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Safety and Pharmacokinetic Profiles of Repeated-Dose Micafungin in Children and Adolescents Treated for Invasive Candidiasis

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Abstract

Background—Micafungin is an echinocandin with proven efficacy against a broad range of fungal infections, including those caused by *Candida* species.

Objective—To evaluate the safety and pharmacokinetics of once-daily 3 mg/kg and 4.5 mg/kg micafungin in children with proven, probable, or suspected invasive candidiasis.

Methods—Micafungin safety and pharmacokinetics were assessed in two Phase I, open-label, repeat-dose trials. In Study 2101, children aged 2–16 years were grouped by weight to receive 3 mg/kg (≥25 kg) or 4.5 mg/kg (<25 kg) intravenous micafungin for 10–14 days. In Study 2102, children aged 4 months to <2 years received 4.5 mg/kg micafungin. Study protocols were otherwise identical.

Results—Safety was analyzed in seventy-eight and nine children in Studies 2101 and 2102, respectively. Although adverse events were experienced by most children (2101: n = 62; 2102: n = 9), micafungin-related adverse events were less common (2101: n = 28; 2102: n = 1), and the number of patients discontinuing due to adverse events was low (2101: n = 4; 2102: n = 1). The most common micafungin-related adverse events were infusion-associated symptoms, pyrexia, and hypomagnesemia (Study 2101), and liver function abnormalities (Study 2102). The micafungin pharmacokinetic profile was similar to that seen in other studies conducted in children, but different than that observed in adults.

Conclusions—In this small cohort of children, once-daily doses of 3 mg/kg and 4.5 mg/kg micafungin were well tolerated. Pharmacokinetic data will be combined in a population pharmacokinetic analysis to support U.S. dosing recommendations in children.

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Keywords

candidiasis; children; micafungin; pharmacokinetics; safety

INTRODUCTION

Invasive candidiasis is a significant cause of morbidity and mortality in seriously ill and immunocompromised children.[1,2] Conventional therapies, such as amphotericin B and fluconazole, are effective in the treatment of *Candida* infections. However, the poor tolerability of amphotericin B and the emergence of fluconazole-resistant *Candida* species necessitate the development of effective and safer alternatives.

The echinocandins, including micafungin, are increasingly recognized as valuable alternatives for the treatment and prevention of invasive *Candida* infections,[3–5] including those caused by *Candida* species resistant to fluconazole.[6–8] In children, micafungin has been shown to be as effective as currently approved antifungal medications for the therapy and prophylaxis of invasive candidiasis.[9,10]

Micafungin is well tolerated in children, including those with severe underlying illnesses.[11–13] In a recent pooled analysis of several Phase I, II, and III trials that assessed safety and tolerability of micafungin in 296 children,[11] adverse events (AEs) and serious adverse events (SAEs) were reported in 92% and 34% of children, respectively. However, AEs and SAEs related to micafungin treatment were less common (27% and 5%, respectively), and rarely led to discontinuation of therapy (2%). Nonetheless, children (particularly those <1 year old) treated with micafungin may be more likely than adults to develop liver function test abnormalities.[11,14]

Micafungin exhibits linear and dose-proportional pharmacokinetics (PK) for a wide range of doses in adults (50–150 mg/day)[15,16] and children (0.5–4.0 mg/kg/day).[13,17] The overall PK profile for micafungin in children is similar to that observed in adults. However, body weight-adjusted clearance appears to be higher in younger (<8 years old) than older (9–17 years old) children.[12,13]

Population PK models suggest that to achieve micafungin exposure in children similar to that achieved in adults administered micafungin 100–200 mg/day may require daily doses of up to 4.5 mg/kg.[12] Therefore, to further examine safety and optimal dosing in children, we conducted two studies in children with esophageal and other types of invasive candidiasis at doses expected to provide exposure similar to that obtained in adults receiving a dose of 150 mg/day. The results of the two studies are presented side-by-side in this article.

METHODS

Study Design and Pediatric Populations

The 9463-CL-2101 (2101; NCT00608335) and 9463-CL-2102 (2102; NCT00607763) studies were Phase I, prospective, multicenter, open-label, repeat-dose trials. Both trials assessed safety and PK of daily intravenous infusions of micafungin in children with esophageal or other invasive candidiasis. With the exception of the enrolled populations and administered doses of micafungin, the two study protocols were identical. Children were excluded if they had significant liver disease (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, or alkaline phosphatase >5 times the upper limit of normal), concomitant medical conditions that in the opinion of the principal investigator

precluded participation, a history of hypersensitivity to echinocandin-class of antifungals, or been treated with an echinocandin within 1 week of study start.

