SYNOPSIS

Name of Sponsor/Company: Astellas Pharma US, Inc. (Successor in interest to Fujisawa Healthcare, Inc.)		
Name of Finished Product: Micafungin		
Name of Active Ingredient: FK463		
Title of Study: A Phase 3, Randomized, Double-Blind, Comparative Study of Micafungin (FK463) Versus Caspofungin as Antifungal Treatment in Patients with Invasive Candidiasis or Candidemia		
Responsible Medical Officer/Investigators: Responsible Medical Officer: [redacted], MD, [redacted], Astellas Pharma US, Inc., [redacted]. Coordinating Investigator: [redacted], MD, FACP, [redacted]		
Study Center(s): This study was conducted at 128 sites in 15 countries: 45 sites in the United States, 14 sites in Brazil, 13 sites in Canada, 13 sites in India, 11 sites in Spain, 9 sites in France, 6 sites in Germany, 5 sites in Belgium, 5 sites in the United Kingdom (Great Britain and Scotland), 2 sites each in Poland and Switzerland, and 1 site each in Austria, Croatia, and The Netherlands.		
Publication (reference): None.		
Study Period: Minimum length of antifungal treatment was 14 days: maximum length of treatment was 4 weeks or, for pre-defined patients, 8 weeks. Patients were followed for 6 weeks posttreatment. **Date of first enrollment:** 15 September 2004 **Date of last evaluation:** 27 April 2006	**Phase of Development:** Phase 3	
Objectives: The objective of this study was to determine the efficacy and safety of two dose levels (100 mg/day and 150 mg/day) of intravenous micafungin versus intravenous caspofungin in the treatment of patients with confirmed invasive candidiasis or candidemia.		
Methodology: This was a phase 3, multicenter, randomized (1:1:1), double-blind, parallel group, non-inferiority study comparing two dose levels of intravenous micafungin to intravenous caspofungin in patients aged 18 years and older with confirmed invasive candidiasis or candidemia. Patients were stratified by region (North America, Europe, Brazil, or India) and Acute Physiology and Chronic Health Evaluation (APACHE II) score (≤ 20 or > 20). Study drug (micafungin 100 mg once daily [qd], micafungin 150 mg qd, or caspofungin 70 mg qd on day 1 and 50 mg qd thereafter) was administered intravenously in a blinded manner. The minimum length of antifungal treatment (intravenous therapy alone or intravenous therapy followed by oral fluconazole) was 14 days. The maximum length of treatment was 4 weeks, except for pre-defined patients with chronic disseminated candidiasis (including hepatosplenic involvement) or *Candida* endophthalmitis, for whom the administration of intravenous study medication could have been prolonged to a maximum of 8 weeks. Patients were followed through 6 weeks posttreatment.		
Number of Patients (enrolled and analyzed): A total of 540 patients were planned for enrollment: 611 patients were actually enrolled. There were 595 patients included in the safety set, 593 patients included in the full analysis set, 578 patients included in the modified full analysis set, and 503 patients included in the per protocol set.		

Diagnosis and Main Criteria for Inclusion: Adult patients (≥18 years old) with candidemia or invasive candidiasis, as documented by at least one typical clinical sign or symptom and confirmed by fungal culture and/or histology were enrolled into the study.

For candidemia or acute invasive candidiasis, preliminary evidence of yeast (by staining and microscopy of the blood culture sample) was required to enroll a patient: a positive culture must have been documented from a sample obtained no more than 96 hours prior to the first dose of study drug. For invasive candidiasis, culture results could be pending at the time of enrollment if histology/cytology revealed yeast. For chronic invasive candidiasis, a positive culture within 4 weeks prior to randomization was acceptable provided the patient had findings of endophthalmitis or hepatosplenic lesions documented by radiographic imaging and the patient had not received > 2 days of prior systemic antifungal therapy with 7 days prior to randomization. Confirmation of *Candida* species was to be obtained within 1 week after enrollment.

Patients whose sole diagnoses were oropharyngeal and/or esophageal candidiasis and/or with positive cultures only from urine specimens, sputum specimens, bronchoalveolar lavage specimens, or samples from indwelling drains were not eligible for enrollment. Furthermore, patients who received an echinocandin within 1 month prior to study entry, received > 2 days of prior systemic antifungal therapy for the current infection, had a yeast or mold-like infection other than invasive candidiasis or candidemia, or who at the time of study entry or within 72 hours postrandomization was known to have *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis were also not eligible for enrollment.

Test Product, Dose and Mode of Administration, Batch Numbers: The test product was intravenous micafungin 100 mg qd or intravenous micafungin 150 mg qd. Study drug was reconstituted and diluted with 0.9% sodium chloride (normal saline) for injection (250 mL) and was administered once daily as an intravenous infusion over 1 hour.

Lot numbers of micafungin used during the study: [redacted]

Duration of Treatment (or Duration of Study, if applicable): The maximum length of antifungal treatment (intravenous therapy alone or intravenous therapy followed by oral fluconazole) was 4 weeks. In pre-defined patients with chronic disseminated candidiasis (including hepatosplenic involvement) or *Candida* endophthalmitis, the administration of intravenous study medication could have been prolonged to a maximum of 8 weeks. Patients were followed through 6 weeks posttreatment.

Reference Product, Dose and Mode of Administration, Batch Numbers: The comparator was intravenous caspofungin 70 mg on day 1 and 50 mg qd thereafter.

Lot numbers of caspofungin used during the study: [redacted]

Criteria for Evaluation: The primary efficacy endpoint was treatment success at the end of blinded intravenous therapy (based on investigator assessments). Success was defined as a positive clinical response (complete or partial) and a positive mycological response (eradication or presumed eradication) as assessed by the investigator at the end of blinded intravenous therapy. Patients who died during blinded intravenous therapy (last dose day plus one day) were counted as treatment failures. Additionally, if a clinical or mycological response was not assessed at the end of blinded intravenous therapy, the patient was counted as a treatment failure.

Secondary efficacy endpoints included: treatment success at the end of blinded intravenous therapy as assessed by the Data Review Panel (DRP); clinical response at the end of blinded intravenous therapy, based on the investigator's assessment at the end of blinded intravenous therapy; mycological response at the end of blinded intravenous therapy, based on the investigator's assessment at the end of blinded intravenous therapy; incidence of emergent invasive fungal infections during the study, based on the investigator's final baseline diagnosis of fungal infection and subsequent diagnoses of fungal infections; and, incidence of recurrent invasive fungal infections (relapse) during the posttreatment period, based on the investigator's evaluation of relapse at the posttreatment visits at 2 weeks and 6 weeks.

