Micafungin Versus Liposomal Amphotericin B for Pediatric Patients With Invasive Candidiasis

Substudy of a Randomized Double-Blind Trial

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Background: Invasive candidiasis is increasingly prevalent in premature infants and seriously ill children, and pediatric data on available antifungal therapies are lacking.

Methods: We conducted a pediatric substudy as part of a double-blind, randomized, multinational trial to compare micafungin (2 mg/kg) with liposomal amphotericin B (3 mg/kg) as first-line treatment of invasive candidiasis. Treatment success was defined as clinical and mycologic response at the end of therapy. Statistical analyses were descriptive, as the sample size meant that the study was not powered for hypothesis testing.

Results: One hundred six patients were included in the intent-to-treat population; and 98 patients—48 patients in the micafungin group and 50 patients in the liposomal amphotericin B group—in the modified intent-to-treat population. Baseline characteristics were balanced between treatment groups. Overall, 57 patients were <2 years old including 19 patients who were premature at birth; and 41 patients were 2 to <16 years old. Most patients (91/98, 92.9%) had candidemia, and 7/98 (7.1%) patients had other forms of invasive candidiasis. Treatment success was observed for 35/48 (72.9%) patients treated with micafungin and 38/50 (76.0%) patients treated with liposomal amphotericin B. The difference in proportions adjusted for neutropenic status was −2.4% [95% CI: (−20.1 to 15.3)]. Efficacy findings were consistent, independent of the neutropenic status, the age of the patient, and whether the patient was premature at birth. Both treatments were well tolerated, but with a lower incidence of adverse events that led to discontinuation in the micafungin group (2/52, 3.8%) compared with the liposomal amphotericin B group (9/54, 16.7%) ($P = 0.05$, Fisher exact test).

Conclusions: Micafungin seems to be similarly effective and as safe as liposomal amphotericin B for the treatment of invasive candidiasis in pediatric patients. (ClinicalTrials.gov number, NCT00106288).

Key Words: micafungin, invasive candidiasis, double-blind trial, pediatric

(*Pediatr Infect Dis J* 2008;27: 820–826)

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Candida is a bloodstream pathogen with mortality rates of approximately 40%.[1–4] In patients with candidemia, *Candida* may spread to other organs causing acute single-site or disseminated infection. Invasive candidiasis may also manifest as chronic disseminated candidiasis.[5] Risk factors for candidemia in pediatric patients include antibiotic therapy, corticosteroid therapy, presence of a central line, granulocytopenia, prior fungal colonization, and prolonged stay in an intensive care unit, with low birth weight and low gestational age being additional risk factors in neonates.[6–9]

The selection of various antifungal therapies in the treatment of neonates and older children with candidemia is chiefly based on case reports and small unblinded trials.[10–12] Recent recommendations for the pediatric population include amphotericin B deoxycholate, liposomal amphotericin B, fluconazole, caspofungin, and voriconazole.[10,13–15] Amphotericin B products tend to be better tolerated in children than in adults, although cases of severe nephrotoxicity have been reported for infants.[16]

Micafungin, an echinocandin lipopeptide, has broad spectrum fungicidal activity against *Candida* species and is associated with minimal toxicity and a low potential for drug interactions.[17] Unlike caspofungin and anidulafungin,[18] a loading dose is not required with micafungin. Micafungin displays linear pharmacokinetics, with minimal systemic accumulation upon repeated administration and steady-state reached within 4 days of once-daily dosing. Although the pharmacokinetics of micafungin is similar for adults and adolescents, a

Accepted for publication March 4, 2008.

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Sponsored by Astellas Pharma GmbH, Munich.