The population of Study 2101 comprised infants and adolescents aged 2–16 years. Children were grouped by weight at baseline to receive either 3 mg/kg (weight ≥25 kg) or 4.5 mg/kg (weight <25 kg) micafungin, with a maximum daily dose of 150 mg. The population of Study 2102 comprised toddlers aged 4 months to less than 2 years. In this study, all children received 4.5 mg/kg micafungin, with a maximum daily dose of 150 mg; however, given the age and the body weight of these children, none received a daily dose of micafungin >42 mg.

Micafungin was administered as once-daily, intravenous infusions for 1 hour for a total duration of 10–14 days. An end of therapy (EOT) visit was performed within 72 hours after the final dose of micafungin. An end of study (EOS) visit was performed 14 days (±2 days) after the final study dose.

Institutional Review Board/Independent Ethics Committee-approved written informed consent was obtained from all children, parent(s), or legal representative(s), where appropriate, prior to any study-related procedures. Written assent was obtained from children based on age-related requirements of each participating institution.

Safety Assessments

Safety evaluations comprised vital sign assessment, physical examination, 12-lead electrocardiograms, and clinical laboratory hematology and serum chemistry evaluations. Vital signs were measured at baseline, twice daily before the start of infusion and within 1 h post-infusion from day 1 to EOT; physical examination was performed at baseline, day 1, and EOT; 12-lead ECG was recorded within 72 hours prior to first dose, once between days 4 and 8, and at EOT; clinical laboratory samples were collected within 72 hours prior to first dose, once between days 2 and 7, once between days 8 and 14, at EOT, and at EOS. An abnormality in these tests (investigational abnormalities) was defined as an adverse event (AE) if the abnormality induced clinical signs or symptoms, needed active intervention, required interruption or discontinuation of micafungin treatment, or was clinically significant in the opinion of the study investigator.

Blood samples (3 mL) were collected for hematology (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, platelet count, and absolute neutrophil count) and serum chemistry (creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase [GGT], sodium, potassium, chloride, calcium, magnesium, total protein, albumin, and lactate dehydrogenase) at baseline, twice during the dosing period (≥3 days apart), at EOT, and at EOS.

Pharmacokinetic Evaluation

The primary PK parameters analyzed were area under the plasma micafungin concentration-time curve from start of infusion to 24 hours (AUC_{tau}) and peak serum micafungin concentration (C_{max}) at steady state. Secondary PK parameters were time to C_{max} (t_{max}), clearance at steady state (CL_{ss}), and clearance at steady state adjusted by body weight (CL_{ss}/wt). Due to the short interval of sampling, drug half-life could not be estimated reliably.

Blood samples (1 mL) were collected to measure plasma analytes (micafungin and metabolites, M-1, M-2, and M-5) on day 7 within 1 hour prior to the start of micafungin infusion, immediately after the end of infusion (1 hour), and at 2, 4, and 10 hours following the start of infusion. Single blood samples were also collected for trough micafungin concentration measurements within 10 minutes prior to infusion start time on days 4, 6, and

8. Blood samples were centrifuged at 3000 rpm for 10 minutes at approximately 4°C within 2 h of collection. Samples were protected from light and maintained at a constant temperature (–70°C) until transferred on dry ice to the analytical lab. Plasma concentrations of micafungin and its analytes were determined using validated high performance liquid chromatography with fluorescence detection methods. The lower limit of quantification for plasma micafungin was 0.05 μg/mL.

Statistical Methods

Data obtained in Study 2101 and Study 2102 were analyzed separately. The safety analysis set (SAF) included all children who received at least one dose of micafungin. All safety analyses were conducted using the SAF. The pharmacokinetic analysis set (PKAS) consisted of all children in the SAF for whom sufficient data were available to calculate at least one PK parameter. All PK analyses were conducted using the PKAS. Descriptive statistics were used to analyze demographics, baseline characteristics, and safety data. Frequencies and percentages were used to describe categorical data. Summaries were presented for each dose cohort and for each age group within a dose cohort. The PK parameters for micafungin were calculated using non-compartmental methods.