Criteria for Evaluation (cont'd): Safety was assessed based on treatment-emergent adverse events, the results of routine clinical laboratory tests, and vital sign measurements.

Statistical Methods: The full analysis set was used for the primary analysis of the primary efficacy endpoint. Two treatment differences were calculated as the experimental regimen minus the comparator as follows: micafungin 150 mg qd – caspofungin; and, micafungin 100 mg qd – caspofungin.

Two-sided 95% and 97.5% confidence intervals (CIs) were constructed for each of the two treatment differences adjusting for region (North America, Europe, Brazil, and India) and APACHE II score (≤ 20 and > 20) using Cochran-Mantel-Haenszel (CMH) weights. To control for the overall level of significance, the following Hochberg procedure was used: 1) the least significant CI (i.e., 95% CI) with the smallest lower bound was considered; if this lower bound was greater than the margin (i.e., -15%), then both micafungin regimens were considered to be non-inferior to caspofungin and superiority of micafungin treatments was further evaluated using the Hochberg method. 2) If the least significant CI failed to demonstrate non-inferiority (or superiority), then the other treatment comparison was considered using a 97.5% CI. Again, if the lower bound was greater than -15%, then that micafungin regimen was considered to be non-inferior to caspofungin (or superior, if the lower bound was greater than zero).

To assess the robustness of the results of the primary analysis, the primary analysis was performed using the modified full analysis set and the per protocol set.

Analyses for the secondary efficacy endpoints were performed using the full analysis, modified full analysis, and per protocol sets. Each secondary efficacy endpoint was summarized by treatment group. Comparative analyses were performed separately for micafungin 150 mg qd versus caspofungin and micafungin 100 mg qd versus caspofungin.

The difference in proportions between each micafungin treatment group and caspofungin was computed for all secondary efficacy endpoints. The 95% (two-sided) CIs for these differences was computed using the CMH method. The CIs for the difference in treatment success (DRP's assessment), clinical response, mycological response, and emergent fungal infections were adjusted for region and APACHE II score. The CI for the difference in relapse rates was adjusted for duration of oral fluconazole following the switch from blinded intravenous study drug therapy (< 2 doses, ≥ 2 doses).

A summary of relapse was presented for patients who had treatment success (investigator's assessment) at the end of blinded intravenous study drug therapy.

All safety analyses were performed using the safety set. Adverse events were summarized using MedDRA version 5.0. Adverse events starting any time between the first day of intravenous study drug administration through 72 hours (3 days) after the last dose of intravenous study drug were classified as treatment-emergent adverse events. For each treatment-emergent adverse event of special interest, the incidence between each micafungin treatment group was compared to the incidence in the caspofungin group using Fisher's exact test. A 0.1 level of significance was used to identify potential differences between treatment groups with respect to adverse events.

The incidence of patient mortality, including relationship to intravenous study drug and relationship to fungal infection, was summarized by treatment group. Additionally, the incidence of the primary reason for patient death was also summarized by treatment group.

Laboratory values (observed and change from baseline) were summarized over time (baseline, weekly, end of intravenous study drug therapy, end of all antifungal therapy, 2 weeks posttreatment, 6 weeks posttreatment) by treatment group. Shift tables for select laboratory parameters (creatinine, alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin [TBil]) were provided to summarize the shift from baseline value to the value observed at the end of blinded intravenous study drug therapy and to the worst value during treatment (including the end of blinded intravenous study drug therapy). The conjoint incidence of elevated liver function tests (AST and ALT versus TBil) for patients with normal (≤ upper limit of normal [ULN]) transaminase values at baseline were summarized for the end of blinded intravenous study drug therapy values and worst laboratory values during blinded intravenous study drug therapy.

Summary

Demographics: Refer to Synopsis Table 1. There were more males (347/595; 58.3%) than females (248/595; 41.7%). The majority of patients were White (404/595; 67.9%); however, Blacks (85/595; 14.3%) and Asian Indians (64/595; 10.8%) were also well-represented. More than half the patients (338/595; 56.8%) were enrolled at sites in North America. The mean age of patients was approximately 56 years. Elderly patients (≥ 65 years old) were well-represented and accounted for 33.6% of the safety set. For the safety, full analysis, and modified full analysis sets, there was a statistically significant difference across treatment groups for baseline weight: p = 0.0447, 0.0455, and 0.0362 for the safety set, full analysis set, and modified full analysis set, respectively (one-way analysis of variance [ANOVA]). This may have been due to the lower average weight of the micafungin 100 mg treatment group; however, the sponsor does not believe these differences had a meaningful impact on the findings and results of the study. For the per protocol set, the difference in baseline weight across the three treatment groups was not statistically significant (p = 0.0569; one-way ANOVA). There were no other statistically significant differences in baseline demographics across the three treatment groups (chi-square test for discrete variables; one-way ANOVA for continuous variables) for any of the analysis sets.

There were no statistically significant differences across treatment groups for the presence of neutropenia (chi-square), APACHE II score (one-way ANOVA), or APACHE II score category (chi-square) at baseline for any of the analysis sets. Within the full analysis set, the majority of patients (542/593; 91.4%) were not neutropenic at baseline. Mean and median APACHE II scores were similar across the treatment groups and the majority of patients (479/593; 80.8%) had APACHE II scores ≤ 20. The incidence of catheter removal and/or replacement for patients who had catheters placed prior to blinded therapy was similar across the treatment groups.

Overall, the primary underlying diseases for patients in the safety set were widely varied and had similar distributions across the three treatment groups. The majority of patients (414/595; 69.6%) enrolled with primary underlying diseases described as non-malignancy-related conditions. The most common non-malignancy related conditions were gastrointestinal diseases/conditions (74/595; 12.4%), lung disorder (50/595; 8.4%), and "other" disease (57/595; 9.6%). Malignancies were noted as the primary underlying disease for 181/595 (30.4%) patients, with 109/595 (18.3%) patients having "other" malignancies. The large proportion of patients with "other" malignancy and non-malignancy-related conditions points to the heterogeneity of the overall study population in terms of primary underlying disease. There were no clear differences in the characteristics of the primary underlying diseases among the various regions (North America, Europe, Brazil, and India).

Refer to Synopsis Table 2. There was no statistically significant difference (chi-square) across the treatment groups for the investigator's assessment of the type of baseline fungal infection for the full analysis, modified full analysis, or per protocol sets. For the full analysis set, the majority of patients (≥ 82.4% in each treatment group) enrolled with candidemia. There were few patients in the full analysis set (three in each treatment group) who had an invasive non-*Candida* infection at baseline.

