

# Micafungin versus Fluconazole for Prophylaxis against Invasive Fungal Infections during Neutropenia in Patients Undergoing Hematopoietic Stem Cell Transplantation

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We hypothesized that chemoprophylaxis with the echinocandin micafungin would be an effective agent for antifungal prophylaxis during neutropenia in patients undergoing hematopoietic stem cell transplantation (HSCT). We therefore conducted a randomized, double-blind, multi-institutional, comparative phase III trial, involving 882 adult and pediatric patients, of 50 mg of micafungin (1 mg/kg for patients weighing <50 kg) and 400 mg of fluconazole (8 mg/kg for patients weighing <50 kg) administered once per day. Success was defined as the absence of suspected, proven, or probable invasive fungal infection (IFI) through the end of therapy and as the absence of proven or probable IFI through the end of the 4-week period after treatment. The overall efficacy of micafungin was superior to that of fluconazole as antifungal prophylaxis during the neutropenic phase after HSCT (80.0% in the micafungin arm vs. 73.5% in the fluconazole arm [difference, 6.5%]; 95% confidence interval, 0.9%–12%;  $P = .03$ ). This randomized trial demonstrates the efficacy of an echinocandin for antifungal prophylaxis in neutropenic patients.

Hematopoietic stem cell transplantation (HSCT) is associated with a high risk of invasive fungal infection due to *Candida* and *Aspergillus* species. The risk of infection is associated with the degree and duration of neutropenia, the disruption of protective skin and mucosal surface barriers, and the use of corticosteroids. Fluconazole, the only antifungal agent approved in the United States for chemoprophylaxis during HSCT, has been widely used as an antifungal prophylactic agent [1–4]. In the 2 largest multicenter trials involving adult

bone marrow transplant recipients, fluconazole was associated with a significant reduction in the frequency of invasive candidiasis, compared with placebo [1, 2]. However, fluconazole does not protect patients from invasive aspergillosis [5, 6].

Echinocandins are a novel class of antifungal agents with antifungal activity against *Candida* and *Aspergillus* species and *Pneumocystis carinii* [7–9]. These compounds interrupt biosynthesis of  $\beta$ -1,3-glucan linkages, an essential component of the fungal cell wall [10, 11]. There is little human toxicity attributed to the mechanism of action, because glucan polymers are not components of mammalian cells. We therefore hypothesized that an echinocandin would be a safe and effective alternative to fluconazole as antifungal prophylaxis with broader-spectrum activity against invasive aspergillosis during neutropenia. To test this hypothesis, we conducted a randomized, double-blind, multicenter clin-

Received 16 August 2003; accepted 9 March 2004; electronically published 27 October 2004.

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**Clinical Infectious Diseases** 2004;39:1407–16

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1058-4838/2004/3910-0001\$15.00

ical trial that compared the echinocandin micafungin (FK463) with fluconazole for prevention of invasive fungal infections during the neutropenic phase of HSCT.

## METHODS

### Participants

Eligible patients were those who were required to receive an allogeneic HSCT, for any indication, or an autologous HSCT, for hematological malignancy. Patients also were required to be at least 6 months of age and free of deeply invasive fungal disease at the time of enrollment. They could not have received systemic antifungal therapy within 72 h before administration of the first dose of study drug. Patients were free of liver disease, as defined by serum aminotransferase levels  $<5$  times the upper limit of normal or by bilirubin levels  $<2.5$  times the upper limit of normal. Study procedures were reviewed and approved by institutional review boards at each of the study centers prior to patient enrollment. Written informed consent was obtained from each patient or guardian prior to randomization. Patients were excluded if they were receiving an autologous transplant for nonhematological malignancies or if they were known to have a history of anaphylaxis attributable to azole or echinocandin compounds.

### Interventions

The study was a prospective, randomized, double-blind comparative trial of micafungin and fluconazole administered during the neutropenic (i.e., pre-engraftment) phase of HSCT. Patients received 50 mg of micafungin (1 mg/kg for patients weighing  $<50$  kg) or 400 mg of fluconazole (8 mg/kg for patients weighing  $<50$  kg) once daily as a 1-h infusion. Randomized treatment was initiated within 48 h of the beginning of the transplant-related conditioning regimen. Outpatient administration of study treatment was permitted. To maintain the blind, all patients received the daily infusion intravenously, in a volume of 200 mL over 1 h, from an infusion set covered by an opaque bag. For patients weighing  $<50$  kg, a volume of 4 mL/kg was infused. Patients who developed a creatinine clearance rate of  $\leq 50$  mL/min had an adjustment of the volume of blinded study drug that reduced the fluconazole dose but maintained the micafungin dose.