RESULTS

Study Populations

Eighty-four children were enrolled in Study 2101 and nine children were enrolled in Study 2102. Of those enrolled, 78 and nine children received at least one dose of micafungin and were included in the SAF for 2101 and 2102, respectively (Figure 1). In Study 2101, fungal infection was proven in 35 children (45%), probable in 29 children (37%), and suspected in 14 children (18%). In Study 2102, fungal infection was proven in five children (56%) and suspected in four children (44%).

There were similar numbers of male (47%) and female (53%) children in the SAF of Study 2101, of whom 56% were Black or African-American. In the SAF of Study 2102, most children were male (78%) and White (89%; Table 1).

The most frequent primary underlying disorder was human immunodeficiency virus (HIV-1; 46%) in Study 2101 and heart disease (44%) in Study 2102. Malignancy (23%) was also a common primary underlying disorder in Study 2101. Liver disease, malignancy, megacystis-microcolon-intestinal-hypopersitalsis, prematurity, and short bowel syndrome were also reported in Study 2102 (one child [11%] each).

Safety Assessments

The majority of children (n = 62/78; 80%) in Study 2101 experienced at least one AE (Table 2). The most common AEs were pyrexia (n = 15/78; 19%), hypokalemia (n = 11/78; 14%), and vomiting (n = 10/78; 13%). The most common AEs considered related to micafungin treatment were infusion-associated symptoms, such as hypotension, hypertension, and cyanosis (n = 9/78; 12%), pyrexia (n = 7/78; 9%), and hypomagnesemia (n = 5/78; 6%).

All 9 children in Study 2102 experienced at least one AE (Table 2). Abnormal liver function tests (NOS) observed in one child (11%) were considered related to micafungin (Table 3).

Four children (5%) died in Study 2101; three of these children died during the study, and one child died after the end of the follow-up period. Causes of death included intracranial hemorrhage, suspected pneumonia, hepatic infarction, hemorrhagic pancreatitis, renal failure, and respiratory failure. One child (11%) in Study 2102 died of severe cardiac failure

during the study. None of the deaths in either study was considered related to micafungin treatment or to fungal infection.

Nine children (12%) in Study 2101 experienced SAEs other than death. In two of these children, the SAEs were considered possibly or probably related to micafungin treatment. One child with acute myelogenous leukemia treated with 3 mg/kg micafungin experienced the SAEs ventricular tachycardia (8-beat run ~15–20 s), hypomagnesemia (1.3 mg/dL), hypokalemia (2.3 mg/dL), and hypocalcemia (7.6 mg/dL), which were considered possibly related to micafungin treatment. The child was treated with magnesium sulphate, potassium, and calcium gluconate for treatment of these SAEs. The second child, who had underlying HIV infection and was treated with 4.5 mg/kg micafungin, experienced febrile convulsion (temperature 40°C), which was considered probably related to micafungin treatment. Fever was treated with paracetamol. Micafungin treatment was discontinued in this child due to this event. The majority of children who experienced SAEs (n = 6/9; 67%) recovered with no residual effects.

Five children (56%) experienced SAEs other than death in Study 2102. Of these, one SAE was considered possibly related to micafungin: a pathological fracture (secondary to osteopenic bones) in a child with cardiac abnormalities. Almost all children with SAEs (n = 4/5; 80%) recovered with no residual effects, with the exception of one child who experienced bacteremia that was persistent at the time of death.

Four children (5%) in Study 2101 experienced AEs that led to permanent discontinuation of micafungin treatment; two were considered SAEs, and all were considered possibly or probably related to micafungin therapy, including infusion-associated symptoms (n = 2/78; 3%), hypomagnesemia (n = 1/78; 1%), and pyrexia (n = 1/78; 1%). Two children (22%) in Study 2102 experienced AEs that led to permanent discontinuation of micafungin treatment. One child had abnormal liver function tests (NOS), which were considered possibly related to micafungin treatment. The second child discontinued micafungin treatment due to a SAE of cardiac failure, which subsequently resulted in the child's death.

Pharmacokinetics Evaluation

Twenty-four children in Study 2101 and eight children in Study 2102 made up the PKAS (Figure 1). Mean plasma micafungin concentrations on day 7 of treatment are shown in Figure 2. In Study 2101, mean plasma concentrations were highest in children aged 12–16 years treated with 4.5 mg/kg micafungin and lowest in children of the same age treated with 3 mg/kg micafungin. Mean plasma concentrations of micafungin were higher in children in Study 2102 compared with all children in Study 2101.