Drug Administration: In the safety set, 123/595 (20.7%) patients received < 10 doses of blinded study drug: proportionally fewer patients (37/202; 18.3%) in the micafungin 150 mg treatment group received < 10 doses of blinded study drug compared to patients in the micafungin 100 mg (43/200; 21.5%) and caspofungin (43/193; 22.3%) treatment groups. The majority of patients (400/595; 67.2%) received ≤ 14 doses of blinded study drug and approximately 90% received ≤ 21 doses. The median duration of treatment with blinded study drug was 14 days for all treatment groups. As expected, the cumulative daily dose of blinded study drug received by patients in the micafungin 150 mg treatment group was approximately 50% higher than that received by patients in the micafungin 100 mg treatment group, and the average daily dose (mg) was consistent with the treatment arm to which patients were randomized.

In the safety set, a total of 112 patients received protocol-defined oral fluconazole and the majority of these patients (80/112; 71.4%) received ≤ 9 days of treatment with this medication. Numerically fewer patients in the micafungin 150 mg treatment group (30/202; 14.9%) received protocol-defined oral fluconazole, compared to patients in the micafungin 100 mg (41/200; 20.5%) or caspofungin (41/193; 21.2%) treatment groups. Median duration of treatment was lower in the caspofungin treatment group (4.00 days), compared to the micafungin 100 mg (8.00 days) or micafungin 150 mg (6.50 days) treatment groups.

Efficacy Results: *Primary Endpoint.* Refer to Synopsis Table 3. A total of 147/199 (73.9%), 142/202 (70.3%), and 137/192 (71.4%) patients in the micafungin 100 mg, micafungin 150 mg, and caspofungin treatment groups, respectively, were assessed by the investigator as treatment successes at the end of blinded therapy. The 95% CI for the comparison of micafungin 100 mg to caspofungin was [-5.9%, 11.0%]. The 95% CI for the comparison of micafungin 150 mg to caspofungin was [-9.3%, 7.8%]. The 95.0% CIs constructed around the treatment differences (experimental regimen – caspofungin) for the investigator's assessment of treatment success at the end of blinded therapy had lower bounds > -15%, indicating both micafungin regimens were non-inferior to caspofungin for the primary endpoint.

The secondary analyses of the investigator's assessment of treatment success at the end of blinded therapy (using the modified full analysis and per protocol sets) also had CIs with lower bounds > -15%. These results supported the results of the primary analysis which indicated micafungin 100 mg and micafungin 150 mg were non-inferior to caspofungin.

Secondary Endpoints. *Treatment success at end of blinded therapy (Data Review Panel assessment).* Refer to Synopsis Table 4. The 95.0% CIs constructed around the treatment differences (experimental regimen – caspofungin) for the DRP's assessment of treatment success at the end of blinded therapy had lower bounds > -15%, indicating both micafungin regimens were non-inferior to caspofungin for this secondary endpoint.

Clinical response at end of blinded therapy (investigator assessment). Refer to Synopsis Table 5. The 95.0% CIs constructed around the treatment differences (experimental regimen – caspofungin) for the investigator's assessment of clinical response at the end of blinded therapy had lower bounds > -15%, indicating both micafungin regimens were non-inferior to caspofungin for this secondary endpoint.

Mycological response at end of blinded therapy (investigator assessment). Refer to Synopsis Table 6. The 95.0% CIs constructed around the treatment differences (experimental regimen – caspofungin) for the investigator's assessment of mycological response at the end of blinded therapy had lower bounds > -15%, indicating both micafungin regimens were non-inferior to caspofungin for this secondary endpoint.

Incidence of emergent invasive fungal infections during the study (investigator assessment). Refer to Synopsis Table 7. Numerically fewer patients in the micafungin 100 mg treatment group (8/199; 4.0%) experienced an emergent fungal infection during the study than patients in the micafungin 150 mg (14/202; 6.9%) or caspofungin (13/192; 6.8%) treatment groups. Most emergent fungal infections occurred during blinded therapy (20 patients, total).

Incidence of recurrent invasive fungal infections (relapse) during the study (investigator assessment). Refer to Synopsis Table 8. Overall, relatively few patients who were considered to have treatment success at the end of blinded therapy had a confirmed relapse during the study. During the posttreatment period (after the last dose protocol-defined oral fluconazole), the majority of patients who were counted as a relapse either received antifungal treatment during the posttreatment period or died, regardless of treatment group. For both micafungin treatment groups, the 95% CIs constructed around the treatment differences (experimental regimen – caspofungin) for the investigator's assessment of relapse when missing values were excluded from analysis indicated both micafungin regimens were comparable to caspofungin at all timepoints examined for this secondary endpoint. Analyses of the investigator's assessment of relapse for patients who were considered to have treatment success at the end of blinded therapy by type of infection, baseline fungal infection species, neutropenic status at baseline, APACHE II score category, duration of antifungal therapy, and catheter status were consistent with the main analyses for relapse.

Safety Results: Refer to Synopsis Table 9. Greater than 88% of the patients in each treatment group experienced a treatment-emergent adverse event. More than 25% of the patients in each treatment group experienced a treatment-emergent adverse event coded under the following system organ classes: gastrointestinal disorders, metabolism and nutrition disorders, infections and infestations, and general disorders and administration site conditions. The majority of treatment-emergent adverse events were mild to moderate in intensity.

Safety Results (cont'd): Refer to Synopsis Table 10. There were relatively few (< 25% in each treatment group) treatment-emergent adverse events considered by the investigator to be related (possibly, probably, or definitely) to blinded study drug. The most common (≥ 2% in any treatment group) treatment-emergent adverse events considered by the investigator to be related to blinded study drug included blood alkaline phosphatase increased, abnormal liver function tests not otherwise specified (NOS), nausea, constipation, hypokalemia, and rash NOS. It was noted that some of the variation of treatment-emergent adverse events observed between treatment groups when adverse events were summarized overall was not apparent when study drug-related adverse events were summarized.

Refer to Synopsis Table 11. A total of 176/595 (29.6%) patients died during the study. Twenty-three deaths were considered by the investigator to be related to a fungal infection. None of the deaths were considered by the investigator to be related (possibly, probably, or definitely) to blinded study drug. The most common primary causes of death were sepsis-related adverse events (septic shock, sepsis NOS, and bacterial sepsis) and respiratory failure. Primary causes of death were comparable across treatment groups.

Refer to Synopsis Table 12. A total of 114/595 (19.2%) patients experienced a serious treatment-emergent adverse event other than death during the study. As with the primary cause of death, the most common serious treatment-emergent adverse events were sepsis-related (septic shock and sepsis NOS) and respiratory failure. There were numerically more serious treatment-emergent adverse events in the micafungin 150 mg treatment group (45/202; 22.3%) than the micafungin 100 mg (36/200; 18.0%) or caspofungin (33/193; 17.1%) treatment groups. Only 19/595 (3.2%) patients experienced a serious treatment-emergent adverse event (7/200 [3.5%] in the micafungin 100 mg treatment group; 6/202 [3.0%] in the micafungin 150 mg treatment group; and, 6/193 [3.1%] in the caspofungin treatment group) considered by the investigator to have a possible or probable relationship to blinded study drug.

