Population Pharmacokinetics of Micafungin and Its Metabolites M1 and M5 in Children and Adolescents

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The aim of this analysis was to identify therapeutic micafungin regimens for children that produce the same micafungin exposures known to be effective for the prevention and treatment of Candida infections in adults. Pediatric pharmacokinetic data from 229 patients between the ages of 4 months and <17 years were obtained from four phase I and two phase III clinical trials. Population pharmacokinetic models were used to simulate the proportion of children who had a steady-state area under the concentration-time curve at 24 hours (AUC24) of micafungin within the 10th to 90th percentile range observed in a population of adults receiving a dose of micafungin with established efficacy for invasive candidiasis (100 mg/day), i.e., 75 to 139 µg · h/ml. Simulated pediatric dosages of 0.5 to 5 mg/kg of body weight/day were explored. A two-compartment model was used that incorporated body weight as a predefined covariate for allometric scaling of the pharmacokinetic parameters. During construction of the model, aspartate aminotransferase and total bilirubin were also identified as covariates that had a significant effect on micafungin clearance. A dose of 2 mg/kg resulted in the highest proportion of children within the predefined micafungin AUC24 target range for invasive candidiasis. Cutoffs of 40 or 50 kg for weight-based dosing resulted in heavier children being appropriately dosed. Thus, dose regimens of 1, 2, and 3 mg/kg/day micafungin are appropriate for the prevention of invasive candidiasis, the treatment of invasive candidiasis, and the treatment of esophageal candidiasis, respectively, in children aged 4 months to <17 years.

Micafungin is an echinocandin antifungal agent with activity against medically important fungal pathogens such as Candida spp. and Aspergillus spp. (1). It is licensed worldwide for the treatment of adults with invasive candidiasis, the prevention of invasive Candida infections, and the treatment of esophageal candidiasis. A dosage of 100 mg/day is used in adults weighing >40 kg with candidemia and/or invasive candidiasis. There is no additional benefit in using a higher dosage of 150 mg/day in these patients (2). A dosage of 50 mg/day is used for the prevention of invasive Candida infections in neutropenic patients, while a dosage of 150 mg/day is used for the treatment of esophageal candidiasis.

The U.S. Food and Drug Administration (FDA) has approved the use of micafungin for pediatric patients >4 months of age for the same indications as adults (3). Micafungin is licensed by the European Medicines Agency (EMA) for the treatment of children (including neonates) and adolescents <16 years of age with invasive candidiasis and as prophylaxis in patients <16 years of age who are undergoing hematopoietic stem cell transplant or who are expected to have neutropenia (1).

The safety and pharmacokinetics (PK) of micafungin in neonates, children, and adolescents have been determined in a number of clinical studies (4, 5). These studies enrolled patients across different age groups and have led to the development of a variety of population PK models (6, 7). The overriding goal has been the identification of regimens that produce drug exposures comparable with those observed in adults, for whom the efficacy has been established in a number of phase II and III clinical trials (2, 8–10). Regulatory authorities, such as the FDA and EMA, accept this approach for the licensure of new agents for children, providing there are adequate safety data, and the pharmacodynamics (PD) and disease entities are comparable with those in adults (11). Such an approach requires the development of robust population PK models and the use of simulation techniques to explore the consequences of PK variability.

Previous studies described the population PK of micafungin in 72 children aged 2 to 17 years with febrile neutropenia (6) and 47 infants aged <120 days with suspected or proven invasive candidiasis (7). In this analysis, we describe the population PK of micafungin in 229 children aged 4 months to <17 years with a range of different diseases. This work represents an extension of previous population PK models and provides a summary of the modeling of the most comprehensive data set of micafungin in pediatric patients that has been compiled to date.

MATERIALS AND METHODS

Design of studies. Pharmacokinetic data for 229 patients were obtained from four pediatric phase I studies (9463-CL-2101 [ClinicalTrials.gov identifier NCT00608335] [12], 9463-CL-2102 [NCT00607763] [12], 9463-CL-2103 [NCT00606268], and 98-0-043 [5]) and two pediatric phase III studies (FG-463-21-08 [NCT00106288] [13] and FJ-463-FP01


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the central compartment; IV, intravenous; Q, intercompartmental clearance; V1, volume of the central compartment; V2, volume of the peripheral compartment; $K_{\text{el}}$, elimination rate constant of M1 or M5; KP, exposure of M1 or M5 relative to micafungin exposure. Note that individual post hoc micafungin pharmacokinetic parameters were obtained from the final micafungin model.