PK parameters obtained in both studies on day 7 are shown in Table 4. In Study 2101, mean AUC_{tau} values were similar in children aged 6–11 years treated with 3 mg/kg micafungin and children aged 2–5 years treated with 4.5 mg/kg micafungin. Mean AUC_{tau} was slightly higher in children aged 6–11 years treated with 4.5 mg/kg micafungin than in children aged 6–11 years treated with 3 mg/kg micafungin. Values were highest in the child aged 12–16 years in the 4.5 mg/kg dose group and lowest in those aged 12–16 years in the 3 mg/kg dose group. Mean AUC_{tau} in children aged 4 months to under 2 years in Study 2102 was higher than in children aged 2–5 years and 6–11 years also treated with 4.5 mg/kg.

Mean C_{max} was comparable between most dose and age groups in Study 2101, with the exception of the child aged 12–16 years treated with 4.5 mg/kg who displayed the highest mean C_{max}. By comparison, the mean C_{max} of children in Study 2102 was higher than the values observed for children in Study 2101.

Mean CL_{ss} generally increased with age in Study 2101. However, mean body weight-adjusted CL_{ss} (CL_{ss}/wt) was highest in children aged 2–5 years in the 4.5 mg/kg dose cohort. Mean CL_{ss}/wt in this group was also higher than mean CL_{ss}/wt in the younger children of Study 2102. A single child in this age group exhibited a CL_{ss}/wt value much higher (40.9 mL/h/kg) than all children in Study 2101 and Study 2102.

DISCUSSION

Studies 2101 and 2102 evaluated the safety and PK of once-daily administration of 3 mg/kg and 4.5 mg/kg micafungin in two small cohorts of children and adolescents with proven, probable, or suspected *Candida* infection.

Micafungin therapy was well tolerated in all groups of children. The AEs reported in both studies were consistent with the underlying illnesses of the child populations and similar to those reported in existing studies.[11,13,14] Although the majority of children in both studies experienced AEs, few were considered related to micafungin treatment.

Liver function abnormalities were uncommon in Study 2101 (4–6%) (Table 3). This is similar to findings in other pediatric studies and those of a pooled analysis of 3028 adult and pediatric patients in whom the overall incidence of liver function abnormalities did not exceed 3%.[11,14]

The incidence of SAEs in previous pediatric studies (~34%) differed from Study 2101 (n = 9/78; 12%) and Study 2102 (n = 5/9; 56%)._ENREF_11 This is likely due to differences in demographics and baseline clinical characteristics between the studies, and the small sample size of Study 2102. The pooled analysis conducted by Arrieta et al[11] included a number of children aged under 1 year old (n = 66/296; 22%), many of whom were born prematurely (n = 38/66; 58%). Most children were undergoing hematopoietic stem cell transplantation (34%), had hematologic malignancy (29%), and/or were severely neutropenic (40%).[11] By comparison, the most common underlying illnesses in Study 2101 were HIV and malignancy, and heart disease in Study 2102.

Despite differences in the overall incidence of SAEs between these studies, SAEs that were considered related to micafungin treatment were comparatively rare in Study 2101 (n = 2/78; 3%), and similar to existing results in children (n = 14/296; 5%).[11] Moreover, the majority of SAEs resolved during therapy and the children experienced no residual effects. The incidence of SAEs considered related to micafungin treatment was higher in Study 2102 (n = 1/9; 11%) compared with Study 2101 and existing data.[11] However, as discussed previously, this finding may be an artifact of the small sample size of this study.

Full PK profiles were available for most age groups of children administered 3 mg/kg and 4.5 mg/kg micafungin in Studies 2101 and 2102. Profiles were not available for children aged 2–5 years in the 3 mg/kg dose cohort and only one child aged 12–16 years was examined in the 4.5 mg/kg dose cohort in Study 2101. Values obtained in the latter child displayed marked differences to those found in the other age groups and may be a consequence of the small population sample.