Patients were to receive the assigned treatment until the earliest of the following:  $\leq 5$  days after engraftment (defined as an absolute neutrophil count of  $\geq 500$  cells/mm<sup>3</sup> after the nadir absolute count); treatment day 42 after HSCT; development of proven, probable, or suspected invasive fungal infection; development of unacceptable drug toxicity; death; withdrawal from study participation (patient's decision); or discontinuation of study treatment (investigator's decision).

### Objectives

The objectives of this study were to compare the noninferiority of micafungin with fluconazole over a difference of 10% and to then assess the superiority of micafungin as antifungal prophylaxis in the neutropenic phase after HSCT.

### Outcomes

The primary end point was treatment success, which was defined as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylaxis therapy and as the absence of a proven or probable systemic fungal infection through the end of the 4-week posttreatment period. The rate of treatment success was calculated as the ratio of the total number of treatment successes to the total number of patients across all strata (defined below in the subsection Sequence generation) who were treated.

Proven infection was defined as biopsy-proven invasive or disseminated infection. Sinus or pulmonary infection with *Aspergillus*, *Fusarium*, or *Zygomycetes* organisms also was considered to be proven if results of cultures of specimens obtained from the respiratory tract were positive in conjunction with compatible diagnostic imaging findings. Patients were deemed to have probable pulmonary aspergillosis if lower respiratory tract diagnostic studies revealed fungal elements in conjunction with compatible clinical and radiographic findings. These criteria for proven and probable infection are consistent with those for invasive fungal infection described by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer, National Institute of Allergy and Infectious Diseases Mycoses Study Group [12]. Fungal infection was defined as suspected if fevers (temperature,  $\geq 38^{\circ}\text{C}$  [ $\geq 100.4^{\circ}\text{F}$ ]) persisted for  $>96$  h during the neutropenic phase, despite broad-spectrum antibacterial therapy, and led to the initiation of empirical antifungal therapy.

The use of systemic antifungal agents for treatment of suspected fungal infections, the frequency of proven or probable fungal infections throughout the posttreatment period, and the pathogen-based frequency of proven infections were analyzed as secondary efficacy variables. Other secondary outcome measurements included the frequency of superficial fungal infection, the frequency of fungal colonization, the time to treatment failure, the time to suspected fungal infection, and mortality. Safety analyses included adverse events, results of clinical laboratory tests, and vital signs. Laboratory-based hematological and serum chemistry analyses and fungal surveillance cultures were performed at the study sites at baseline, at least twice weekly while study drugs were administered, and on the final day of therapy.

## Sample Size

The sample size estimation was based on the primary end point, which was treatment success at the end of study. On the basis of prior multicenter, randomized prophylactic trials with fluconazole in adult bone marrow transplant recipients [1, 2], the most frequent reason for therapy failure was the use of empirical systemic antifungal agents in 50%–60% of the patients. Therefore, the rate of treatment success for fluconazole was estimated to be 40%. On the basis of this assumption and a 1-sided, large-sample, normal-approximation noninferiority test with a statistical significance of 2.5% [13], 400 patients per treatment group would provide  $\geq 80\%$  power and a type I error of 0.05 over a difference in treatment success of 10%.

In accordance with standards of good clinical practice, adverse events that occurred up to 72 h after the administration of the final dose of study drug were captured on report forms. A data safety monitoring board reviewed all serious adverse event reports on a monthly basis during the study. Because patient enrollment occurred faster than expected, a planned interim analysis of efficacy and safety data was not performed.

## Randomization

**Sequence generation.** Patients providing informed consent were randomly assigned to receive micafungin or fluconazole using a 1:1 schedule. Randomization was stratified according to age (6 months to 12 years and  $\geq 13$  years), study center, and type of transplant (autologous, matched-sibling allogeneic, or matched unrelated donor). Patients receiving an allogeneic transplant were further stratified according to risk of transplant-related mortality. High-risk allogeneic transplant criteria included acute leukemia in relapse or in complete remission for at least the third time, chronic myelogenous leukemia in other than the first chronic phase, Hodgkin lymphoma or non-Hodgkin lymphoma in relapse or greater than or equal to the second complete or partial remission, myelodysplastic syndrome, myeloproliferative syndrome, breast cancer in relapse or greater than or equal to the second complete or partial remission, ovarian carcinoma, peripheral neuroectodermal tumor, sarcoma, immunodeficiency disease, inborn metabolic errors, and familial erythrophagocytic disorders.

**Concealment and implementation of patient randomization.** Pharmacists involved in the investigation randomized the patients via an interactive central telephone service. The randomization schedule was generated by the Research Data Operations Department of Fujisawa Healthcare.

