High-Dose Micafungin in Neonates and Young Infants with Invasive Candidiasis: Results of a Phase 2 Study

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ABSTRACT Limited data are available on the most appropriate dosing, efficacy, and safety of micafungin in neonates and young infants with invasive candidiasis (IC). This study evaluated plasma levels, efficacy, and safety of micafungin at a dose of 8 mg/kg daily for a mean of 13.3 days (± 5.2 days) in 35 neonates and young infants with IC. Micafungin plasma concentrations were 5.70 mg/liter preadministration and 17.23, 15.59, and 10.27 mg/liter after 1, 2, and 8 h, respectively. The resolution of the infection was achieved in 86.7% of patients treated for ≥ 14 days. In 20.0% of patients, we observed a transient hypertransaminasemia. Micafungin at a dose of 8 mg/kg daily is effective and well tolerated in neonates and young infants with IC. (This study has been registered at ClinicalTrials.gov under identifier NCT03421002 and in the EU Clinical Trials Register under number 2014-003087-20.)

KEYWORDS echinocandins, invasive candidiasis, micafungin, neonatal intensive care unit

Infants hospitalized in neonatal intensive care units are at a high risk of invasive candidiasis (IC) (1–3), which is the second-most common cause of infection related death, with a mortality rate of 26% to 24% (4–7). Furthermore, the probability of central nervous system (CNS) involvement during infection and of severe long-term neurodevelopmental impairment varies between 45% and 63% of cases (4). Approximately 50% of infants with IC who survive have severe long-term neurodevelopmental impairment (8–10).

Because the diagnosis of IC in infants is difficult, initial therapy is often empirical. The combination of prematurity, thrombocytopenia, and prolonged use of broad-spectrum antibiotics has been suggested as criteria for guiding antifungal initiation (11). Current Infectious Diseases Society of America guidelines recommend amphotericin B deoxycholate and fluconazole as first-line therapies in neonates with IC (12), whereas European guidelines recommend amphotericin B formulations, fluconazole, and micafungin (3). All of these antifungal drugs have inadequate evidence to support their use in neonates, and there is a need for alternative antifungals with increased specificity and reduced toxicity in neonatal populations (13).

The echinocandins, the most recently developed antifungal drug class, have broad-spectrum efficacy against *Candida* spp. and some activity against *Aspergillus* spp. (14). Micafungin is the only echinocandin approved by the European Medicines Agency for use in neonates (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000734/WC500031075.pdf); however, data on pharmacokinetics, dosing, efficacy, and safety in neonates are limited. Because the body-weight-adjusted clearance of micafungin is higher in neonates than in adults and older children (15),

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infants require higher body-weight-based doses of micafungin. Moreover, the high risk of early neurological localization of *Candida* spp. in preterm infants requires plasma levels that are sufficiently able to penetrate the blood-brain barrier. Micafungin at a dose from 0.75 to 15 mg/kg daily is well tolerated in neonates, with no unexpected safety concerns observed (16–18). Furthermore, micafungin at a dose of ≥ 7 mg/kg daily may be sufficient to penetrate the blood-brain barrier (19, 20).

To further explore the optimal micafungin dose in severely ill neonates and infants with confirmed or suspected IC, we performed an open-label, prospective phase 2 study, registered at <http://www.clinicaltrials.gov> (NCT03421002) and <https://www.clinicaltrialsregister.eu/ctr-search/search> (2014-003087-20).

Our primary aim was to study the pharmacokinetics (PK) profile of micafungin (8 mg/kg daily) through quantification of micafungin concentrations in plasma, obtained by heel-stick capillary sampling. Secondary objectives were to identify a conversion factor to relate plasma levels of micafungin into capillary and venous blood samples collected simultaneously from the heel and a peripheral vein of a subgroup of patients and to evaluate the safety of micafungin through the assessment of adverse events (AEs), physical examination results, vital signs, and 12-lead electrocardiogram evaluations.

The study took place in the neonatal intensive care unit of Bambino Gesù Children's Hospital in Rome, Italy, during a period of 27 months, after ethics committee approval. Full details of inclusion criteria, exclusion criteria, and definitions of success and failure of the treatment are provided in Table S1 in the supplemental material. All patients' parents or legal guardians gave consent to enrollment of the babies.

Micafungin was diluted in 0.9% saline solution at a concentration of 2 mg/ml and infused intravenously by central venous catheter over 1 h once daily. Blood samples were collected from the neonates by heel-stick capillary sampling, and in a subset of patients ($n = 8$) by a simultaneous central venous catheter sample draw, 1 h before infusion of the drug and 1, 2, and 8 h after the end of the intravenous infusion (21). Estimation of sample size was not deemed necessary given that the primary endpoint was exploratory. PK and safety analyses were represented as mean (standard deviation [SD]) and median (range). AEs (death included) were coded by MedDRA v20.1 (see Tables S2 and S3 in the supplemental material). The full analysis set (FAS) ($n = 34$, 97.1% of patients), used for PK analysis, and the safety analysis set (SAS) ($n = 35$, 100.0% of patients) included all enrolled patients who received at least one dose of study medication. The modified FAS (mFAS, $n = 21$, 60.0% of patients) was defined as patients in the SAS who had been affected by confirmed IC at baseline and was used for summaries and analysis of efficacy data.