Overall, the PK profiles of children in the two studies were consistent with existing pediatric studies that used similar doses of micafungin.[13] The mean AUC_{tau} in Study 2101 was between ~190–340 h*μg/mL and the mean AUC_{tau} in Study 2102 was ~300 h*μg/mL. By comparison, in febrile, neutropenic children with deep mycoses, the mean micafungin AUC_{tau} was 190.5 h*μg/mL and 301.9 h*μg/mL for 3 mg/kg and 4.0 mg/kg doses, respectively.[13] By contrast, the mean AUC_{tau} obtained in Study 2101 and Study 2102 exceeded the AUC_{tau} obtained in adults treated with 100 mg/day (101.6 h*μg/mL) and 150

mg/day (166.7 h*μg/mL), which are the approved doses for treatment of invasive candidiasis and esophageal candidiasis in adults, respectively.[3,16]

Mean C_{max} was similar in most age groups in Study 2101 (~21 μg/mL). However, the mean C_{max} in the youngest children in Study 2102 was substantially higher (~32 μg/mL). Values observed in Studies 2101 and 2102 were lower than those reported in children treated with similar doses of micafungin ie, 3 mg/kg (30.4 μg/mL) and 4 mg/kg (43.5 μg/mL).[13] Instead, they resembled those observed in children treated at lower doses such as 2 mg/kg (~21 μg/mL).[13] Differences in body weight and the underlying illnesses displayed by the children in each study may have contributed to these disparities.

Mean micafungin CL_{ss} increased with age in our studies. Overall, these differences in clearance may be explained by increasing body weight in children. As such, mean weight-adjusted CL_{ss} was generally comparable between age groups in each dose cohort and consistent with existing results in children treated with 3 mg/kg (17.0 mL/h/kg) and 4 mg/kg (14.2 mL/h/kg) micafungin.[13] Similar to mean C_{max}, CL_{ss}/wt values reported in Studies 2101 and 2102 were generally higher than those reported in adult studies. [15,18,19]

Mean CL_{ss}/wt was higher in younger children (2–5 years) who received 4.5 mg/kg micafungin than older children in this dose cohort. This may be due to a disproportionately high value (40.9 mL/h/kg) in a single child in this age group. However, previous findings in children also suggest that PK parameters may differ between age groups during early development which may account for this difference.[12,13,17]

Some limitations of these studies should be noted. The small number of children in each age group may limit the generalizability of the results, especially given the variety of underlying illnesses of the children. In addition, the studies were not powered to demonstrate clinical efficacy, therefore the small sample size does not permit conclusions to be drawn on the efficacy of micafungin in these child populations.

CONCLUSIONS

The results obtained in Studies 2101 and 2102 suggest that the once-daily 3 mg/kg and 4.5 mg/kg doses of micafungin are well tolerated in children and adolescents with proven, probable, or suspected *Candida* infection. Micafungin-related adverse events were relatively uncommon, and generally did not lead to discontinuation of treatment. The PK data obtained in these studies will be combined with PK data from previous micafungin studies in children in a population PK analysis to support U.S. dosing recommendations in children.

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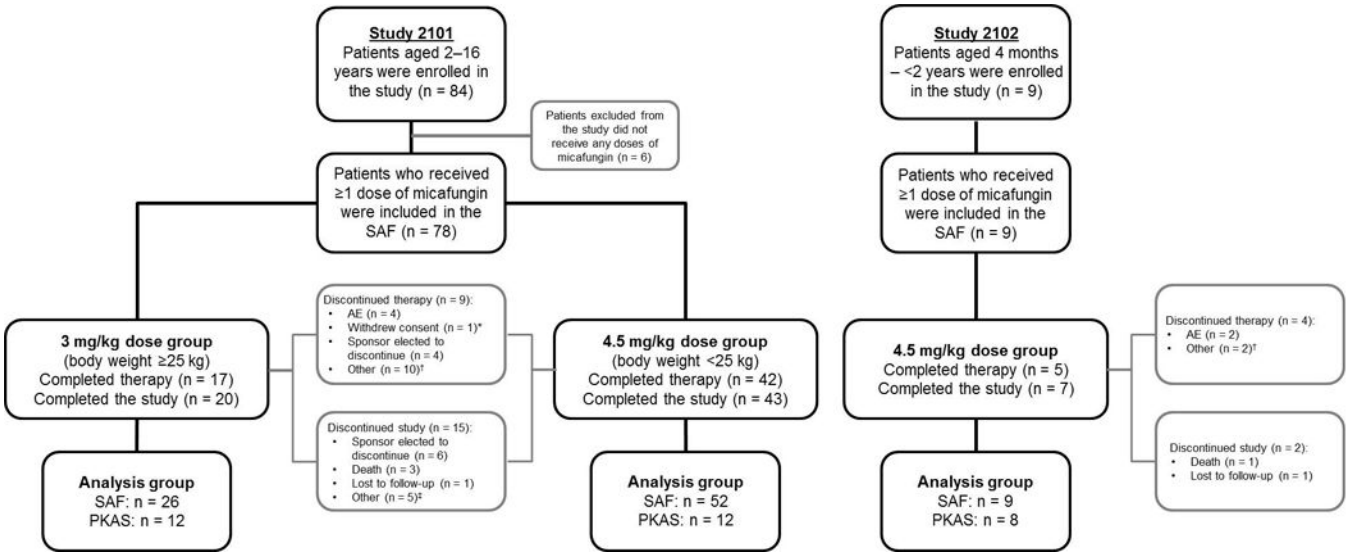