FIG 1 Base models for micafungin (A) and M1 or M5 (B). CL, clearance from the central compartment; IV, intravenous; Q, intercompartmental clearance; V1, volume of the central compartment; V2, volume of the peripheral compartment; $K_{\text{el}}$, elimination rate constant of M1 or M5; KP, exposure of M1 or M5 relative to micafungin exposure. Note that individual post hoc micafungin pharmacokinetic parameters were obtained from the final micafungin model.

[unpublished data]). All studies received ethical approval from the respective institutional committees.

The details of these studies are as follows: (i) 9463-CL-2101 (n = 64) was an open-label study that examined the safety and PK of repeat dosing of micafungin 3 mg/kg of body weight (weight, ≥ 25 kg) or 4.5 mg/kg (weight, < 25 kg) to a maximum of 150 mg in children aged 2 to 11 years and adolescents (aged 12 to 16 years) with invasive candidiasis or esophageal candidiasis; (ii) 9463-CL-2102 (n = 9) was an open-label study that examined the PK and safety of micafungin 4.5 mg/kg for infants and toddlers (aged ≥ 4 months to 2 years) with invasive candidiasis or esophageal candidiasis; (iii) 9463-CL-2103 (n = 40) was an open-label study of the safety and PK of micafungin 1.5 mg/kg (weight, < 25 kg) or 1 mg/kg (weight, ≥ 25 kg) for antifungal prophylaxis in children and adolescents (aged 4 months to 16 years) who were undergoing hematopoietic stem cell transplantation; (iv) 98-0-043 (n = 70) was an open-label, single-group dose-escalation and PK study in PK study in patients aged ≥ 12 years with febrile neutropenia who received 0.5, 1, 1.5, 2, 3, or 4 mg/kg/day to a maximum of 200 mg/day; (v) FG-463-21-08 (n = 27) was a randomized double-blind trial of micafungin versus liposomal amphotericin B in children aged 0 to 15 years with candidemia and/or invasive candidiasis receiving micafungin 2 mg/kg/day if ≤ 40 kg or 100 mg/day if > 40 kg; and (vi) FJ-463-FP01 (n = 19) was an open-label study that examined the safety, PK, and efficacy of micafungin for invasive fungal infections caused by Aspergillus spp. or Candida spp. at an initial dosage of 1 mg/kg/day, with the possibility of dose escalation to 6 mg/kg/day.

Sample collection and analytical methods. In all six studies, concentrations of micafungin and metabolites M1 and M5 were measured. Metabolite M5 was measured in all studies, except for 98-0-043 and FJ-463-FP01. The sampling schedule varied across studies but was generally performed within 1 h before the start of infusion and then 1, 2, 4, 10, and 24 h after the start of infusion. However, in subsets of patients (n = 59) enrolled in studies 9463-CL-2101 and FG-463-21-08, only trough concentrations (24 h after the start of infusion) were assessed.

All plasma concentrations of micafungin and the metabolites were measured using high-performance liquid chromatography (HPLC) as described in previous publications related to these studies (5, 12, 13). In brief, acidified plasma samples were precipitated with acetonitrile and centrifuged prior to dilution with buffer and injection into an HPLC system. Separation of micafungin and metabolites was achieved with a reverse-phase octadeccysil column. The analytes were quantified by fluorescence detection. The lower limit of quantitation for micafungin and metabolites was 0.05 μg/ml in plasma.

Pharmacokinetic analysis. All data were scrutinized prior to population PK analyses. Eighty-five plasma concentrations from 13 patients at two study sites in study 9463-CL-2101 had markedly low micafungin concentrations (mean, 2.8 μg/ml). These low concentrations were attributed to mishandling at the study sites and shipping to the central laboratory. In preliminary analyses, clearance values obtained using these samples were higher than the model-derived 99th percentile boundary; therefore, these outlier samples were excluded from further assessments.

