacin, cefepime, vancomycin, or amphotericin. The 3 other reports include a case of nonserious polyuria occurring on the same day as the initiation of therapy with caspofungin, nephrotic syndrome in a patient with borderline renal function (inadequate information on concomitant medications and medical history), and acute tubular necrosis in a patient with a complicated postoperative course status post bowel resection, where the reporter did not believe to be associated with caspofungin.

Additionally, in 5 reports, pre-existing elevated serum creatinine (3), renal failure and renal tubular acidosis were described in the patient's concurrent condition/medical history. Increased serum creatinine is included in the "Side Effects" section of the current CCDS for caspofungin. At this time there is inadequate evidence of a causal relationship between the other described renal dysfunctions and treatment with caspofungin, based on available data.

Allergic Adverse Experiences

Thirty-nine reports with allergic adverse experience terms and reported in temporal association with administration of caspofungin were identified (32 were spontaneous reports and 7 occurred in a patient

who received caspofungin from compassionate-use, named-patient, or temporary-use-authorization programs). Eighteen of the 39 reports were considered serious. Nine of these patients had a concurrent condition/medical history of previous drug allergy/reaction; one had a history of asthma. Anaphylaxis, and possible histamine-mediated symptoms, including isolated reports of rash, facial swelling, pruritus, sensation of warmth, or bronchospasm are labeled in the CCDS for caspofungin. The above reports were consistent with the current CCDS and safety profile for caspofungin, and pose no additional concerns regarding potential allergic adverse experiences temporally associated with administration of caspofungin.

Safety reports from ongoing studies

At the time of this application, there were 3 ongoing open-label noncomparative clinical studies in the caspofungin development program.

Since the submission of the Worldwide Clinical Summary (submitted 06-Mar-2002) for Invasive Candidiasis, there were 24 patients who received caspofungin in the Salvage Aspergillosis study *(Protocol 019)* during the period from 06-Nov-2001 to 15-Mar-2003. During this time period, 35 serious adverse experiences were reported in 19 patients, none of which were drug related. Nineteen (in 14 patients) of the 35 serious adverse experiences reported were fatal. The adverse experiences reported were consistent with the serious underlying diseases, concurrent conditions, and concomitant medications in these seriously ill patients.
Thirty-one patients, aged 2 to 17 years, were treated with caspofungin in the Pediatric Pharmacokinetic study *(Protocol 033)* during the period from 06-Nov-2001 to 15-Mar-2003. Sixteen serious adverse experiences were reported in 10 patients, none of which were drug related. One patient experienced the fatal serious adverse experience of fungal pneumonia.

One patient was enrolled in the Combination Therapy study *(Protocol 037*) from 06-Nov-2001 to 15-Mar-2003. There were no serious adverse experiences reported for this patient prior to the in-house data cutoff date of 15-Mar-2003.

2.4.3 Conclusion of clinical safety

A total of 1111 patients received at least one dose of therapy (564 received caspofungin and 547 received AmBisome) in the submitted Empirical Therapy Study. By comparison, 876 individuals had received single or multiple doses of caspofungin in prior applications for caspofungin. As a result, this study provides the largest increase to the safety database of caspofungin to date.

Overall, drug-related clinical and laboratory adverse experiences were significantly less frequent in the caspofungin group than in the AmBisome group.
The most common drug-related clinical adverse experiences in the caspofungin group were: fever (17.0%), chills (13.8%), rash (6.2%), and headache (4.3%). Chills, nausea, and vomiting were significantly less common in the caspofungin than the AmBisome group.
The most frequently reported drug-related laboratory adverse experiences in the caspofungin group included increased ALT (8.7%), hypokalemia (7.3%), increased alkaline phosphatase (7.0%), increased AST (7.0%), and total blood bilirubin increased (3.0%). A significant difference between the 2 treatment groups was noted for drug-related increased alkaline phosphatase, hypokalemia, and increased serum creatinine in favour of caspofungin.