Figure 1. CONSORT study design

*Withdrawal of consent was not due to an adverse event.

†"Other" reasons for discontinuing therapy were children discharged from hospital (Study 2101; n = 6), death (Study 2101; n = 1), unable to establish intravenous access (Study 2101; n = 1), worsening of retroviral disease (Study 2101; n = 1), insufficient venous access (Study 2101; n = 1), treatment failure (Study 2102; n = 1), and fungal infection cleared by day 8, child was clinically stable and ready for hospital discharge (Study 2102; n = 1).

‡"Other" reasons for discontinuing the study were child discharged from hospital (n = 1), child did not return for final visit (n = 1), only 9 days of treatment were administered due to improvement (n = 1), loss of intravenous access (n = 1), and child withdrew consent (n = 1).

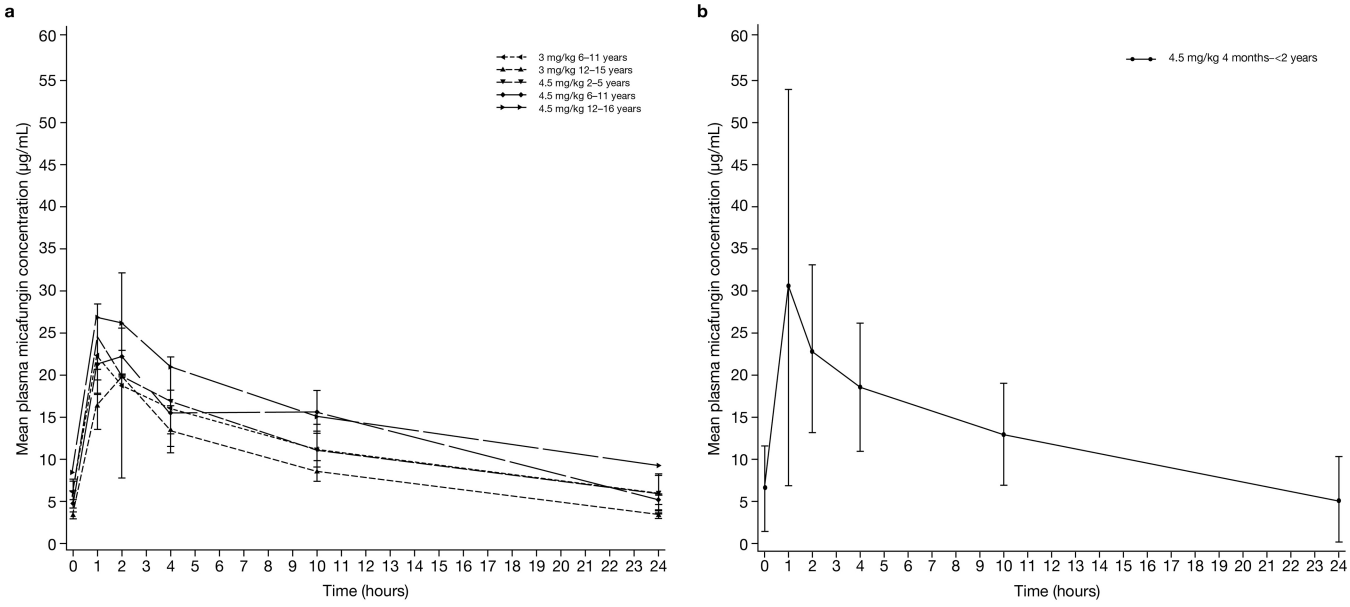

Figure 2.
Mean plasma micafungin concentrations on day

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Table 1

Demographics and summary of drug exposure (SAF)