Refer to Synopsis Table 13. A total of 99/595 (16.6%) patients experienced a treatment-emergent adverse event resulting in permanent discontinuation of blinded study drug. As with serious treatment-emergent adverse events, the most common adverse events resulting in permanent discontinuation of study drug were sepsis-related adverse events (septic shock, sepsis NOS, and bacterial sepsis) and respiratory failure. Overall, numerically more patients in the micafungin 150 mg treatment group experienced an adverse event leading to permanent discontinuation of blinded study drug; however, blinded study drug discontinuation for these patients could not be consistently attributed to particular adverse events.

A total of 80/595 (13.4%) patients experienced a treatment-emergent hepatic adverse event. The incidence of treatment-emergent hepatic adverse events was comparable among the three treatment groups. Of the 80 patients who experienced a treatment-emergent hepatic adverse event, 49 (61.3%) patients experienced a hepatic adverse event considered by the investigator to have a possible, probable, or definite relationship to blinded study drug. The most common hepatic events were associated with abnormal liver function test results, including increases in ALP, TBil, and aminotransferases.

A total of 56/595 (9.4%) patients experienced a treatment-emergent renal adverse event. Of the 56 patients who experienced a treatment-emergent renal adverse event, 7 (12.5%) experienced a renal adverse event considered by the investigator to have a possible or probable relationship to blinded study drug. Numerically more patients in the micafungin 150 mg treatment group (25/202; 12.4%) experienced a renal adverse event compared to patients in the micafungin 100 mg (16/200; 8.0%) or caspofungin (15/193; 7.8%) treatment groups.

A total of 14/595 (2.4%) patients experienced a treatment-emergent injection site reaction. Of the 14 patients who experienced a treatment-emergent injection site reaction, only 3 (21.4%) experienced an injection site reaction considered by the investigator to be related (possibly, probably, definitely) to blinded study drug. All of the injection site reactions considered by the investigator to be related to blinded study drug occurred in the micafungin 100 mg treatment group.

A total of 53/595 (8.9%) patients experienced a treatment-emergent histamine release/allergic-type reaction. Of the 53 patients who experienced a treatment-emergent histamine release/allergic-type reaction, 18 (34.0%) experienced a histamine release/allergic-type reaction considered by the investigator to have a possible, probable, or definite relationship to blinded study drug. Numerically more patients in the caspofungin treatment group (20/193, 10.4%) experienced a histamine release/allergic-type reaction compared to the micafungin 100 mg (15/200; 7.5%) or micafungin 150 mg (18/202; 8.9%) treatment group.

Safety Results (cont'd): Five patients each in the micafungin 100 mg and caspofungin treatment groups experienced a treatment-emergent infusion-related reaction: no patients in the micafungin 150 mg treatment group experienced an infusion-related reaction. All treatment-emergent infusion-related reactions were considered by the investigator to have either a possible or probable relationship to blinded study drug. All treatment-emergent infusion-related reactions occurred as single, unique events.

One patient in the micafungin 150 mg treatment group and three patients in the caspofungin treatment group experienced treatment-emergent adverse events that were possibly due to hemolysis: no patients in the micafungin 100 mg treatment group experienced an adverse event possibly due to hemolysis. None of the treatment-emergent events possibly due to hemolysis were considered by the investigator to be related (possibly, probably, or definitely) to blinded study drug.

Mean and median change from baseline for creatinine values were negative for all three treatment groups at most time points, indicating creatinine values were lower than baseline during most of the study. Creatinine values observed throughout the study do not indicate any clinically significant differences in renal function among the three treatment groups.

The number of patients with normal (< 2.5 x ULN) ALP, AST, ALT, and TBil values at baseline who had elevated values for any of these parameters at the end of blinded therapy was comparable for all three treatment groups. Overall, there were no notable differences across the three treatment groups for the conjoint incidence of elevated liver function tests for patients with normal transaminase values at baseline. There were no other clinically significant changes in chemistry values among the three treatment groups.

Changes in systolic and diastolic pressure, pulse rate, and temperature throughout the study were consistent with the infection status or complicating adverse events such as sepsis NOS or septic shock.

CONCLUSIONS: This study has determined that micafungin at a dose of 100 mg/day is a safe and effective treatment for candidemia and invasive candidiasis. Micafungin 100 mg/day and micafungin 150 mg/day both proved to be non-inferior to the comparator, caspofungin (70 mg on day 1 followed by 50 mg/day thereafter). No efficacy advantages appeared to be gained by increasing the dose of micafungin from 100 mg/day to 150 mg/day. All three study drug regimens were safe and well-tolerated, with only 18 of the 595 patients studied discontinuing blinded study drug therapy due to a study drug-related adverse event. Overall, the study results support the conclusion that micafungin 100 mg/day should be the recommended dose for the treatment of invasive candidiasis and candidemia.

Date of Report: 9 November 2006.

Synopsis Table 1: Baseline Demographics

Parameter Variable	**Micafungin 100 mg (n = 200)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 193)**
Gender			
Male	113 (56.5%)	118 (58.4%)	116 (60.1%)
Female	87 (43.5%)	84 (41.6%)	77 (39.9%)
Race			
White (non-Hispanic)	141 (70.5%)	131 (64.9%)	132 (68.4%)
Black	23 (11.5%)	36 (17.8%)	26 (13.5%)
Asian-Indian	20 (10.0%)	21 (10.4%)	23 (11.9%)
White – Hispanic	4 (2.0%)	5 (2.5%)	6 (3.1%)
Asian	8 (4.0%)	4 (2.0%)	0
Mestizo	3 (1.5%)	2 (1.0%)	4 (2.1%)
Native American – Alaskan Native	1 (0.5%)	1 (0.5%)	0
Black – Hispanic	0	1 (0.5%)	0
Other†	0	1 (0.5%)	2 (1.0%)
Region (Location of Site)			
North America	113 (56.5%)	116 (57.4%)	109 (56.5%)
Europe	40 (20.0%)	39 (19.3%)	41 (21.2%)
Brazil	26 (13.0%)	25 (12.4%)	23 (11.9%)
India	21 (10.5%)	22 (10.9%)	20 (10.4%)
Age (years)			
Mean ± SD	56.80 ± 16.442	55.41 ± 16.761	55.52 ± 16.871
Median	58.00	57.00	56.00
Range	18.0 – 92.0	18.0 – 90.0	19.0 – 95.0
Age Group (years)			
16 to 64‡	127 (63.5%)	139 (68.8%)	129 (66.8%)
≥ 65	73 (36.5%)	63 (31.2%)	64 (33.2%)
Weight (kg)§*			
Mean ± SD	70.49 ± 18.603	75.38 ± 22.835	74.52 ± 20.687
Median	68.20	71.45	70.00
Range	33.5 – 132.0	32.5 – 172.5	21.0 – 144.5

Patient base: Safety set; all randomized patients who received at least one dose of blinded study drug.