A total of 35 hospitalized neonates and infants (20 [57.1%] male; 21 [69%] with gestational age ≤ 28 weeks, all aged < 180 days from the gestational age corrected at 37 weeks [median age, 1.9 months; range, 0.3 to 8.1 months]) affected by confirmed or suspected IC were enrolled and treated with micafungin (8 mg/kg daily) according to therapeutic need. Among them, 20 patients (57.1%) completed the study treatment (≥ 14 days micafungin) (Table 1). Among the 21 patients (60.0%) with proven IC, the most common *Candida* species coisolated were *Candida albicans* (52.4%) and *Candida parapsilosis* (28.6%). At baseline, the MIC of micafungin was 0.008 to 0.015 $\mu\text{g/ml}$ for *C. albicans* (10 values), 1.000 to 2.000 $\mu\text{g/ml}$ for *C. parapsilosis* (4 values), and 0.060 $\mu\text{g/ml}$ for *Candida lusitanae* (1 value); no postbaseline MIC value was higher than the baseline value. The mean micafungin plasma level was highest at 1 h postdose and decreased over 8 h (fig. 1). Micafungin concentrations from venous plasma were slightly higher than those from heel-stick capillary samples over the time points sampled (1, 2, and 8 h after 3- and 10-day dosing [see Fig. S1 in the supplemental material]).

The success of the therapy with micafungin was achieved in the 86.7% of 15 mFAS patients who completed a minimum of 14 days of micafungin therapy. The percentage of total resolution of infection at the end of therapy was higher for 20 proven infections than for 5 suspected infections (75.0% versus 60.0%, respectively) (Table 2). Mycological eradication was achieved by 61.9% of all mFAS patients at the end of treatment and 90.5% at the end of the study. Overall, 86 treatment-emergent AEs (TEAEs) were experienced by 88.6%

TABLE 1 Patient demographics and baseline characteristics

Characteristic	Micafungin results (n = 35) (n [%] ^a)
Sex	
Male	20 (57.1)
Female	15 (42.9)
Race	
Caucasian	32 (91.4)
Black/African American	2 (5.7)
Other ^b	1 (2.9)
Median (range) age (mo)	1.90 (0.3–8.1)
Age group	
0 to ≤4 wk	8 (22.9)
>4 wk to ≤4 mo	20 (57.1)
>4 mo to ≤6 mo	3 (8.6)
>6 mo to <2 yr	4 (11.4)
Gestational age group	
≤28 wk	21 (60.0)
>28 wk	14 (40.0)
Median (range) birth weight (kg)	1.0 (0.4–3.1)
Risk factor to fungal infection at baseline	
Mechanical ventilation	27 (77.1)
Ongoing treatment with steroids	11 (31.4)
Ongoing treatment with anti-H2 drugs	8 (22.9)
Proven systemic candidiasis diagnosis (n = 21)	
<i>C. albicans</i>	11 (52.4)
<i>C. glabrata</i>	1 (4.8)
<i>C. krusei</i>	1 (4.8)
<i>C. lusitaniae</i>	1 (4.8)
<i>C. parapsilosis</i>	6 (28.6)
<i>C. tropicalis</i>	1 (4.8)
Common medical history (≥20%)	
Anemia	34 (97.1)
Premature baby	31 (88.6)
Coagulopathy	18 (51.4)
Patent ductus arteriosus	17 (48.6)
Thrombocytopenia	16 (45.7)
Respiratory failure	16 (45.7)
Atrial septal defect	15 (42.9)
Cholestasis	13 (37.1)
Bronchopulmonary dysplasia	13 (37.1)
Retinopathy of prematurity	11 (31.4)
Increased gamma-glutamyl transferase	9 (25.7)
Metabolism and nutrition disorders	9 (25.7)
Hypoalbuminemia	8 (22.9)
Pulmonary hypertension	8 (22.9)
Hyperbilirubinemia	7 (20.0)
Cerebral hemorrhage	7 (20.0)

^aUnless otherwise indicated. Safety analysis set comprises all enrolled patients who had received at least 1 administration of study medication.

^bNot Asian, not Hispanic.

of the patients (Table 3). The most common TEAEs are summarized in Table S3 in the supplemental material. No TEAE led to study drug discontinuation or dose reduction. Three TEAEs led to death, and there were 5 deaths (14.2%) in the study, none related to micafungin administration (Table S2). In 20.0% of patients, a transient increase in aspartate transaminase and alanine transaminase was observed.

FIG 1 Plasma concentrations of micafungin measured in heel-stick capillary samples from 34 patients. Safety analysis set comprised all enrolled patients who had received at least one dose of study drug. One patient died before the complete pharmacokinetic draw could take place. SD, standard deviation.