	Study 2101				Study 2102
	3 mg/kg*		4.5 mg/kg†		4.5 mg/kg
	6–11 years (n = 13)	12–16 years (n = 12)	2–5 years (n = 31)	6–11 years (n = 20)	4 months–2 years (n = 9)
Sex, n (%)					
Male	6 (46)	6 (50)	14 (45)	9 (45)	7 (78)
Race, n (%)					
White	6 (46)	9 (75)	12 (39)	3 (15)	8 (89)
Black	7 (54)	3 (25)	17 (55)	17 (85)	0
Asian	0	0	1 (3)	0	1 (11)
Other	0	0	1 (3)	0	0
Ethnicity, n (%)					
Non-Hispanic or Latino	12 (92)	8 (67)	23 (74)	19 (95)	3 (33)
Age, years					
Mean (SD)	9 (1)	15 (2)	3 (1)	8 (2)	9 months (5)
Median (range)	9 (7–11)	15 (12–17)	3 (2–6)	8 (7–11)	9 (4–19)
Weight, kg					
Mean (SD)	32 (6)	54 (15)	14 (2)	19 (4)	7 (2)
Median (range)	30 (25–44)	54 (26–74)	13 (9–19)	20 (12–24)	7 (4–9)
Treatment duration, days					
Mean (SD)	11 (6)	11 (5)	10 (2)	10 (2)	10 (2)
Median (range)	10 (4–27)	11 (4–22)	10 (5–17)	10 (7–14)	10 (8–14)
Cumulative dose, mg/kg					
Mean (SD)	33 (17)	30 (15)	45 (10)	44 (6)	44 (10)
Daily dose, mg/kg					
Mean (SD)	3 (0)	3 (0)	4.5 (0)	4.5 (0)	4.4 (0)

*Not shown: one white, Hispanic/Latino male, aged 4 years old, who weighed 28 kg, and was treated with a mean daily dose of 3 mg/kg for 10 days.

†Not shown: one white, non-Hispanic/Latino male, aged 16 years old, who weighed 23 kg, and was treated with a mean daily dose of 4.5 mg/kg for 10 days.

SD: standard deviation.

Table 2

Frequency of adverse events in Study 2101 and Study 2102 (SAF)

	Study 2101					Study 2102
	3 mg/kg*		4.5 mg/kg†			4.5 mg/kg
Event	6–11 years (n = 13)	12–16 years (n = 12)	2–5 years (n = 31)	6–11 years (n = 20)	Total (n = 78)	4 months–<2 years (n = 9)
Any AE	9 (69)	11 (92)	25 (81)	16 (80)	62 (80)	9 (100)
AE leading to discontinuation	0	2 (17)	1 (3)	1 (5)	4 (5)	2 (22)
Any SAE	1 (8)	3 (25)	3 (10)	2 (10)	9 (12)	5 (56)
Deaths	0	1 (8)	0	2 (10)	3 (4)	1 (11)

AE: adverse event; SAE: serious adverse event.

*Not shown: one child aged 2–5 years experienced AEs, but no SAEs or AEs leading to discontinuation.

†Not shown: one child aged 12–16 years experienced no AEs or SAEs.

Table 3

Hepatic and renal abnormalities

Parameter	Criteria	Study 2101					Study 2102
		3 mg/kg*		4.5 mg/kg*			4.5 mg/kg
		6–11 years (n = 13)	12–16 years (n = 12)	2–5 years (n = 31)	6–11 years (n = 20)	Total (n = 78)	4 months–<2 years (n = 9)
AST†	>3× ULN	0	0	3 (10)	1 (5)	4 (5)	1 (11)
ALT†	>3× ULN	0	0	4 (13)	1 (5)	5 (6)	2 (22)
AST or ALT	>3× ULN	0	0	5 (16)	1 (5)	6 (8)	2 (22)
Total bilirubin‡	>2× ULN	1 (8)	2 (17)	0	0	3 (4)	1 (11)
Creatinine	>2× ULN	0	1 (8)	1 (3)	0	2 (3)	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

ULNs: 75 U/L (AST); 45 U/L (ALT); 2 mg/dL (total bilirubin); 0.4 mg/dL (creatinine; 4 months–<2 years), 0.7 mg/dL (2–11 years), and 1.0 mg/dL (12–16 years).