## Blinding

Hospital staff at study centers and all nonpharmacist study staff involved in the investigation were blinded to the randomized drug assignment. Twelve patients were unblinded during

the study. The unblinding occurred prior to the assessment of efficacy for only 1 patient, who was then excluded from the efficacy analysis.

## Statistical Methods

Patients who received at least 1 dose of study treatment were included in the modified intent-to-treat (MITT) analysis group. Patients who received at least 7 doses of study drug and had no major protocol violations constituted the efficacy-evaluable group. Primary and secondary end points were examined for the MITT group and the evaluable group. Breakthrough invasive fungal infections that were determined by investigators to be proven or probable were reviewed in a blinded manner by means of predetermined protocol criteria.

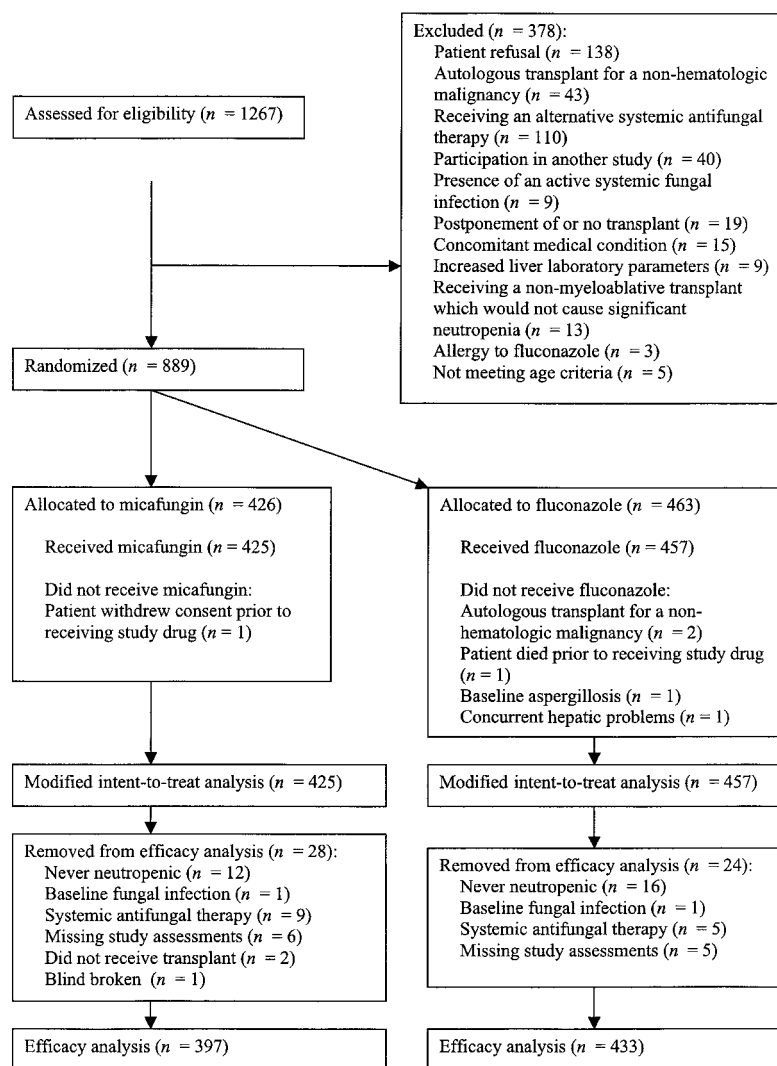
For the primary analysis of treatment success, micafungin was considered not to be statistically inferior to fluconazole if the 95% lower confidence bound on the difference in success rates between micafungin and fluconazole was more than  $-10\%$  and was considered to be statistically superior if the lower confidence bound was  $>0\%$ . A secondary analysis of the primary end point was performed by the Cochran-Mantel-Haenszel test, adjusting for study center and strata. A treatment-by-study center interaction was assessed using the Breslow-Day test for homogeneity of ORs.

For all secondary end points, except for time of treatment failure, the treatment arms were compared using the Cochran-Mantel-Haenszel  $\chi^2$  test or Fisher's exact test for analysis of proportions, when appropriate (i.e., depending on the numbers per cell in the  $2 \times 2$  analysis). Time to treatment failure and time to suspected fungal infection were analyzed using the log rank test and Cox's proportional hazards models. All comparisons were 2-sided, with a significance level of 5%. All data were reviewed and analyzed by the MSG Central Biostatistics Unit (University of Alabama, Birmingham).