This prospective study follows a previous retrospective study of micafungin administration in neonates with invasive and CNS candidiasis, which evaluated doses that were 4- to 7.5-fold higher than those approved by regulatory agencies for use in neonates with IC (22). We aimed to expand the previous findings and determine the most appropriate micafungin dosing regimen in neonates and young infants to reach the efficacy of therapy without side effects. We demonstrated a high response to micafungin therapy at 8 mg/kg daily in most of the 21 treated patients with proven IC. Overall, treatment success with micafun-

TABLE 2 Response at end of treatment and by certainty of diagnosis

Treatment response	Micafungin results (<i>n</i> = 35) (% [<i>n</i>], 95% CI) ^a	
	SAS	mFAS
End of treatment		
Completed ^b	20	15
Success	80.0 (16), 56.34–94.27	86.7 (13), 59.54–98.34
Failure	20.0 (4)	13.3 (2)
All patients	35	21
Completed 14 days of therapy	45.7 (16), 28.83–63.35	61.9 (13), 38.44–81.89
Failure of the therapy	11.4 (4)	9.5 (2)
Did not complete the 14 days of therapy	42.9 (15)	28.6 (6)
Certainty of diagnosis ^c		
Overall	20	15
No. of infections	25	20
Success (resolution of the infection)	72.0 (18), 50.61–87.93	75.0 (15), 50.90–91.34
Failure	28.0 (7)	25.0 (5)
Proven	15	15
No. of infections	20	20
Success (<i>Candida</i> eradication)	75.0 (15), 50.90–91.34	75.0 (15)
Failure	25.0 (5)	25.0 (5)
Suspected	5	0
No. of infections	5	
Success (recovery from infection)	60.0 (3), 14.66–94.73	
Failure	40.0 (2)	

^aCI, 2-sided exact confidence interval; SAS, safety analysis set, all enrolled patients who had received at least 1 dose of study drug; mFAS, modified full analysis set, patients in the SAS who had been affected by systemic candidiasis and/or *Candida* infection at baseline.

^bPatients completing a minimum of 14 days of study drug therapy.

^cFor each diagnosis, percentages were taken from the number of infections with that diagnosis. Only patients who completed 14 days of study drug therapy were evaluable for treatment response.

TABLE 3 Overview of TEAEs

TEAE ^a	Patients treated with micafungin (n = 35)	
	Patients with TEAEs (n [%])	No. of events
Any	31 (88.6)	86
Mild	4 (11.4)	23
Moderate	14 (40.0)	41
Severe	6 (17.1)	11
Life threatening	4 (11.4)	8
Death	3 (8.6)	3
Drug related ^b	1 (2.9)	1
With unknown relationship ^b to study drug	15 (42.9)	26
Serious ^c	12 (34.3)	18
Drug-related ^b serious ^c	0 (0.0)	0
Serious ^c with unknown relationship to study drug	3 (8.6)	3
Leading to death	3 (8.6)	4
Drug related ^b leading to death	0 (0.0)	0
Leading to death with unknown relationship ^b to study drug ^b	0 (0.0)	0
Leading to withdrawal of treatment	0 (0.0)	0
Drug related ^b leading to withdrawal of treatment	0 (0.0)	0
Leading to withdrawal of treatment with unknown relationship ^d to study drug	0 (0.0)	0
Death ^d	5 (14.3)	8

^aTEAE defined as an AE experienced any time during study drug administration through 72 h after the last dose of study drug. Within a system organ class, patients may have experienced more than one adverse event. Safety analysis set comprised all enrolled patients who had received at least 1 dose of study drug.

^bA reasonable possibility that the event could have been caused by the study drug as assessed by the investigator. If relationship missing, it is considered drug related. Causal relationship case report form options were "related/not related/unknown."

^cIncludes serious AEs upgraded by the sponsor based on review of the sponsor's list of "always serious" terms, if any upgrade was done.

^dAll deaths reported after the first study drug administration. Two patients were reported to have died outside the 30-day window; however, no further details were available.

gin was achieved in 61.9% of patients with IC, regardless of treatment duration, and in 86.7% who completed a minimum of 14 days of micafungin therapy. Most patients did not have shifts from baseline to postbaseline for the selected hematology tests. Moreover, we confirmed that heel-stick capillary samples represent a valid alternative for intravenous blood sampling in very-preterm and at-term neonates for micafungin dose optimization.

Despite the small sample size, the study reflects the complexity associated with the conduct of clinical trials in critically ill neonates. Micafungin was well tolerated in this patient population, and this study adds to the growing literature on use of higher body-weight-based doses in children aged <4 months.

Data availability. Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx>.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

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C.A. and B.M.G. designed the study, fine-tuned the technique for carrying out the PK assays, and checked the results. B.M.G. and S.C. carried out the laboratory measurements.

C.A., M.P.R., and F.P. monitored patients during therapy, checked laboratory tests, and collected parental consent of enrolled patients. I.B. followed enrolled patients, collected clinical and laboratory data, and entered the data in the case report form. A.D., P.B., and M.P.P. contributed to the design of the study. All authors contributed to interpretation of the data and drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

C.A., M.P.R., I.B., and A.D. report other from Astellas during the conduct of the study; F.P. and P.B. report nonfinancial support from Astellas during the conduct of the study; B.M.G., S.C., and M.P.P. have nothing to disclose.

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