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ISSN: 0891-3668/08/2709-0820
DOI: 10.1097/INF.0b013e31817275e6

shorter half-life and faster clearance is observed in premature infants and young children.[19,20] An early noncomparative, open-label study showed promising efficacy and safety findings in 106 adults and 20 pediatric patients with refractory and newly diagnosed candidemia treated with micafungin.[21] More recently, noninferiority and a better safety profile for micafungin relative to liposomal amphotericin B were demonstrated for first-line treatment of invasive candidiasis in a study that included more than 500 adult patients.[22]

The present pediatric substudy shared the same basic study design as the larger phase III study in adults.[22] While the adult study was powered to assess noninferiority compared with liposomal amphotericin B, the pediatric substudy was not, although planned recruitment was anticipated to be sufficient to allow descriptive assessment in this population. Liposomal amphotericin B was selected as the reference therapy because it combines broad spectrum antifungal activity with reduced toxicity relative to amphotericin B deoxycholate and is widely used in the pediatric population.[23]

MATERIALS AND METHODS

Selection of Patients. Patients were eligible for enrolment if they were less than 16 years old, had clinical signs of systemic *Candida* infection and had one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days. Patients were excluded if they had positive cultures only from oropharyngeal, esophageal, urine, sputum, or bronchoalveolar lavage specimens, or from an indwelling catheter sample; had more than 3 days of systemic antifungal therapy within the previous week (except for patients with neutropenia, who were allowed antifungal prophylaxis); or had significant liver disease, defined as transaminase values 10-fold or bilirubin 5-fold above the normal reference range.

This study was conducted in accordance with the Declaration of Helsinki. The protocol and amendments for the study were reviewed and approved by the ethics committee of participating centers. Written informed consent was provided by the patients' legal guardians, and patients gave their assent if they were old enough to grasp a basic understanding of the trial.

Study Design. Patients were randomized to double-blind therapy with either micafungin (Astellas Pharma GmbH, Munich) or liposomal amphotericin B (AmBisome, Gilead Sciences, Inc., Uxbridge, United Kingdom). Randomization was 1:1 and was stratified by center and baseline neutropenic status. Neutropenia was defined as an absolute neutrophil count of less than 500 cells/μL. Investigators and study monitors were blinded to the treatment allocation. Preparation of the study drug infusion bottle and changes in dose were managed by an unblinded staff member of the center, and an unblinded study monitor reviewed drug accountability records. Bottles and lines were covered with an opaque plastic bag.

Removal of intravenous catheters was recommended and was to be done before the first dose of study drug was administered. Study drugs were administered as a 1-hour infusion. Patient weight, based on the latest available measurement during the study, was used to determine drug dose. Micafungin was administered at a daily dose of 2 mg/kg of body weight for patients who weighed $\leq$40 kg and 100 mg for patients who weighed $>$40 kg. These doses of micafungin were found to be well tolerated and efficacious for the majority of *Candida* species in Phase 2 trials. Liposomal amphotericin B was administered at a daily dose of 3 mg/kg of body weight, a dose known to be effective and within the approved dose range of 3–6 mg/kg/d. Starting with a low dose of both drugs provided an option for increasing the dose if required. The initial dose was to remain fixed during the first 5 days of the study. Demonstration of mycologic persistence or clinical signs and symptoms of the *Candida* infection had to be seen before an increase in dose was made. The dose increase was to 4 mg/kg of body weight for micafungin (200 mg for patients who weighed $>$40 kg) and to 5 mg/kg of body weight for liposomal amphotericin B. A dose decrease of 50% for liposomal amphotericin B was indicated for drug-related nephrotoxicity. Nephrotoxicity was defined as a doubling of serum creatinine concentration or an increase of at least 1 mg/dL compared with the baseline value. No decrease in dose was allowed for micafungin. The recommended minimum duration of study drug therapy was 14 days. For patients with candidemia, treatment was to continue for 1 week after demonstration of 2 sequential negative cultures and resolution of all clinical signs and symptoms. The maximum treatment period was 4 weeks, except for patients with chronic disseminated candidiasis, *Candida* osteomyelitis, or endocarditis, for whom study drug could be administered for up to 8 weeks.

Assessments for mycology and clinical signs and symptoms of *Candida* infection were performed at baseline, weekly during the treatment phase and at the end of therapy. Blood samples for fungal culture were taken 3 times per week during treatment for patients with candidemia, and otherwise once per week or as clinically indicated. Assessments were continued during the 12-week post-treatment period for patients whose infection did not resolve at the end of therapy or who were suspected of having a recurrent or emergent infection.

Evaluation of Efficacy. The primary end point was the response rate based on the investigator's assessment of overall treatment success, which required both a clinical and mycologic response at the end of therapy. Clinical response was defined as a complete or partial resolution of signs and symptoms, and mycologic response was defined as eradication or presumed eradication. An outcome of presumed eradication required complete resolution of all attributable signs and symptoms, and repeat culture or biopsy was contraindicated (cases of noncandidemia).