SD: Standard deviation.

† Other race: Arabic; native North-African; and, North-African.

‡ The youngest patient was 18 years old.

§ For weight: n = 199 for micafungin 100 mg; n = 200 for micafungin 150 mg; and, n = 192 for caspofungin.

* p = 0.0447 (one-way ANOVA).

Source: Table 12.2.1.1 and Appendix 13.4.1.2.

Synopsis Table 2: Baseline Fungal Infections (Investigator Assessment)

Type of Infection Class	**Micafungin 100 mg (n = 199)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 192)**
Candidemia (Fungemia)	164 (82.4%)	169 (83.7%)	162 (84.4%)
Invasive *Candida* Infection	29 (14.6%)	30 (14.9%)	26 (13.5%)
Acute Disseminated	7 (3.5%)	11 (5.4%)	8 (4.2%)
Abscess	5 (2.5%)	6 (3.0%)	9 (4.7%)
Peritonitis	6 (3.0%)	7 (3.5%)	5 (2.6%)
Endophthalmitis	5 (2.5%)	3 (1.5%)	1 (0.5%)
Chorioretinitis	2 (1.0%)	1 (0.5%)	0
Chronic Disseminated	1 (0.5%)	0	0
Organ†	0	1 (0.5%)	0
Other‡	3 (1.5%)	1 (0.5%)	3 (1.6%)
Non-*Candida* Infection	3 (1.5%)	3 (1.5%)	3 (1.6%)
Fungemia	2 (1.0%)	2 (1.0%)	3 (1.6%)
Acute Disseminated	1 (0.5%)	0	0
Peritonitis	0	1 (0.5%)	0
No Fungal Infection	3 (1.5%)	0	1 (0.5%)

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

Patients with an invasive infection may have also had positive blood cultures. These patients were classified as having an invasive infection only and were not counted twice.

† Patient Number [redacted] thoracic aorta.

‡ Other, as described by the investigator: pleural infection/empyema (three patients); intraabdominal infection (two patients); cholangitis (one patient); and, pyelonephritis and blood (one patient).

Source: Table 12.2.2.2.1 and Appendix 13.4.1.4.1.

Synopsis Table 3: Treatment Success at End of Blinded Therapy (Investigator Assessment)

Parameter Variable	**Micafungin 100 mg (n = 199)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 192)**
Success	147 (73.9%)	142 (70.3%)	137 (71.4%)
Failure	52 (26.1%)	60 (29.7%)	55 (28.6%)
Died During Blinded Therapy	28 (14.1%)	30 (14.9%)	27 (14.1%)
Unsuccessful	18 (9.0%)	29 (14.4%)	24 (12.5%)
Not Evaluable	6 (3.0%)	1 (0.5%)	4 (2.1%)
Comparison of Success Rates			
Treatment difference†	2.5%	-1.1%	
[95.0% CI]‡	[-5.9%, 11.0%]	[-9.3%, 7.8%]	
[97.5% CI]‡	[-7.1%, 12.2%]	[-10.6%, 9.0%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

Success was defined as a positive clinical response (complete or partial) and a positive mycological response (eradication or presumed eradication) at the end of blinded therapy. Patients who died during blinded therapy (first dose day through last dose day + 1 day) were considered a failure.

CI: Confidence interval.

† Micafungin minus caspofungin.

‡ Based on Cochran-Mantel-Haenszel method, controlling for region and APACHE II score.

Source: Table 12.5.1.1.

Synopsis Table 4: Treatment Success at End of Blinded Therapy (Data Review Panel Assessment)

Parameter Variable	**Micafungin 100 mg (n = 199)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 192)**
Success	140 (70.4%)	139 (68.8%)	135 (70.3%)
Failure	59 (29.6%)	63 (31.2%)	57 (29.7%)
Died During Blinded Therapy	28 (14.1%)	30 (14.9%)	27 (14.1%)
Unsuccessful	26 (13.1%)	32 (15.8%)	28 (14.6%)
Not Evaluable	5 (2.5%)	1 (0.5%)	2 (1.0%)
Comparison of Success Rates			
Treatment difference†	0.0%	-1.5%	
[95.0% CI]‡	[-9.0%, 8.5%]	[-10.1%, 7.2%]	
[97.5% CI]‡	[-10.2%, 9.7%]	[-11.3%, 8.4%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

Success was defined as a positive clinical response (complete or partial) and a positive mycological response (eradication or presumed eradication) at the end of blinded therapy. Patients who died during blinded therapy (first dose day through last dose day + 1 day) were considered a failure.

Investigator's assessment was used for patients who were not evaluable (i.e., marked as not assessable on the case report form). If both the data review panel and investigator deemed the patient not evaluable, then the patient was counted as not evaluable (failure).

CI: Confidence interval.

† Micafungin minus caspofungin.

‡ Based on Cochran-Mantel-Haenszel method, controlling for region and APACHE II score.

Source: Table 12.5.2.1.

Synopsis Table 5: Clinical Response at End of Blinded Therapy (Investigator Assessment)

Parameter Variable	**Micafungin 100 mg (n = 199)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 192)**
Success	168 (84.4%)	174 (86.1%)	165 (85.9%)
Complete	143 (71.9%)	153 (75.7%)	139 (72.4%)
Partial	25 (12.6%)	21 (10.4%)	26 (13.5%)
Failure	31 (15.6%)	28 (13.9%)	27 (14.1%)
Stable	18 (9.0%)	17 (8.4%)	16 (8.3%)
Progression	6 (3.0%)	8 (4.0%)	7 (3.6%)
Not Done	7 (3.5%)	3 (1.5%)	4 (2.1%)
Comparison of Success Rates			
Treatment difference†	-1.5%	0.2%	
[95.0% CI]‡	[-8.2%, 5.4%]	[-6.3%, 6.7%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

CI: Confidence interval.

† Micafungin minus caspofungin.

‡ Based on Cochran-Mantel-Haenszel method, controlling for region and APACHE II score.

Source: Table 12.5.3.1.