*Not shown: one child aged 2–5 years in the 3 mg/kg dose group and one child aged 12–16 years in the 4.5 mg/kg dose group experienced no abnormal liver function tests.

†No children experienced elevated AST or ALT >5x ULN.

‡One child in Study 2102 experienced elevated AST and/or ALT >3x ULN and total bilirubin >2x ULN.

Table 4

Plasma micafungin pharmacokinetic parameters on day 7 (PKAS)

	Study 2101					Study 2102
	3 mg/kg*		4.5 mg/kg			4.5 mg/kg
Parameter	**6–11 years (n = 4)**	**12–16 years (n = 8)**	**2–5 years (n = 8)**	**6–11 years (n = 3)**	**12–16 years (n = 1)**	**4 months–<2 years (n = 8)**
Maximum micafungin daily dose, mg	132.0	153.1†	85.5	108.0	104.0	41.5
AUC_{tau}, h*µg/mL						
Mean (SD)	247.5 (46.4)	193.3 (30.9)	248.9 (68.1)	278.4 (41.6)	339.0	299.4 (140.2)
CV	18.7	16.0	27.4	14.9	–	46.8
Median	249.0	184.5	247.5	264.4	339.0	263.8
Min–Max	191.8–300.1	158.9–240.1	110.0–335.4	245.7–325.2	–	188.0–622.2
Geo. mean	244.1	191.2	238.3	276.4	339.0	278.4
C_{max}, µg/mL						
Mean (SD)	20.8 (4.1)	20.5 (10.3)	21.1 (6.1)	20.7 (3.1)	24.9	32.8 (22.7)
CV	19.9	50.3	28.9	14.9	–	69.2
Median	20.8	16.2	21.9	20.2	24.9	21.7
Min–Max	16.8–24.8	12.2–44.5	8.4–28.7	17.9–24.0	–	18.2–84.8
Geo. mean	24.5	18.9	20.1	20.6	24.9	28.3
t_{max}, hours						
Mean (SD)	1.1 (0.1)	1.3 (0.4)	1.3 (0.5)	2.1 (0.0)	1.1	1.3 (0.4)
CV	7.7	33.2	35.1	2.3	–	32.5
Median	1.1	1.1	1.1	2.1	1.1	1.1
Min–Max	1.0–1.2	1.0–2.0	1.0–2.1	2.0–2.1	–	1.0–2.0
Geo. mean	1.1	1.3	1.2	2.1	1.1	–
CL_{ss}, mL/h						
Mean (SD)	432.6 (129.8)	748.8 (155.1)	241.5 (106.9)	324.1 (65.1)	306.8	110.3 (56.4)
CV	30.0	20.7	44.3	20.1	–	51.1
Median	379.9	757.2	222.9	332.1	306.8	104.1
Min–Max	344.8–625.7	512.6–944.2	132.7–490.9	255.3–384.7	–	46.6–220.2

Parameter	Study 2101					Study 2102
	3 mg/kg*		4.5 mg/kg			4.5 mg/kg
	6–11 years (n = 4)	12–16 years (n = 8)	2–5 years (n = 8)	6–11 years (n = 3)	12–16 years (n = 1)	4 months–<2 years (n = 8)
Geo. mean	420.1	734.1	226.0	319.5	306.8	98.3
CL_{ss}/wt, mL/h/kg						
Mean (SD)	12.3 (2.4)	13.5 (3.1)	20.0 (8.9)	16.4 (2.3)	13.3	16.7 (5.3)
CV	19.6	22.9	44.5	14.1	–	31.8
Median	11.9	12.6	18.3	17.0	13.3	16.4
Min–Max	10.0–15.4	9.5–19.0	13.4–40.9	13.8–18.3	–	7.3–24.2
Geo. mean	12.1	13.2	18.8	16.3	13.3	15.8

*Full PK profiles were not available for the single child in the 2–5 years age group in this dose cohort.

†Four children received the maximum daily dose of 150.0 mg; one additional child received 153.1 mg.

AUC_{tau} and C_{max} values were not dose normalized.

SD: standard deviation; CV: coefficient of variance; Min–Max: minimum to maximum; Geo. Mean: geometric mean.

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