Four safety hypotheses were predefined for this study. The primary safety analysis for this study was a comparison of the incidence of nephrotoxicity between the 2 treatment groups; 2.6 % of the patients in the caspofungin group versus 11.5 % of patients in the AmBisome group met the definition of nephrotoxicity, indicating that caspofungin is superior to AmBisome with respect to the occurrence of nephrotoxicity.
Similarly, in this study caspofungin was superior to AmBisome with respect to the 3 other predefined safety comparisons, including infusion-related events, drug-related adverse experiences, and discontinuations due to drug-related adverse experiences.

Safety data on caspofungin from ongoing studies and from the postmarketing environment are quite consistent with what has been previously reported in other Phase II and III studies within the caspofungin development program.

Thus, in general caspofungin safety results from this study together with postmarketing data do not seem to raise any new concerns, but vigilance still remains mandatory.

2.5 Benefit Risk assessment and conclusion

Invasive fungal infections are an important cause of morbidity and mortality in patients with neutropenia and cancer chemotherapy, with *Candida* and *Aspergillus* being the most commonly identified pathogens. No early diagnostic procedure for establishing an accurate diagnosis of invasive fungal infections is available, therefore empirical administration of antifungal agents has become standard practice in neutropenic patients who remain febrile despite adequate antibacterial therapy. A pre-emptive approach is currently being evaluated, using more advanced diagnostic measures such as PCR techniques, ELISA antigen and chest CT, but at present these tests are not standardised for this use and there is no real consensus for defining a target population for pre-emptive therapy yet. Although the pre-emptive approach is currently being used in certain European centres, empirical therapy is still considered relevant clinical practice.

There are some major problems with assessing true efficacy in empirical therapy, since the indication should be based solely on the successful treatment of any fungal infections documented from examination of specimens taken just before adding the antifungal agent. The sole inclusion criterion is neutropenic fever without response to parenteral antibiotics, and the rate of fever caused by non-infectious causes is difficult to evaluate. Given that all patients with and without fungal infections are treated, the true efficacy of the antifungal drug is difficult to evaluate. The controlled trials on empirical antifungal therapy performed so far have all used a non-inferiority design and composite endpoints. However, to compare two antifungal drugs and show that they are equivalent without a well defined primary endpoint is not optimal. A superiority trial design would be more appropriate for new antifungals, as stated in the recently adopted CPMP PtC. However, at the time of the initiation of the caspofungin empirical therapy trial (1999), the prevailing approach for empirical antifungal therapy studies was the non-inferiority design using a delta of -10%. The CPMP PtC did not come into operation until recently, in November 2003. The P026 study was modelled on the earlier large randomised comparative trials in empirical therapy, including the one that led to the approval of AmBisome in this indication. For all these reasons, the CPMP considered that a superiority trial cannot be considered an absolute requirement for granting this indication. The CPMP also believes, in accordance with the MAH's position, that the efficacy of caspofungin in documented invasive fungal infections has been satisfactorily demonstrated in previous studies.

The response assessment reports clearly demonstrate the multitude of prognostic factors (e.g. persistent neutropenia, change in antibacterial regimen, pre-existing renal impairment, underlying disease…) that might affect the outcome of all the separate secondary endpoints and thereby also the primary composite efficacy endpoint. All these variables are impossible to control for and contribute to the difficulties of assessing true efficacy of a drug in empirical therapy. A cautious attitude towards the results achieved in empirical antifungal trials is indeed indicated. As shown, there was a trend for prolonged neutropenia in patients with baseline infections in the AmBisome group, favouring caspofungin, which likely influenced on the outcome of baseline infections.

The MAH has responded in many ways satisfactorily to the list of outstanding issues. Regarding the major issue of an imbalance for persistent neutropenia (defined as ANC <500/µl at the end of study therapy (EOT)) between treatment groups favouring caspofungin in the "baseline fungal infection" secondary endpoint, the MAH claimed that this was due to the fact that there were more unfavourable responses and a related shorter duration of therapy in the AmBisome group. This circular reasoning (the time to end-of-therapy itself depends on the resolution of neutropenia) cannot be endorsed. Overall, there was a clear trend for prolonged neutropenia in the AmBisome group, irrespective of the time to end-of-therapy. However, this analysis is based on very few patients (27 subjects in each

treatment group, i.e. 5% of the whole population) and a reanalysis of the study with adjustment for a post-entry outcome ("persistent neutropenia") is inappropriate. Therefore it is difficult to draw any firm conclusions.