## RESULTS

From 13 November 1999 to 12 December 2000, 1267 patients at 72 study centers were screened for eligibility, and 889 patients were enrolled. A total of 882 patients (425 in the micafungin arm and 457 in the fluconazole arm) received at least 1 dose of study drug at the beginning of the neutropenic or pre-engraftment phase of HSCT; data from these patients were used to determine the primary end point in the MITT analysis set. Reasons for ineligibility during study recruitment and for non-receipt of allocated study treatment are outlined in figure 1. Two patients in the MITT analysis, both of whom were in the micafungin arm, received study drug but never underwent HSCT.

The rates of therapeutic response for patients in the MITT analysis paralleled those for patients in the evaluable analysis.



**Figure 1.** Flow diagram of the progress of the study. Eight participants did not complete the study protocol (7 withdrew consent and 1 was not compliant with the protocol). Eight participants (5 in the micafungin arm and 3 in the fluconazole arm) inadvertently received the wrong study drug or dose during the course of study.

Thus, results of the MITT analysis alone are presented throughout the remainder of this report.

**Demographic characteristics.** The 2 treatment groups were similar with regard to age, sex, race, weight, underlying disease, and risk of transplant-related mortality (table 1). The 2 treatment arms also were similarly balanced with respect to the proportion of patients who developed and then recovered from neutropenia, the median time to neutrophil recovery, the median time to a second HSCT, the number of patients who developed graft-versus-host disease, and the use of hematopoietic growth factors. The median duration of therapy was 18 days for adult patients overall and was similarly balanced in both study arms for patient subgroups.

**Treatment outcome.** The overall treatment success rate for patients in the micafungin arm was significantly higher than

that for patients in the fluconazole arm (80.0% vs. 73.5%; absolute difference, +6.5%; 95% CI, 0.9%–12%;  $P = .03$ ). The Kaplan-Meier estimate of treatment success also was greater in the micafungin group than in the fluconazole group ( $P = .025$ , by the log rank test;  $P = .026$ , by the Cochran-Mantel-Haenszel test for pooled centers) (figure 2). This treatment difference was consistent in all subgroups of patients (table 2).

**Breakthrough infections.** There were 6 breakthrough infections due to *Candida* species recovered from the bloodstream. Three micafungin-treated patients had candidemia due to *Candida lusitanae*, *Candida albicans*, and *Candida parapsilosis* during prophylactic treatment, whereas a fourth patient had candidemia due to *Candida glabrata* during the posttreatment follow-up period (table 3). The micafungin dosages for these patients were comparable with the overall mean dosage

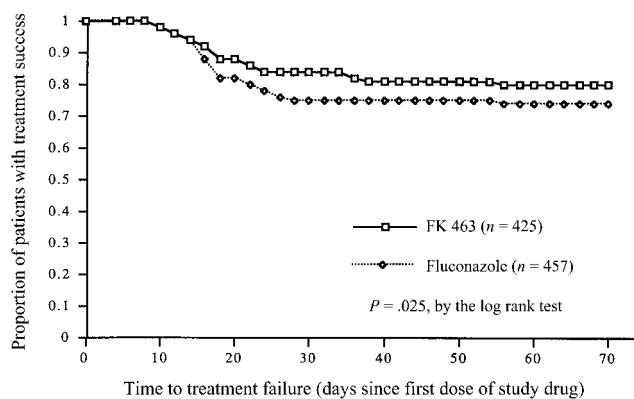
**Table 1. Demographic and clinical characteristics of study subjects.**