Recurrence was assessed for patients who experienced overall treatment success at the end of therapy and was defined as re-emergence of the baseline fungal infection during the 12-week post-treatment follow-up. The recurrent fungal infection had to be of the same species and site as those defined at baseline.

Evaluation of Drug Safety. Adverse events were recorded, irrespective of causality. Treatment-related adverse events are those ascribed by the investigator as having a possible, probable, or highly probable relationship to the study drug as well as those deemed as not assessable. Serum chemistry laboratory assessments were conducted weekly during treatment, at the end of therapy and during the 12-week follow-up.

The estimated glomerular filtration rate was calculated for patients ≥2 years of age.[24]

To ensure patient safety using blinded conditions during the study, a Data Safety Monitoring Board regularly reviewed reports of serious adverse events.

Statistical Analysis. No formal sample size calculations were performed for this pediatric substudy. It was reasoned that recruitment of approximately 100 patients (expected to result in 80 patients who met eligibility criteria and received at least 5 doses of study medication) would ensure sufficient data to perform meaningful descriptive analyses. The investigator's assessment of overall treatment success at the end of therapy was analyzed by calculating a 2-sided 95% CI based on normal approximation for the difference in proportions (micafungin minus liposomal amphotericin B) stratified by whether the patient had neutropenia at baseline. The intent-to-treat (ITT) population was defined as patients who received at least 1 dose of study drug. The modified intent-to-treat (MITT) population in addition had to have a confirmed *Candida* infection at baseline. Criteria for the per protocol set (PPS) in addition required at least 5 doses of study drug, the investigator's assessment of overall treatment success available at the end of therapy, and no non-*Candida* fungal pathogen.

RESULTS

Patient Enrolment and Analysis Sets. The study was conducted from January 2003 to December 2005. Investigators from 27 study sites in Europe, North and South America, South Africa, India, and Thailand enrolled 109 patients. Study drug was received by 106 patients (ITT), and 98 patients were included in the MITT (Fig. 1, available online only).

Demographics and Baseline Characteristics. The micafungin and liposomal amphotericin groups did not significantly differ for any demographic or baseline characteristic, including neutropenia ($P = 0.216$, Fisher exact test) and other established risk factors, and all pediatric age groups were well represented (Table 1, available online only).

Study Drug Exposure. The median duration of study drug administration was 15 days for micafungin (range, 3–42 days) and 14.5 days for liposomal amphotericin B (range, 2–34 days) (MITT). The median daily dose was 2 mg/kg of body weight for micafungin and 3 mg/kg of body weight for liposomal amphotericin B.

Efficacy. The rate of overall treatment success was similar for micafungin (72.9%, 35/48) compared with liposomal amphotericin B (76.0%, 38/50), with an adjusted difference between treatment groups of −2.4 (95% CI: −20.1 to 15.3) when stratified by neutropenic status (MITT) (Fig. 2). Consistent findings were observed for the per protocol set, which showed success rates of 85.4% (35/41) and 88.1% (37/42) in the micafungin and liposomal amphotericin B groups, respectively, with an adjusted difference between treatment groups of −1.8 (95% CI: −16.4 to 12.7) when stratified by neutropenic status.

Age Group and Whether Patient Received a Dose Increase. All pediatric age groups were well represented, and a large cohort of patients with premature birth were included in the study. Treatment success rates for both micafungin and liposomal amphotericin B were consistent across age groups and whether the patient was prematurely born (Table 2). Treatment success rates were numerically greater with liposomal amphotericin B versus micafungin for the 4 weeks to <2

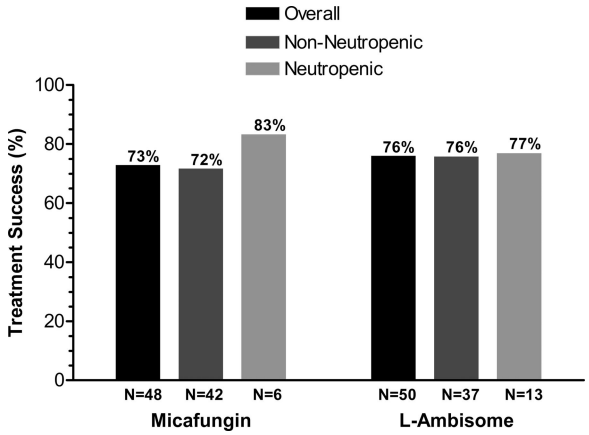

FIGURE 2. Treatment success in the MITT population. MITT population: patients who received at least one dose of study drug and had a confirmed *Candida* infection at baseline.