Synopsis Table 6: Mycological Response at End of Blinded Therapy (Investigator Assessment)

Parameter Variable	**Micafungin 100 mg (n = 199)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 192)**
Success	170 (85.4%)	166 (82.2%)	159 (82.8%)
Eradication	160 (80.4%)	151 (74.8%)	151 (78.6%)
Presumed Eradication	10 (5.0%)	15 (7.4%)	8 (4.2%)
Failure	29 (14.6%)	36 (17.8%)	33 (17.2%)
Persistence	23 (11.6%)	32 (15.8%)	30 (15.6%)
Not Done	6 (3.0%)	4 (2.0%)	3 (1.6%)
Comparison of Success Rates			
Treatment difference†	2.6%	-0.6%	
[95.0% CI]‡	[-4.3%, 9.9%]	[-7.8%, 6.9%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

CI: Confidence interval.

† Micafungin minus caspofungin.

‡ Based on Cochran-Mantel-Haenszel method, controlling for region and APACHE II score.

Source: Table 12.5.4.1.

Synopsis Table 7: Incidence of Emergent Fungal Infections During the Study (Investigator Assessment)

Parameter Variable	**Micafungin 100 mg (n = 199)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 192)**
During Study (Overall)			
Incidence of Emergent Infection	8/199 (4.0%)	14/202 (6.9%)	13/192 (6.8%)
Treatment Difference†	-2.8%	0.2%	
[95% CI]‡	[-7.2%, 1.6%]	[-5.0%, 4.8%]	
During Blinded Therapy			
Incidence of Emergent Infection	4/199 (2.0%)	7/202 (3.5%)	9/192 (4.7%)
Treatment Difference†	-2.7%	-1.2%	
[95% CI]‡	[-6.1%, 0.9%]	[-5.3%, 2.5%]	
During Protocol-Defined Oral Fluconazole Therapy§			
Incidence of Emergent Infection	1/41 (2.4%)	0/30	0/40
Treatment Difference†	2.4%	0.0%	
[95% CI]‡	[-2.2%, 7.0%]	[0.0%, 0.0%]	
2 Weeks Posttreatment§			
Incidence of Emergent Infection	1/155 (0.6%)	4/152 (2.6%)	3/141 (2.1%)
Treatment Difference†	-1.5%	0.5%	
[95% CI]‡	[-3.9%, 0.7%]	[-2.8%, 3.6%]	
6 Weeks Posttreatment§			
Incidence of Emergent Infection	2/126 (1.6%)	2/114 (1.8%)	1/114 (0.9%)
Treatment Difference†	0.7%	0.9%	
[95% CI]‡	[-2.0%, 3.2%]	[-2.2%, 3.7%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

Prior to analysis, an evaluation was treated as "no emergent fungal infection" if it was not done and the subsequent evaluation was assessed as "no emergent fungal infection" or the patient subsequently died without any documented emergent fungal infection. Patients who did not have a posttreatment evaluation (not done or n/a) were excluded from the analysis. Patients who were counted as having an emergent fungal infection at a prior visit/period were not included in the analysis.

Patient Number [redacted] (micafungin 150 mg) had an emergent fungal infection during the study that was noted outside the windows for the treatment periods/posttreatment visits but was included "overall".

CI: Confidence interval.

† Micafungin minus caspofungin.

‡ Based on the Cochran-Mantel-Haenszel method controlling for region and APACHE II score.

§ Patients who had an emergent fungal infection at a previous visit were not included in the analysis.

Source: Table 12.5.5.1.

Synopsis Table 8: Incidence of Relapse During the Posttreatment Period for Patients with Treatment Success at the End of Blinded Therapy (Investigator Assessment – Excluding Missing Values)

Parameter Variable	Micafungin 100 mg (n = 147)	Micafungin 150 mg (n = 142)	Caspofungin (n = 137)
Week 2 Visit§			
Relapse	31/136 (22.8%)	27/132 (20.5%)	28/124 (22.6%)
Relapsed	3/136 (2.2%)	1/132 (0.8%)	1/124 (0.8%)
Received Antifungal Medication	14/136 (10.3%)	12/132 (9.1%)	16/124 (12.9%)
Died	14/136 (10.3%)	14/132 (10.6%)	11/124 (8.9%)
Comparison of Relapse Rates			
Treatment difference†	0.2%	-2.1%	
95% CI‡	[-10.3%, 9.7%]	[-14.4%, 5.2%]	
Week 6 Visit§			
Relapse	9/99 (9.1%)	8/97 (8.2%)	7/88 (8.0%)
Relapsed	2/99 (2.0%)	2/97 (2.1%)	2/88 (2.3%)
Received Antifungal Medication	3/99 (3.0%)	0/97	0/88
Died	4/99 (4.0%)	6/97 (6.2%)	5/88 (5.7%)
Comparison of Relapse Rates			
Treatment difference†	1.1%	0.3%	
95% CI‡	[-6.9%, 8.8%]	[-8.8%, 7.4%]	
Through Week 6¶			
Relapse	40/130 (30.8%)	38/127 (29.9%)	36/117 (30.8%)
Relapsed	5/130 (3.8%)	3/127 (2.4%)	4/117 (3.4%)
Received Antifungal Medication	17/130 (13.1%)	13/127 (10.2%)	16/117 (13.7%)
Died	18/130 (13.8%)	22/127 (17.3%)	16/117 (13.7%)
Comparison of Relapse Rates			
Treatment difference†	0.0%	-0.8%	
95% CI‡	[-11.3%, 11.0%]	[-14.3%, 8.5%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

An evaluation was treated as "no relapse" if it was not done, the subsequent evaluation was assessed as "no relapse", and the patient did not die or receive any systemic antifungal medication for treatment or empirical use other than for an emergent fungal infection during or prior to the posttreatment window.

Patient Number [redacted] (caspofungin) was counted as a failure for having received antifungal medication for treatment (amphotericin B on day 52) but had a culture-confirmed relapse on day 56.

Week 2 visit window: (Last dose day + 2 days) – (Last dose day + 21 days).

Week 6 visit window: (Last dose day + 22 days) – (Last dose day + 49 days).

CI: Confidence interval.

Excluding missing values: Patients who did not have an evaluation (not done or n/a) were excluded from the analysis.

† Micafungin minus caspofungin.

‡ Based on the Cochran-Mantel-Haenszel method controlling for duration of protocol-defined oral fluconazole use following the switch from blinded therapy (< 2 days, ≥ 2 days).

§ Patients who were not counted as a relapse at a prior visit/period were excluded from the analysis.

¶ Patients who were not counted as a relapse at any visit/period and did not have an assessment at week 6 were excluded from the analysis.

Source: Table 12.5.6.1.1, Appendices 13.4.3.3.3 and 13.4.9.1.