A similar trend in the outcome of the 7-day survival favouring caspofungin was demonstrated. Since the differences in successful treatment response for baseline infections and 7-day survival between treatment groups were small and barely/not statistically significant, the superiority of caspofungin to AmBisome cannot be claimed for these two secondary endpoints. However, the non-inferiority of caspofungin to AmBisome in the primary efficacy endpoint (i.e. favourable overall response for the 5-part composition endpoint) remains unchanged.

Regarding the requested supplementary data on possible breakthrough infections it was clarified that the majority of patients (56/57) had pneumonia and that only 3 of these subjects had microbiological data, whereof only one fulfilled the microbiological criteria for IFI as defined by EORTC/MSG. Although it can be agreed that the occurrence of possible infections should be regarded with a high level of uncertainty, and that in the setting of an empirical therapy trial in febrile neutropenic patients, analysis of documented invasive fungal infections should be limited to the probable and proven categories, the higher numbers of possible breakthrough infections in the caspofungin group vs the AmBisome group (38 vs 19) raises some concern.

Data of this pivotal comparative phase III trial, P026, including more than 1000 patients, indicate that caspofungin performs similarly to liposomal amphotericin B in the treatment of suspected fungal infection due to Aspergillus and Candida in patients with persistent febrile neutropenia. Also, caspofungin showed similar efficacy to AmBisome for the prevention of breakthrough infections with no appreciable difference between groups in total rates or in by-pathogen rates. Caspofungin has in earlier clinical studies convincingly been shown to be efficacious in the treatment of refractory invasive aspergillosis and invasive candidiasis in non-neutropenic patients. Limited data in neutropenic patients with documented candidaemia as well as deep-sited Candida infections indicate that caspofungin has similar efficacy in these patients. In the P026 trial, the safety profile of caspofungin was demonstrated to represent an advantage compared with Ambisome.

The indication, as proposed by the MAH, " *Empirical therapy for presumed fungal infections in febrile, neutropaenic adult patients*, should be revised.
The requested indication is misleading since it implies that caspofungin will be useful regardless of the identity of any fungal pathogen, a fact which is not supported by the data provided. Therefore the CPMP decided to adopt an alternate wording, as follows: **"***Empirical therapy for presumed fungal infections (such as Candida and Aspergillus) in febrile, neutropaenic adult patients*". Together with this revised indication, a warning statement regarding uncommon yeast and non-aspergillus moulds was added to section 4.4 of the SPC as follows: "*Limited data suggest that less common non-Candida yeasts and non-Aspergillus moulds are not covered by caspofungin. The efficacy of caspofungin against these fungal pathogens has not been established.*"

Considering all the above aspects and the revision of the SPC as requested, **the risk/benefit relationship is considered favourable**.

2.6 Adopted changes in the Summary of Product Characteristics and Package Leaflet

2.6.2 Summary of Product Characteristics

Section 4.1 "Therapeutic indications"

The requested indication is misleading since it implies that caspofungin will be useful regardless of the identity of any fungal pathogen, a fact which is not supported by the data provided. Therefore the CPMP decided to adopt an alternate wording, as follows: **"***Empirical therapy for presumed fungal infections (such as Candida and Aspergillus) in febrile, neutropaenic adult patients*".

The current indication for invasive candidasis (IC) is inconsistent with the extension of indication, since it includes only **non-neutropenic** patients. The number of neutropenic patients with IC who have received caspofungin has increased with the data from the empirical trial and now totals 26 patients (14 patients from the invasive candiasis trial (P014) trial and 12 patients from the current trial). In comparison with the 22 neutropenic patients who received AmBisome/amphotericin B in these trials, favourable response rates were slightly higher in the caspofungin group (15/26 (58%) vs 9/22 (41%)). It will read as follows: " *Treatment of invasive candidiasis in ~~non-neutropenic~~ adult patients*".

Section 4.2 "Posology and method of administration"

The recommendation of a dose increase of caspofungin to 70 mg in case of inadequate clinical response cannot be endorsed due to lack of supportive data. The wording in section 4.2 of the SPC as proposed by the MAH is as follows*: "Doses higher than 70 mg daily have not been adequately studied."* This new wording applies to the existing indications of Invasive Aspergillosis and Invasive Candidiasis as well as to the empirical treatment indication.