TABLE 2. Treatment Success in the MITT Population by Prognostic Parameters

	Micafungin		Liposomal Amphotericin B	
	n	No. (%)	n	No. (%)
Age group				
0 d to <4 wk	7	7 (100)	7	4 (57.1)
4 wk to <2 yr	19	14 (73.7)	24	20 (83.3)
2 to <12 yr	15	10 (66.7)	16	12 (75.0)
12 to <16 yr	7	4 (57.1)	3	2 (66.7)
Premature birth				
Yes	10	7 (70.0)	9	6 (66.7)
Dose increase*				
No	37	28 (75.7)	38	31 (81.6)
Yes	11	7 (63.6)	12	7 (58.3)
Neonate (<4 wk)	0	—	1	0
4 wk to <2 yr	8	5	7	6
≥2 yr	3	2	4	1
No catheter at baseline†	11	7 (63.6)	12	8 (66.7)
Existing catheter at baseline†	33	26 (78.8)	35	28 (80.0)
Replaced at baseline	13	10 (76.9)	16	14 (87.5)
Not replaced at baseline	20	16 (80.0)	19	14 (73.7)
Replaced during treatment	14	13 (92.9)	12	10 (83.3)
Not replaced during treatment	6	3 (50.0)	7	4 (57.1)
Blood	44	33 (75.0)	47	36 (76.6)
Invasive Candidiasis	4	2 (50.0)	3	2 (66.7)
Acute disseminated (blood, eye, CNS/brain)	1	1	0	—
Acute disseminated (blood, eye, heart valve)	1	0	0	—
Ventriculo-peritoneal shunt	1	0	0	—
Peritoneum	1	1	1	1
Brain/CNS	0	—	1	1
Endocardium	0	—	1	0

MITT population: patients who received at least 1 dose of study drug and had a confirmed *Candida* infection at baseline.

*The dose increase was to 4 mg/kg body weight for micafungin (starting dose 2 mg/kg) and to 5 mg/kg body weight for liposomal amphotericin B (starting dose 3 mg/kg).

†Calculated only for patients with candidemia; patients with invasive forms of the disease were excluded.

years group, the 2 to <12 years group, and the 12 to <16 years group. By contrast, treatment success rates were numerically greater with micafungin versus liposomal amphotericin B for the 0 days to <4 weeks group and patients born prematurely.

Approximately one-fifth of patients received a dose increase during the study; the majority of these patients in both groups (69.6%, 16/23) were less than 2 years old (Table 2). The overall rate of treatment success for patients who had a dose increase was 7/11 (63.6%) for micafungin and 7/12 (58.3%) for liposomal amphotericin B.

Site of Infection. Most patients (91/98, 92.9%) had candidemia, with treatment success experienced by 33/44 (75.0%) patients in the micafungin group and 36/47 (76.6%) patients in the liposomal amphotericin B group. For the few cases of invasive disease, 2/4 patients in the micafungin group and 2/3 patients in the liposomal amphotericin B group experienced treatment success (Table 2).

Mycologic Persistence and Recurrence of Fungal Infection. Mycologic persistence at the end of therapy was observed for 7/45 (15.6%) patients in both the micafungin and liposomal amphotericin B groups (MITT) (Table 3). Three patients in the micafungin group and none in the liposomal amphotericin B group had a proven recurrent fungal infection during the post-treatment phase. The cases in the micafungin group (all *Candida albicans*) comprised 2 patients with candidemia (recurrence occurred 2 and 6 weeks, respectively, after completion of therapy) and one 4-week-old patient with acute disseminated candidiasis [blood, central nervous system (CNS), eye] who had recurrence of candidiasis of the CNS/brain approximately 3 weeks after completing treatment.