Synopsis Table 9: Incidence of Common Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug

MedDRA v 5.0 System Organ Class Preferred Term	**Micafungin 100 mg (n = 200)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 193)**
All Systems			
Any Adverse Event	183 (91.5%)	187 (92.6%)	171 (88.6%)
Gastrointestinal Disorders			
Diarrhoea NOS	15 (7.5%)	26 (12.9%)	14 (7.3%)
Nausea	19 (9.5%)	15 (7.4%)	20 (10.4%)
Vomiting NOS	18 (9.0%)	15 (7.4%)	16 (8.3%)
Constipation	11 (5.5%)	6 (3.0%)	11 (5.7%)
Abdominal Pain NOS	5 (2.5%)	4 (2.0%)	10 (5.2%)
Metabolism and Nutrition Disorders			
Hypokalaemia	28 (14.0%)	34 (16.8%)	28 (14.5%)
Hypomagnesaemia	11 (5.5%)	17 (8.4%)	14 (7.3%)
Hypoglyceamia NOS	12 (6.0%)	14 (6.9%)	9 (4.7%)
Hypernatraemia	8 (4.0%)	13 (6.4%)	8 (4.1%)
Hyperkalaemia	10 (5.0%)	8 (4.0%)	5 (2.6%)
Infections and Infestations			
Bacteraemia	10 (5.0%)	18 (8.9%)	11 (5.7%)
Septic Shock	15 (7.5%)	9 (4.5%)	9 (4.7%)
Sepsis NOS	11 (5.5%)	10 (5.0%)	11 (5.7%)
Pneumonia NOS	3 (1.5%)	11 (5.4%)	4 (2.1%)
General Disorders and Administration Site Conditions			
Pyrexia	14 (7.0%)	22 (10.9%)	15 (7.8%)
Oedema Peripheral	11 (5.5%)	12 (5.9%)	14 (7.3%)
Vascular Disorders			
Hypotension NOS	20 (10.0%)	12 (5.9%)	15 (7.8%)
Hypertension NOS	6 (3.0%)	10 (5.0%)	12 (6.2%)
Investigations			
Blood Alkaline Phosphatase NOS Increased	11 (5.5%)	16 (7.9%)	8 (4.1%)
Blood and Lymphatic System Disorders			
Thrombocytopenia	8 (4.0%)	8 (4.0%)	11 (5.7%)
Anaemia NOS	5 (2.5%)	6 (3.0%)	13 (6.7%)
Anaemia NOS Aggravated	4 (2.0%)	10 (5.0%)	5 (2.6%)
Cardiac Disorders			
Tachycardia NOS	6 (3.0%)	7 (3.5%)	13 (6.7%)
Bradycardia NOS	5 (2.5%)	10 (5.0%)	8 (4.1%)
Atrial Fibrillation	5 (2.5%)	10 (5.0%)	0
Nervous System Disorders			
Headache NOS	4 (2.0%)	10 (5.0%)	11 (5.7%)
Skin and Subcutaneous Tissue Disorders			
Decubitus Ulcer	9 (4.5%)	12 (5.9%)	9 (4.7%)
Psychiatric Disorders			
Insomnia	11 (5.5%)	8 (4.0%)	16 (8.3%)

Patient base: Safety set; all randomized patients who received at least one dose of blinded study drug.

Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%.

Treatment-emergent: Any time from first dose day of blinded study drug through last dose day of blinded study drug + 3 days. Common: Incidence ≥ 5% in any treatment group. NOS: Not otherwise specified.

Source: Table 12.6.1.1.

Synopsis Table 10: Incidence of Common Treatment-Emergent Adverse Events Related to Blinded Study Drug

MedDRA v 5.0 System Organ Class Preferred Term	**Micafungin 100 mg (n = 200)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 193)**
All Systems			
Any Adverse Event	44 (22.0%)	46 (22.8%)	46 (23.8%)
Investigations			
Blood Alkaline Phosphatase NOS Increased	7 (3.5%)	11 (5.4%)	5 (2.6%)
Liver Function Tests NOS Abnormal	5 (2.5%)	2 (1.0%)	1 (0.5%)
Alanine Aminotransferase Increased	1 (0.5%)	2 (1.0%)	3 (1.6%)
Gamma-Glutamyltransferase Increased	0	1 (0.5%)	2 (1.0%)
Blood Potassium Decreased	0	2 (1.0%)	0
Gastrointestinal Disorders			
Nausea	2 (1.0%)	1 (0.5%)	5 (2.6%)
Vomiting NOS	3 (1.5%)	2 (1.0%)	3 (1.6%)
Diarrhoea NOS	3 (1.5%)	1 (0.5%)	2 (1.0%)
Constipation	0	0	4 (2.1%)
Metabolism and Nutrition Disorders			
Hypokalaemia	4 (2.0%)	5 (2.5%)	3 (1.6%)
Hypomagneasaemia	1 (0.5%)	1 (0.5%)	2 (1.0%)
Skin and Subcutaneous Tissue Disorders			
Rash NOS	2 (1.0%)	3 (1.5%)	5 (2.6%)
Pruritus NOS	1 (0.5%)	0	2 (1.0%)
Erythema	0	2 (1.0%)	0
General Disorders and Administration Site Conditions			
Oedema Peripheral	2 (1.0%)	2 (1.0%)	1 (0.5%)
Rigors	1 (0.5%)	2 (1.0%)	1 (0.5%)
Pyrexia	2 (1.0%)	0	1 (0.5%)
Hepatobiliary Disorders			
Hepatic Failure	1 (0.5%)	2 (1.0%)	1 (0.5%)
Hyperbilirubinaemia	3 (1.5%)	0	1 (0.5%)
Blood and Lymphatic System Disorders			
Thrombocytopenia	1 (0.5%)	1 (0.5%)	3 (1.6%)
Thrombocythaemia	1 (0.5%)	1 (0.5%)	2 (1.0%)
Nervous System Disorders			
Headache NOS	1 (0.5%)	2 (1.0%)	2 (1.0%)
Convulsions NOS	0	2 (1.0%)	0
Vascular Disorders			
Phlebitis NOS	0	0	2 (1.0%)
Infections and Infestations			
Colitis Pseudomembranous	2 (1.0%)	0	0

Patient base: Safety set; all randomized patients who received at least one dose of blinded study drug.

Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%.

Treatment-emergent: Any time from first dose day of blinded study drug through last dose day of blinded study drug + 3 days. Common: Incidence ≥ 1% in any treatment group. Related: Considered by the investigator to have a possible, probable, or definite relationship to blinded study drug. NOS: Not otherwise specified.

Source: Table 12.6.1.2.