Characteristic	Micafungin group	Fluconazole group <sup>a</sup>	P
Male sex	253/425 (59.5)	274/457 (60.0)	.897
Race			.560
White	387/425 (91.1)	411/457 (89.9)	
Black	30/425 (7.1)	37/457 (8.1)	
Other	8/425 (1.9)	9/457 (2.0)	
Age, years			.735
Pediatric subjects: <16	39/425 (9.2)	45/457 (9.8)	
Adult subjects			
16–64	353/425 (83.0)	389/457 (85.1)	
>64	33/425 (7.8)	23/457 (5.0)	
Mean (range)	43.2 (0.6–73.0)	41.9 (0.6–71.0)	.238
Weight, mean kg (range)	75.6 (5.9–149.7)	77.2 (6.1–172.7)	.335
Underlying disease			
Active	178/425 (41.9)	187/457 (40.9)	
Adult subjects			.660
Non-Hodgkin lymphoma	104/386 (26.9)	104/412 (25.2)	
Multiple myeloma	83/386 (21.5)	90/412 (21.8)	
Acute myelogenous leukemia	46/386 (11.9)	62/412 (15.0)	
Chronic myelogenous leukemia	48/386 (12.4)	54/412 (13.1)	
Pediatric subjects			.231
Acute lymphocytic leukemia	15/39 (38.5)	11/45 (24.4)	
Acute myelogenous leukemia	7/39 (17.9)	12/45 (26.7)	
Transplant type			
Syngeneic or autologous	203/425 (47.8)	201/457 (44.0)	
Allogeneic, by mortality risk	220/425 (51.8)	256/457 (56.0)	
High	127/425 (29.9)	152/457 (33.3)	
Low	94/425 (22.1)	104/457 (22.8)	
Stem cell source			
Bone marrow	112/425 (26.4)	132/457 (28.9)	
Peripheral blood	297/425 (69.9)	309/457 (67.6)	
Cord blood	14/425 (3.3)	16/457 (3.5)	
Neutrophil recovery			
Achieved	407/425 (95.8)	432/457 (94.5)	.395
Interval between engraftment and recovery, median days (range)	13 (3–54)	13 (7–44)	.792
Study treatment			
Completed	319/425 (75.1)	310/457 (67.8)	
Duration, mean days			
All patients (range)	19.2 (1–51)	18.7 (1–51)	
Adult subjects			
Autologous/syngeneic	16.8	16.2	
Allogeneic	21.6	20.7	
Pediatric subjects, allogeneic/autologous	23.2	23.4	
Growth factor receipt			
During treatment	326/425 (76.7)	340/457 (74.4)	.426
Duration, mean days (range)	9.4 (1–33)	9.2 (1–44)	.490
Graft-versus-host disease			
Present	96/425 (22.6)	102/457 (22.3)	.924
Interval between transplantation and onset, median days (range)	20 (3–49)	20 (1–66)	.327
Second stem cell transplant			
Received	9/425 (2.1)	11/457 (2.4)	.773
Interval between first and second transplantation, mean days (range)	34 (15–65)	22 (1–52)	.471

**NOTE.** Data are no. of subjects/total no. evaluated (%), unless otherwise indicated.

<sup>a</sup> The dosage of fluconazole was adjusted for 5.3% of fluconazole-treated patients because of renal insufficiency. No fluconazole-treated patients underwent dialysis.





**Figure 2.** Modified intent-to-treat analysis (i.e., patients received at least 1 dose of study drug) showing Kaplan-Meier estimates of the proportion of patients who received micafungin (FK 463) or fluconazole and experienced treatment success, by time after initiation of study therapy. Two patients who had a systemic fungal infection in the 72 h before receiving study drug were excluded from the analysis. Time to treatment success was superior for the micafungin recipients ( $P = .025$ , by the log-rank test;  $P = .026$ , by the Cochran-Mantel-Haenszel test for pooled centers). There was no significant treatment-by-study center interaction ( $P = .26$ ).

of  $0.70 \pm 0.16$  mg/kg per day for all micafungin-treated patients. Two fluconazole-treated patients had candidemia due to *Candida krusei* and *C. parapsilosis* during prophylactic treatment.

There was 1 case of probable breakthrough aspergillosis among patients treated with micafungin and 7 cases (4 proven and 3 probable) among patients treated with fluconazole ( $P = .071$ ). There was 1 case of fusariosis among patients treated with micafungin and 2 cases among those who received fluconazole. The only episode of zygomycosis occurred in a patient treated with micafungin.

**Use of empirical therapy.** A total of 64 (15.1%) of 425 patients in the micafungin arm and 98 (21.4%) of 457 patients in the fluconazole arm received empirical antifungal therapy ( $P = .024$ ). Twenty-three patients had minor protocol deviations, in that empirical therapy was instituted after 72 h of fever, rather than after 96 h of fever. Seventeen patients (9 in the micafungin arm and 8 in the fluconazole arm) who received empirical therapy were judged to have substantial protocol deviations. Three patients did not have fever that reached a temperature of at least  $38^{\circ}\text{C}$ , 6 patients were no longer neutropenic, and 8 patients had fever for  $<72$  h.

**Colonization.** Oropharyngeal colonization was similar at baseline, with *C. albicans* and *C. glabrata* accounting for the majority of isolates in both the micafungin arm (71.3% and 10.4%, respectively) and the fluconazole arm (60.1% and 13.0%, respectively). During treatment, *C. albicans* was recovered from any site from 55.1% of micafungin-treated patients and 30.2% of fluconazole-treated patients, whereas *C. glabrata*

was recovered from any site from 4.9% of micafungin-treated patients and 32.4% of fluconazole-treated patients.