Mortality. The mortality rate during the treatment phase was 1.9% (1/52) for micafungin and 11.1% (6/54) for liposomal amphotericin B (ITT). During the entire study, including the 12-week follow-up, the mortality rates were 25.0% (13/52) and 24.1% (13/54) of patients, respectively. The fungal infection was considered by the investigator to have contributed to the cause of death for 7.7% (4/52) and 5.6% (3/54) of patients, respectively.

Adverse Events. In general, the nature and incidence of adverse events—recorded irrespective of causality—were much the same for both treatment groups and reflect the multimorbid conditions of this patient population. The more frequently reported adverse events (5 or more patients in either treatment group) were sepsis, fever, vomiting, diarrhea, anemia, thrombocytopenia, and hypokalemia (Table 4). The incidence of adverse events that led to treatment discontinuation was lower in the micafungin group than in the liposomal amphotericin B group [3.8% (2/52) and 16.7% (9/54), respectively; $P = 0.05$, Fisher exact test].

Two patients in the micafungin group experienced a serious adverse event that was suspected of being related to treatment. For one of the patients the event was a moderate increase in the serum creatinine value [57 μmol/L (0.64 mg/dL) at baseline to 73 μmol/L (0.83 mg/dL) on day 3/end of therapy; this patient discontinued treatment]; and for the other patient renal failure was a worsening of a baseline condition. In the liposomal amphotericin B group, there were 5 patients with a treatment-related serious adverse event: 1 patient each with liver damage, bilirubinemia, or worsening candidemia—these 3 events having led to treatment discontinuation—as well as 1 patient with cholestatic jaundice and 1 with kidney dysfunction.

Laboratory Assessments. Few patients experienced a clinically meaningful change in creatinine, aspartate transaminase, alanine transaminase, or bilirubin during treatment with micafungin or liposomal amphotericin B (Table 5, available online only).

The mean peak decrease in the estimated glomerular filtration rate for pediatric patients (≥2 years) was smaller for micafungin (2.6 mL/min/1.73 m^2, N = 21) than for liposomal amphotericin B (17.9 mL/min/1.73 m^2, N = 15), but the difference was not significant ($P = 0.220$, analysis of covariance).

TABLE 3. Mycologic Persistence at End of Therapy by *Candida* Species at Baseline in the MITT Population

Species*	Micafungin N = 48		Liposomal Amphotericin B N = 50	
	n†	No. (%)	n†	No. (%)
Any *Candida* species	45	7 (15.6)	45	7 (15.6)
Candida albicans	18	2 (11.1)	13	0
Non-*C. albicans*	28	5 (17.9)	32	7 (21.9)
C. parapsilosis	13	3 (23.1)	17	6 (35.3)
C. tropicalis	11	1 (9.1)	14	1 (7.1)
C. krusei	2	0	0	—
C. glabrata	1	1	1	0
C. guilliermondii	1	0	1	0
C. lusitaniae	1	0	1	0
More than 1 *Candida* species	3	1	2	0

MITT population: patients who received at least 1 dose of study drug and had a confirmed *Candida* infection at baseline.

*The *Candida* species was determined by a central laboratory (Mitsubishi Kagaku Bio Clinical Laboratory, Tokyo, Japan).

†The number of patients with the respective *Candida* species at baseline. Some patients had more than one species.

DISCUSSION

To date, this substudy represents the largest comparative, randomized, double-blind assessment of therapies for first-line treatment of invasive candidiasis in pediatric patients and provides evidence that micafungin is effective in this population. All pediatric age groups were represented. The overall treatment success rate was high for micafungin and similar to that observed for liposomal amphotericin B. Micafungin was well tolerated, and fewer patients randomized to micafungin discontinued therapy.