Synopsis Table 11: Incidence of Mortality

Parameter	Micafungin 100 mg (n = 200)	Micafungin 150 mg (n = 202)	Caspofungin (n = 193)
Died During the Study	58 (29.0%)	67 (33.2%)	51 (26.4%)
Died During Blinded Therapy	28 (14.0%)	30 (14.9%)	27 (14.0%)
Died During Oral Fluconazole Treatment	0	2 (1.0%)	0
Died During Any Protocol-Defined Treatment	28 (14.0%)	32 (15.8%)	27 (14.0%)
Died During Posttreatment Period	30 (15.0%)	35 (17.3%)	24 (12.4%)
Death Related to Fungal Infection	7 (3.5%)	9 (4.5%)	7 (3.6%)
Death Related to Study Drug			
Definite	0	0	0
Probable	0	0	0
Possible	0	0	0
Unlikely	8 (4.0%)	15 (7.4%)	7 (3.6%)
No Relationship	50 (25.0%)	53 (26.2%)	44 (22.8%)

Patient base: Safety set; all randomized patients who received at least one dose of blinded study drug. Table does not include the one patient in the micafungin 150 mg treatment group (Patient Number [redacted] who died after the final assessment (post-study) and was included in the database.

During Blinded Therapy: From first dose day of blinded study drug to last dose day of blinded study drug + 1 day.

During Oral Fluconazole Treatment: From last dose day of blinded study drug + 2 days or first dose day of protocol-defined oral fluconazole (whichever was later) to last dose day of protocol-defined oral fluconazole + 1 day.

During Any Protocol-Defined Treatment: From first dose day of blinded study drug to last dose day of blinded study drug or last dose day of protocol-defined oral fluconazole (whichever was later) + 1 day.

During Posttreatment Period: From last dose day of protocol-defined treatment + 2 days to the day the final assessment was performed.

Related to Study Drug: Causal relationship to study drug, as assessed by the investigator.

Sources: Table 12.6.5.1 and Appendix 13.4.1.1.

Synopsis Table 12: Incidence of Common Treatment-Emergent Serious Adverse Events Without an Outcome Death

MedDRA v 5.0 System Organ Class Preferred Term	**Micafungin 100 mg (n = 200)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 193)**
All Systems			
Any Adverse Event	36 (18.0%)	45 (22.3%)	33 (17.1%)
Infections and Infestations			
Septic Shock	5 (2.5%)	1 (0.5%)	1 (0.5%)
Sepsis NOS	2 (1.0%)	2 (1.0%)	2 (1.0%)
Bacterial Sepsis	1 (0.5%)	2 (1.0%)	1 (0.5%)
Pneumonia Aggravated	0	2 (1.0%)	0
Respiratory, Thoracic, and Mediastinal Disorders			
Respiratory Failure	2 (1.0%)	4 (2.0%)	3 (1.6%)
Acute Respiratory Distress Syndrome	1 (0.5%)	0	2 (1.0%)
Respiratory Distress	0	1 (0.5%)	2 (1.0%)
Hypoxia	0	2 (1.0%)	0
Cardiac Disorders			
Acute Pulmonary Oedema	0	1 (0.5%)	2 (1.0%)
Cardiac Failure Congestive	0	2 (1.0%)	0
Pulmonary Oedema NOS	0	2 (1.0%)	0
Gastrointestinal Disorders			
Peritonitis	2 (1.0%)	2 (1.0%)	0
Gastrointestinal Haemorrhage NOS	0	3 (1.5%)	0
Blood and Lymphatic System Disorders			
Thrombocytopenia	1 (0.5%)	0	3 (1.6%)
Renal and Urinary Disorders			
Renal Failure NOS	1 (0.5%)	2 (1.0%)	1 (0.5%)
Renal Impairment NOS	2 (1.0%)	1 (0.5%)	1 (0.5%)
Vascular Disorders			
Hypotension NOS	2 (1.0%)	2 (1.0%)	0
Nervous System Disorders			
Convulsions NOS	0	2 (1.0%)	0
Metabolism and Nutrition Disorders			
General Nutrition Disorder	2 (1.0%)	0	0
Metabolic Acidosis NOS Exacerbated	2 (1.0%)	0	0
Investigations			
Liver Function Tests NOS Abnormal	3 (1.5%)	1 (0.5%)	0
Hepatobiliary Disorders			
Hepatic Failure	0	1 (0.5%)	2 (1.0%)

Patient base: Safety set; all randomized patients who received at least one dose of blinded study drug.

Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%.

Common: Incidence ≥ 1% in any treatment group. Treatment-emergent: Any time from first dose day of blinded study drug through last dose day of blinded study drug + 3 days.

NOS: Not otherwise specified.

Source: Table 12.6.2.3.

Synopsis Table 13: Incidence of Common Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug

MedDRA v 5.0 System Organ Class Preferred Term	**Micafungin 100 mg (n = 200)**	**Micafungin 150 mg (n = 202)**	**Caspofungin (n = 193)**
All Systems			
Any Adverse Event	33 (16.5%)	37 (18.3%)	29 (15.0%)
Infections and Infestations			
Septic Shock	8 (4.0%)	6 (3.0%)	7 (3.6%)
Sepsis NOS	2 (1.0%)	2 (1.0%)	2 (1.0%)
Bacterial Sepsis	1 (0.5%)	3 (1.5%)	1 (0.5%)
Respiratory, Thoracic, and Mediastinal Disorders			
Respiratory Failure	3 (1.5%)	1 (0.5%)	2 (1.0%)
Acute Respiratory Distress Syndrome	2 (1.0%)	0	0
Respiratory Arrest	2 (1.0%)	0	0
Cardiac Disorders			
Cardiac Arrest	0	2 (1.0%)	2 (1.0%)
Cardio-Respiratory Arrest	1 (0.5%)	2 (1.0%)	0
Acute Myocardial Infarction	2 (1.0%)	0	0
Nervous System Disorders			
Convulsions NOS	0	2 (1.0%)	0
Hepatobiliary Disorders			
Hepatic Failure	0	2 (1.0%)	1 (0.5%)
Blood and Lymphatic System Disorders			
Leukopenia NOS	0	2 (1.0%)	0
Vascular Disorders			
Hypotension NOS	0	0	2 (1.0%)
Investigations			
Liver Function Tests NOS Abnormal	2 (1.0%)	0	0
Skin and Subcutaneous Tissue Disorders			
Rash NOS	0	0	2 (1.0%)

Patient base: Safety set; all randomized patients who received at least one dose of blinded study drug.

Common: Incidence ≥ 1% in any treatment group.

NOS: Not otherwise specified.

Source: Table 12.6.3.1.