**Mortality.** A total of 18 (4.2%) of 425 micafungin-treated patients and 26 (5.7%) of 457 fluconazole-treated patients died during the study ( $P = .322$ ). None of the deaths were related to the study drug. The median time to death was 29 days in both treatment arms. Three patients died of causes associated with a fungal infection: 1 patient in the micafungin arm died from zygomycosis, and 2 patients in the fluconazole arm died from pulmonary aspergillosis.

**Adverse events.** Fewer micafungin-treated patients discontinued use of the study drug because of an adverse event (4.2% in the micafungin arm and 7.2% in the fluconazole arm;  $P = .058$ ) (table 4). Study drug administration was interrupted because of adverse events for 2.8% of micafungin-treated patients and 2.4% of fluconazole-treated patients. The reasons for interrupting micafungin treatment included abnormal liver function parameters ( $n = 7$ ), rash ( $n = 2$ ), central line catheter leak ( $n = 1$ ), hypervolemia ( $n = 1$ ), and dysrhythmia ( $n = 1$ ). The reasons for interrupting fluconazole treatment included abnormal liver function parameters ( $n = 7$ ), nausea ( $n = 1$ ), coagulation disorder ( $n = 1$ ), fever ( $n = 1$ ), and allergy with dizziness ( $n = 1$ ).

All patients experienced at least 1 adverse event while receiving study drug therapy. A total of 64 micafungin-treated patients (15.1%) and 77 fluconazole-treated patients (16.8%) experienced an adverse event that was considered by the investigator to have some association with the study drug (table 4). There were no significant differences in aminotransferase levels between the 169 patients receiving cyclosporine immunosuppressive therapy concomitantly with micafungin and the 194 patients receiving cyclosporine with fluconazole. There were no significant differences in the frequency of related adverse events between pediatric patients and adult patients. There also were no differences in the frequency of infusion-related adverse events.

## DISCUSSION

This randomized trial demonstrates the efficacy of an echinocandin for prophylaxis in neutropenic hosts. The overall success rate was significantly higher for patients in the micafungin arm (80.0%, compared with 73.5% in the fluconazole arm). This treatment difference was consistently in favor of micafungin across all major patient subgroups. The time to treatment success was significantly shorter for micafungin. Micafungin also was more effective in reducing the need for empirical antifungal therapy. Although both study drugs were effective for preventing candidiasis, there were fewer episodes of aspergillosis among patients receiving micafungin. Micafungin therapy also was at least as safe as fluconazole therapy for adult and pediatric patients.

**Table 2. Treatment success by prespecified demographic and clinical characteristics.**

Characteristic	Micafungin group	Fluconazole group	Difference in treatment success, %
Transplant type			
Syngeneic/autologous	181/203 (89.2)	161/201 (80.1)	+9.1
Allogeneic	157/220 (71.4)	175/256 (68.4)	+3.0
Sex			
Male	203/253 (80.2)	205/274 (74.8)	+5.4
Female	137/172 (79.7)	131/183 (71.6)	+8.1
Age, years			
Pediatric subjects: <16	27/39 (69.2)	24/45 (53.3)	+15.9
Adult subjects			
16–64	313/386 (81.1)	312/412 (75.7)	+5.4
>64	32/33 (97.0)	16/23 (69.6)	+27.4
Graft-versus-host disease			
Present	65/96 (67.7)	58/102 (56.9)	+10.8
Absent	275/329 (83.6)	278/355 (78.3)	+5.3
Fungal colonization at baseline			
Present	211/266 (79.3)	183/241 (75.9)	+3.4
Absent	129/159 (81.1)	153/216 (70.8)	+10.3
Overall	340/425 (80.0)	336/457 (73.5)	+6.5 <sup>a</sup>

**NOTE.** Data are no. of subjects/total no. evaluated (%). Treatment success was defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of prophylactic therapy and as the absence of a proven or probable systemic fungal infection through the end of the 4-week period after treatment.

<sup>a</sup> 95% CI, 0.9%–12.0%.

Micafungin is a member of the novel class of antifungal agents, the echinocandins [8, 9, 14–19]. Killing occurs in the region of active cell growth of the hyphae of *Aspergillus fumigatus* [20]. This unique antifungal effect of echinocandins on *Aspergillus* species poises these agents for optimal prophylactic effect early during hyphal growth. In a persistently neutropenic rabbit model involving pulmonary aspergillosis due to *A. fumigatus*, micafungin-treated animals demonstrated decreased blood vessel invasion, prevention of organism-mediated pulmonary injury, and improved survival, compared with untreated controls [9].

Compatible with the aforementioned preclinical and initial clinical studies, our clinical trial demonstrated that micafungin administered to high-risk neutropenic patients was able to prevent both suspected and proven invasive fungal infections and was superior to fluconazole in overall efficacy. These benefits were observed across all population subgroups, including pediatric patients.