The results of this pediatric substudy are consistent with those of the large adult study, which demonstrated noninferiority of micafungin relative to liposomal amphotericin B and a significantly better safety profile.[22] This smaller substudy provides evidence that micafungin is effective and safe in the pediatric population. In general, treatment success rates with micafungin and liposomal amphotericin B in age groups beyond 4 weeks were consistent with those demon-

TABLE 4. Summary of Adverse Events in the ITT Population

	Micafungin N = 52	Liposomal Amphotericin B N = 54	*P* (Fisher Exact Test)
Incidence of adverse events, irrespective of causality			
Serious	15 (28.8)	20 (37.0)	0.41
Treatment discontinuation	2 (3.8)	9 (16.7)	0.05
Overall*	48 (92.3)	50 (92.6)	>0.99
Sepsis	12 (23.1)	11 (20.4)	0.82
Hypokalemia	5 (9.6)	11 (20.4)	0.18
Fever	5 (9.6)	10 (18.5)	0.27
Anemia	9 (17.3)	6 (11.1)	0.41
Thrombocytopenia	6 (11.5)	3 (5.6)	0.32
Vomiting	8 (15.4)	7 (13.0)	0.79
Diarrhea	4 (7.7)	5 (9.3)	>0.99
Infusion-related reaction†	9 (17.3)	10 (18.5)	>0.99
Incidence of treatment-related adverse events			
Serious	2 (3.8)	5 (9.3)	0.44
Treatment discontinuation	1 (1.9)	3 (5.6)	0.62
Overall*	19 (36.5)	23 (42.6)	0.56
Fever	2 (3.8)	6 (11.1)	0.27
Hypokalemia	3 (5.8)	6 (11.1)	0.49
Infusion-related reaction†	7 (13.5)	10 (18.5)	0.60

ITT population: patients who received at least 1 dose of study drug.
Adverse events were coded using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART).
*Individual adverse events are listed, which had an incidence of 5 or more patients in either treatment group.
†Whether an adverse event was infusion-related was indicated by the investigator on the study case report form.

strated in the adult population, with no meaningful differences observed for different age groups or for premature birth status. There was a trend for treatment success rates to favor liposomal amphotericin B above 4 weeks of age and to favor micafungin below 4 weeks of age. However, because of the sample size of the pediatric substudy, these efficacy findings should not be over interpreted.

The daily micafungin dose of 2 mg/kg in pediatric patients provides systemic exposure similar to that achieved with a daily dose of 100 mg in adult patients, which was used in the large adult noninferiority trial.[19,22] These doses were selected on the basis of a large randomized, double-blind dose-response study in the indication of esophageal candidiasis,[25] and on dosing data from an open-label efficacy and safety study in the indication of invasive candidiasis.[21] Although the small sample size of the present study precludes a definitive analysis of dose-response, there seemed to be no discernible trend in the data to suggest that increasing the dose resulted in added benefit. Even so, the increases in micafungin dose were carried out with no compromise in safety, and the majority of these patients responded to therapy after having shown a lessened response at the lower dose. Thus, increasing the dose is safe and may be a useful option for selected patients.

Of the 3 documented recurrent infections in the micafungin group, one was a CNS recurrence in a 4-week old neonate. The dose of 2 mg/kg provided good efficacy in the neonate patients in this experience. However, in view of a higher clearance of micafungin in neonates,[20] higher doses up to 15 mg/kg have been under investigation in this population.[26] The purpose is to achieve drug exposure adequate to ensure CNS penetration.[27] In view of the demonstrated safety of dose escalation in this study, consideration should be given to higher doses of micafungin in patients with known CNS disease.

All infective *Candida* species were associated with low rates of mycologic persistence after both micafungin and liposomal amphotericin B treatment. Consistent with large epidemiologic studies that investigated pediatric patients with candidemia,[1,3,9,28] *C. albicans* and *Candida parapsilosis* were the most common isolates. Slightly higher rates of mycologic persistence for *C. parapsilosis* relative to *C. albicans* were observed for both micafungin and liposomal amphotericin in the present study but not in the larger adult study.[22] Given the strong tendency of *C. parapsilosis* to adhere to foreign surfaces and to be transmitted horizontally by care workers and others,[1,28] it is reasonable to speculate that factors such as management of intravascular devices and hospital hygiene are important in terms of explaining the higher rates of mycologic persistence associated with *C. parapsilosis*. It is recognized that, for the echinocandin drug class, minimum inhibitory concentrations against *C. parapsilosis* are higher than for other *Candida* species. However, micafungin has shown clear efficacy benefit in patients with *C. parapsilosis* infection.[21,30] It is not clear whether the differences in micafungin in vitro minimum inhibitory concentrations—1–2 μg/mL for *C. parapsilosis* versus 0.03 μg/mL for *C. albicans*[29]—are clinically predictive of response to micafungin therapy.