The CPMP agreed on the wording as proposed by the MAH at the time of the application: "*Duration of empirical therapy should be based on the patient's clinical response. Therapy should be continued until up to 72 hours after resolution of neutropaenia (ANC≥500). Patients found to have a fungal infection should be treated for a minimum of 14 days and treatment should continue for at least 7 days after both neutropaenia and clinical symptoms are resolved*."

Section 4.4 "Special warnings and special precautions for use"

Together with this revised indication, a warning statement regarding uncommon yeast and non-aspergillus moulds was added to section 4.4 of the SPC as follows: "*Limited data suggest that less common non-Candida yeasts and non-Aspergillus moulds are not covered by caspofungin. The efficacy of caspofungin against these fungal pathogens has not been established.*"

The CPMP agreed on the modified wording as proposed by the MAH at the time of the application: "*The safety information on treatment durations longer than 4 weeks is limited, however, available data suggest that caspofungin continues to be well tolerated with longer courses of therapy (up to 162 days)."*

Section 4.8 "Undesirable effects"

Based on the results of the empirical therapy study, adverses events were updated in this section 4.8, as follows: "*In clinical studies, 1440 individuals received single or multiple doses of CANCIDAS: 564 febrile neutropaenic patients (empirical therapy study), 125 patients with invasive candidiasis, 72 patients with invasive aspergillosis, 285 patients with localised Candida infections, and 394 individuals enrolled in Phase I studies. In the empirical therapy study patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation (including 39 allogeneic transplantations). In the studies involving patients with documented Candida infections, the majority of the patients with invasive Candida infections had serious underlying medical conditions (e.g., haematologic or other malignancy, recent major surgery, HIV) requiring multiple concomitant medications. Patients in the non-comparative Aspergillus study often had serious predisposing medical conditions (e.g., bone marrow or peripheral stem cell transplants, haematologic malignancy, solid tumours or organ transplants) requiring multiple concomitant medications.*"
…
" *Reported clinical and laboratory abnormalities among all patients treated with CANCIDAS (total 989) were typically mild and rarely led to discontinuation.*"…

Furthermore, *tachycadia, dyspnea* and *sweating* were added as adverse events reported.

The MAH proposed to delete the word *"isolated"* since there were 39 post-marketing reports of suspected allergic reaction of which 18 were serious. The CPMP accepted this proposal.

Section 5.1 "Pharmacodynamic properties"

The CPMP agreed on the update of the numbers in the *in vitro* activity of caspofungin:
"*Caspofungin has in vitro activity against Aspergillus species (Aspergillus fumigatus [N = 75], Aspergillus flavus [N = 111], Aspergillus niger [N = 31], Aspergillus nidulans [N = 8], Aspergillus terreus [N = 52], and Aspergillus candidus [N = 3]). Caspofungin also has in vitro activity against Candida species (Candida albicans [N = 1032], Candida dubliniensis [N = 100], Candida glabrata [N = 151], Candida guilliermondii [N = 67], Candida kefyr [N = 62], Candida krusei [N = 147], Candida lipolytica [N = 20], Candida lusitaniae [N = 80], Candida parapsilosis [N = 215], Candida rugosa [N = 1], and Candida tropicalis [N = 258]), including isolates with multiple resistance transport mutations and those with acquired or intrinsic resistance to fluconazole, amphotericin B, and 5-flucytosine.*"

Considering the great difficulties in recruiting a large number of neutropenic patients with documented IC, the CPMP is of the opinion that efficacy for caspofungin has been sufficiently demonstrated to delete the restriction of the IC indication to non-neutropenic patients. Therefore, the paragraph on *Invasive Candidiasis* was modified to read: "*These limited data are supported by the outcome of the empirical therapy study*."