This double-blind trial compared the efficacy and safety of micafungin with that of fluconazole for prevention of invasive fungal infections during neutropenia by means of a design similar to that of the study by Goodman et al. [1]. In that study, systemic fungal infections developed in 28 patients (15.8%) who received placebo, compared with 5 patients (2.8%) who

received fluconazole. Our study describes enrolled neutropenic patients who were at similar risk, as evidenced by deeply invasive fungal infections that developed in 2.4% of patients who also received fluconazole. The study by Goodman et al. [1] and the clinical trial we report also were both designed to study the efficacy of antifungal therapy during neutropenia. Neither study was designed to address prophylaxis during the period after engraftment, which would not be practical for the parenterally administered micafungin.

The emergence of resistance to fluconazole is well known [21]. This study documented an ~8-fold increase in the frequency of *C. glabrata* colonization in the fluconazole arm, compared with the echinocandin arm. Although there was no difference in the frequency of fungemia due to *C. glabrata*, this trend in colonization suggests selective pressure of the triazole that does not occur with the echinocandin. At the same time, there also was an increase of *C. albicans* colonization in the micofungin arm.

Consistent with its pathogen-based specific mechanism of action, excess toxicity associated with micafungin was not greater than that for fluconazole. Further underscoring the safety of the echinocandin, fewer micafungin-treated patients were withdrawn from the study because of an adverse event. Fluconazole interacts with other drugs that are hepatically me-

**Table 3. Frequency of fungal infection and colonization by secondary end points.**

Secondary end point	Study group, no. (%) of subjects		P
	Micafungin group (n = 425)	Fluconazole group (n = 457)	
Occurred during prophylaxis and 4-week posttreatment period			
Breakthrough infections	7 (1.6)	11 (2.4)	.481
Aspergillosis	1 (0.2)	7 (1.5)	.071
Proven	0	4 (0.9)	.126
Probable	1 (0.2)	3 (0.7)	
Candidiasis (all due to candidemia) <sup>a</sup>	4 (0.9)	2 (0.4)	.436
Fusariosis	1 (0.2)	2 (0.4)	
Zygomycosis	1 (0.2)	0	
Suspected fungal infection <sup>b</sup>	64 (15.1)	98 (21.4)	.024
Colonization	266 (62.6)	241 (52.7)	.003
Treatment failure <sup>c</sup>	78	112	.026
Colonization during prophylaxis only			
<i>Candida albicans</i>	136 (32.0)	49 (10.7)	<.001
<i>Candida glabrata</i>	19 (4.5)	62 (13.6)	<.001
<i>Candida parapsilosis</i>	17 (4.0)	5 (1.1)	.003
Other <i>Candida</i> species <sup>d</sup>	51 (12.0)	41 (9.0)	
Total	223 (52.3)	155 (33.9)	<.001
Use of systemic antifungal agents during posttreatment period only	253 (59.5)	298 (65.2)	.153
Death	18 (4.2)	26 (5.7)	.322

<sup>a</sup> Three micafungin-treated patients had candidemia due to *Candida lusitanae*, *C. albicans*, and *C. parapsilosis* during prophylaxis, whereas a fourth patient had candidemia due to *C. glabrata* during follow-up after treatment ended. Two fluconazole-treated patients had candidemia due to *Candida krusei* and *C. parapsilosis* during prophylaxis.

<sup>b</sup> Determined on the basis of initiation of empirical antifungal therapy.

<sup>c</sup> Treatment response was not evaluable for 7 patients in the micafungin group and 9 patients in the fluconazole group. The mean time to treatment failure in each study group was 17 days.

<sup>d</sup> *C. guilliermondii*, *C. kefyr*, *C. krusei*, *C. lambica*, *C. lusitanae*, *C. magnoliae*, *C. norvegiensis*, *C. parapsilosis*, *C. rugosa*, *C. tropicalis*, non-*albicans* species of *Candida*, species of *Candida* not otherwise specified, and species of yeast not otherwise specified.

tabolized through the cytochrome P450 3A4 pathway, whereas micafungin does not interact with compounds metabolized through this route. Micafungin appears to be metabolized through the O-methyl transferase pathway, thus minimizing the probability of drug interactions in complicated patients with neutropenia. In summary, this randomized, double-blind, multicenter trial demonstrates that the echinocandin micafungin is at least as effective as fluconazole and is an appropriate alternative for antifungal prophylaxis in neutropenic patients.