The nature and incidence of adverse events were consistent with those expected from a population of pediatric patients with severe and life-threatening underlying conditions. The significantly lower incidence of adverse events that led to treatment discontinuation in the micafungin group compared with the liposomal amphotericin B group suggests a safety advantage for micafungin in this population. In general, liposomal amphotericin B showed the expected pattern of renal toxicity, infusion-related reactions, and hypokalemia but to a lesser degree than typically observed in adult patients. As in the adult population,[22] hepatic laboratory

values in the pediatric population showed no marked changes between baseline and end of therapy for either treatment group.

In conclusion, this randomized, double-blind study showed micafungin to be well tolerated with efficacy comparable to liposomal amphotericin B in the treatment of invasive candidiasis and candidemia in pediatric patients.

ACKNOWLEDGMENTS

Members of the Data and Safety Monitoring Board were P. Freeman (Consultant Statistician, Ship Cottage, Cadgwith, Helston, Cornwall, United Kingdom); H von Wulffen (Allgemeines Krankenhaus St. Georg, Hamburg, Germany); I. Klompmaker (Academisch Ziekenhuis Groningen, Groningen, The Netherlands); T. Lang (Universitäts-Kinderklinik u. Poliklinik, München, Germany); and K Wagner (Allgemeines Krankenhaus Barmbek, Hamburg, Germany).

The authors thank Frank Beier (lead statistician) and Dorothea Wessiepe for statistical analyses, Astrid Schaefer for coordination of the study, and Connie Grogan for author's editing, all members of Astellas Pharma GmbH, Munich.

Investigators of the Micafungin Invasive Candidiasis Study Group were as follows. Australia—Michael Nissen, Royal Children's Hospital, Herston. Brazil—Lopes Arnaldo Colombo, Universidade Federal de Sao Paulo UNIFESP, Sao Paulo; Evandro Roberto Baldacci, Instituto da Crianca-HC–FMUSP–CCIH, Sao Paulo; Flavio De Queiróz Telles Filho, Hospital de Clinicas da Universidade Federal do Parana, Curitiba; Eitan Naaman Berezin, Santa Casa de Misericordia de Sao Paulo, Sao Paulo; Carlos Jorge Lotfi, Hospital do Cancer A C Camargo–CCIH, Sao Paulo; Antonio Tarcisio de Faria Freire, Santa Casa de Misericordia de Belo Horizonte CCIH, Belo Horizonte. Belgium—Johan Decruyenaere, UZ Gent, Gent. Croatia—Boris Grcic-Filipovic, Clinical Hospital Center Zagreb, Zagreb; Josip Konja, Clinical Hospital Centre Zagreb, Zagreb, Croatia. France—Guy Leverger, Hopital d'Enfants Armand Trousseau, Paris. India—Makwana. Mansukh, Sheth Vadilal Sarabhai General Hospital, Ahmedabad; N. Krishna Reddy, Care Hospital, The Institute of Medical Sciences, Hyderabad; D. Raghunadharao, Nizam's Institute of Medical Sciences, Hyderabad; Adhikari Prabha, Kasturba Medical College Hospital, Mangalore; B.M. Vadhiraja, Shirdi Sai Baba Cancer Hospital & Research Centre, Manipal; V Ramasubramanian, Apollo Hospitals Infectious Disease, Chennai. Poland—Jerzy Kowalczyk, Dzieciecy Szpital Kliniczny. Lublin, Poland. Portugal—Manuel Abecassis, Instituto Portuges de Oncologia de Francisco Gentil, Lisboa. South Africa—Janet Poole, Johannesburg Hospital, Houghton, Johannesburg; Ae Van Der Vyver, University of the Free State, Bloemfontein. Thailand—Tawee Chotpitayasunondh, Queen Sirikit National Institute of Child Health, Bangkok; Amorn Leelarasamee, Siriraj Hospital-Mahidol University, Bangkok; Chitsanu Pancharoen, Chulalongkom University, Bangkok, Thailand. United States—Gloria Heresi, University of Texas Houston, Houston, TX; Edythe Albano, University of Colorado Children's Hospital, Denver, CO; Antonio Arrieta, Children's Hospital of Orange County, Orange, CA.

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