The CPMP agreed on the following wordings to reflect data on empirical therapy as follows:
"*Empirical Therapy in Febrile, Neutropaenic Adult Patients: A total of 1111 patients with persistent fever and neutropaenia were enrolled in a clinical study and treated with either caspofungin 50 mg once daily following a 70-mg loading dose or liposomal amphotericin B 3.0 mg/kg/day. Eligible patients had received chemotherapy for malignancy or had undergone hematopoietic stem-cell transplantation, and presented with neutropaenia (<500 cells/mm^3 for 96 hours) and fever (>38.0°C) not responding to ≥96 hours of parenteral antibacterial therapy. Patients were to be treated until up to 72 hours after resolution of neutropaenia, with a maximum duration of 28 days. However, patients found to have a documented fungal infection could be treated longer. If the drug was well tolerated but the patient's fever persisted and clinical condition deteriorated after 5 days of therapy, the dosage of study drug could be increased to 70 mg/day of caspofungin (13.3 % of patients treated) or to 5.0 mg/kg/day of liposomal amphotericin B (14.3 % of patients treated).There were 1095 patients included in the primary Modified Intention-To-Treat (MITT) efficacy analysis of overall favourable response; caspofungin (33.9 %) was as effective as liposomal amphotericin B (33.7 %) [% difference 0.2 (95.2 % CI –5.6, 6.0)]. An overall favourable response required meeting each of 5 criteria: (1) successful treatment of any baseline fungal infection (caspofungin 51.9 % [14/27], liposomal amphotericin B 25.9 % [7/27]), (2) no breakthrough fungal infections during administration of study drug or within 7 days after completion of treatment (caspofungin 94.8 % [527/556], liposomal amphotericin B 95.5 % [515/539]), (3) survival for 7 days after completion of study therapy (caspofungin 92.6 % [515/556], liposomal amphotericin B 89.2 % [481/539]), (4) no discontinuation from the study drug because of drug-related toxicity or lack of efficacy (caspofungin 89.7 % [499/556], liposomal amphotericin B 85.5 % [461/539]), and (5) resolution of fever during the period of neutropaenia (caspofungin 41.2 % [229/556], liposomal amphotericin B 41.4 % [223/539]). Response rates to caspofungin and liposomal amphotericin B for baseline infections caused by Aspergillus species were, respectively, 41.7 % (5/12) and 8.3 % (1/12), and by Candida species were 66.7 % (8/12) and 41.7 % (5/12). Patients in the caspofungin group experienced breakthrough infections due to the following uncommon yeasts and moulds: Trichosporon species (1), Fusarium species (1), Mucor species (1), and Rhizopus species (1)."*

Section 5.2 "Pharmacokinetic properties"

The CPMP agreed on the proposed wording to update the paragraph on elderly patients as follows:

"*In patients who were treated empirically or who had invasive candidiasis, a similar modest effect of age was seen in older patients relative to younger patients.*"

2.6.2 Package Leaflet

The CPMP agreed on the proposed wordings to reflect the change from the SPC in the PL, as follows:

1. What is CANCIDAS and what is it used for?

*"Persistent fever due to infection may occur following chemotherapy or medical conditions that lower the body's resistance to disease by lowering counts of certain white blood cells. If the fever is not reduced by treatment with an antibiotic, your doctor may suspect that you have a fungal infection and prescribe CANCIDAS to treat it."*is added.

4. What undesirable effects may CANCIDAS have?

This section of the PL is udated as follows:
"The most common side effect is fever.
Other reported side effects include:

- *Headache,*
- *rapid heart beat,*
- *flushing,*
- *shortness of breath,*
- *abdominal pain, nausea, vomiting, diarrhoea,*
- *rash, itching, sweating,*
- *pain, chills, vein irritations at the infusion site (including itching, redness, discharge, swelling, burning sensation, or clotting),*
- *allergic reactions (including swelling of the face and/or lips, itching, rash, sensation of warmth, or trouble breathing),*
- *swelling of the hands, ankles or feet,*
- *impaired liver function,*
- *alterations in some laboratory blood tests (including decreased red blood cell count and increased values of some liver and kidney tests, high calcium)."*

In addition, the MAH has completed the list of local representatives in the Package Leaflet in accordance with EMEA/QRD templates, to include the 10 accession countries.

III. CONCLUSION

The majority of the CPMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics, based on the observations and the appropriate conclusions.

The CPMP adopted on 24 March 2004 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.