## PARTICIPATING INVESTIGATORS AND CENTERS

In addition to the authors, the following investigators, subinvestigators, and coordinators participated in this study: In Canada, E. Bow (Winnipeg, Manitoba), J. Doyle (Toronto, On-

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**Table 4. Adverse events, by study group.**

Adverse event	Study group, no. (%) of subjects	
	Micafungin ( <i>n</i> = 425)	Fluconazole ( <i>n</i> = 457)
Hepatic related		
All	119 (28)	131 (28.7)
Related to study treatment	22 (5.2)	31 (6.8)
Hyperbilirubinemia	14 (3.3)	14 (3.1)
Results of liver function tests		
Abnormal	4 (0.9)	10 (2.2)
Increased AST level	3 (0.7)	9 (2.0)
Increased ALT level	4 (0.9)	9 (2.0)
Gastrointestinal related		
All	421 (99.1)	452 (98.9)
Associated with study treatment	25 (5.9)	42 (9.2)
Nausea	10 (2.4)	12 (2.6)
Diarrhea	9 (2.1)	15 (3.3)
Urogenital related		
All	184 (43.3)	222 (48.6)
Related to study treatment	3 (0.7)	2 (0.4)
Cardiovascular related		
All	276 (64.9)	327 (71.6)
Related to study treatment	8 (1.9)	14 (3.1)
Hematologic related		
All	401 (94.4)	422 (92.3)
Associated with study treatment	6 (1.4)	8 (1.8)
Leukopenia	5 (1.2)	4 (0.9)
Anemia	4 (0.9)	3 (0.7)
Thrombocytopenia	4 (0.9)	5 (1.1)
Reactions associated with study treatment		
Infusion related	2 (0.5)	4 (0.9)
Injection site	9 (2.1)	10 (2.2)
Allergy or histamine related	15 (3.5)	17 (3.7)
Rash	8 (1.9)	6 (1.3)
Hypokalemia	8 (1.9)	8 (1.8)
Unspecified, possibly or probably associated with study treatment	64 (15.1)	77 (16.8)
Unspecified, led to discontinuation of study treatment <sup>a</sup>	18 (4.2)	33 (7.2)
Severe		
All	259 (60.9)	280 (61.3)
Other than death	80 (18.8)	74 (16.2)
Sepsis	14 (3.3)	13 (2.8)
Fever	13 (3.1)	6 (1.3)
Hypotension	9 (2.1)	3 (0.7)
Dyspnea	3 (0.7)	8 (1.8)
Unspecified, associated with study treatment	4 (0.9)	10 (2.2)

**NOTE.** ALT, alanine aminotransferase; AST, aspartate aminotransferase.

<sup>a</sup> *P* = .058.

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## Acknowledgments

Trial registry information: National Institutes of Allergy and Infectious Disease Mycoses Study Group Protocol 46 (MSG #46). Principal investigator: William E. Dismukes, University of Alabama at Birmingham, 205-934-5191. MSG #46 protocol chairperson: Thomas J. Walsh, National Cancer Institute, 301-493-8432.

**Financial support.** Funding for this study was provided by Fujisawa Healthcare through individual grants to the participating sites. The work in this article was supported in part by the National Institute of Allergy and Infectious Disease Mycoses Study Group NO1-AI-65296 and by funds from Fujisawa Healthcare.

**Potential conflicts of interest.** J.H.L.: Consultant for Merck Frosst, Novartis, Fujisawa Canada, and Hoffman LaRoche; recent research funding from Bayer; and clinical study per patient funding from Novartis, Schering Canada, Hoffman LaRoche, Fujisawa, and Johnson & Johnson. J.W.H.: Consultant for Merck, Schering-Plough, Fujisawa, and Enzon; recent research funding from Merck and Schering-Plough; and speakers' bureau of Pfizer, Merck, and Enzon. T.J.W.: Cooperative research and development agreement from Fujisawa Healthcare, and consultant for Fujisawa Healthcare and Pfizer. V.R.: Consultant for Fujisawa; recent research funding from Fujisawa; and speakers' bureau of Fujisawa. D.A.W.: Consultant for AstraZeneca and Aventis Pharmaceuticals; recent research funding from Bayer Corporation and Bristol-Myers Squibb Co.; and speakers' bureau of Pfizer and Wyeth-Ayerst Laboratories. J.-A.H.v.B.: Consultant for Pfizer, Fujisawa Healthcare, Enzon, and Schering-Plough; recent research funding from Fujisawa Healthcare, Schering-Plough, Merck, Genome Therapeutics, and Roche; and speakers' bureau of Pfizer and Fujisawa Healthcare. Y.S.: Employee of Fujisawa Healthcare.

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