In addition, one M5 plasma concentration observation from one patient in study FG-463-21-08 was excluded as no micafungin concentration was measurable. From the remaining patients, a total of 4,280 concentration measurements of micafungin and metabolites M1 and M5 were detectable and available for analysis. Concentrations of M2 were measured concomitantly but were persistently at or below the limit of quantification, did not yield data that were readily interpreted or modeled, and were not evaluated further in this analysis.

Records with incomplete dosing information or missing date and/or time of sample collection were excluded. All samples that were beneath the lower limit of quantification were excluded from the analysis. Data that were clearly implausible within the expected time course and likely to be attributable to labeling or data collection errors were excluded. A total of 47, 35, and 17 concentration observations of micafungin and M1 and M5 metabolites, respectively, were excluded from the analyses on this basis.

A total of 1,919, 1,421, and 844 concentration observations of micafungin, M1, and M5, respectively, were used for analysis. The average numbers of available samples per patient were 8.4, 6.2, and 3.7 for micafungin, M1, and M5 metabolites, respectively. The combined pediatric data set for analyses was prepared using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Population PK models for micafungin, M1, and M5. The population PK analysis for micafungin was conducted prior to incorporating data from the metabolites M1 and M5. Initially, a standard two-compartment model was used (Fig. 1), in which micafungin was infused into the central compartment. The structural model parameters were clearance from the central compartment (CL, liter/h), intercompartmental clearance (Q, liter/h), volume of the central compartment (V1, liter), and volume of the peripheral compartment (V2, liter).

Preliminary studies suggested that there was a relationship between body weight and clearance. As a result, body weight was directly incorporated into a structural model using an allometric scaling term. This approach was used previously for micafungin (for both neonates and children [6, 7]) and enables the nonlinear relationship between size (approximated using body weight) and the structural parameters to be estimated.

As there is a strong correlation between age and weight, especially in
children, and because a relationship between age and clearance was previously identified (5), age was also tested in the structural model using an allometric scaling term. However, when allometric scaling using age was employed, model fitting was worse in terms of the object function value compared with allometric scaling using weight.

Once the final micafungin model was established (see “Random-effect modeling,” “Covariate model building,” and “Model validation” below), analyses of the metabolites were conducted using individual post hoc micafungin PK parameters from the final micafungin model. The structural model for the metabolites was a single compartment connected to the central compartment of micafungin (Fig. 1). The model parameters were relative exposure (KP), i.e., exposure of the metabolite relative to that of micafungin at steady state, and the elimination rate constant (k30). In the model fitting process, the parameters describing the PK of micafungin were obtained from the final micafungin model and fixed.

Analysis of the potential relationships between the Bayesian post hoc estimates for KP and covariates was undertaken. The model was refitted with these covariates to develop final models for the metabolites M1 and M5. The models were validated using a bootstrapping technique as described below (see “Model validation”).

The fits of the models (for micafungin and metabolites) to the data were assessed by a visual inspection of goodness-of-fit plots (Fig. 2), including the individual and population observed-versus-predicted plots, the conditional weighted residuals-versus-predicted values, and the conditional weighted residuals versus time.

Random-effect modeling. A log-normal random effect was assumed for intersubject variability on each structural PK parameter, and a combination of proportional and constant random errors was assumed for the residual-error model on the measurements of micafungin and its metabolites, taking the forms $CL_j = CL_{pop} \times \exp(\eta_j)$ and $C_{obs,ij} = C_{pred,ij} \times (1 + \epsilon_{prop,ij}) + \epsilon_{const,ij}$, where CL is the structural parameter for the jth individual, $CL_{pop}$ is the typical value for the parameter CL in the population, and $\eta_j$ is a random variable representing intersubject variability of the parameter, with mean zero and variance $\omega_\eta^2$. The variables $C_{obs,ij}$ and $C_{pred,ij}$ represent the ith observed and predicted concentrations, respectively, for the jth patient, while $\epsilon_{prop,ij}$ and $\epsilon_{const,ij}$ are the proportional or constant random residual errors, which are normally distributed with mean zero and variance $\sigma_{prop}^2$ or $\sigma_{const}^2$.

In preliminary studies, correlations between individual post hoc CL, V1, Q, and V2 were observed; hence, a common random effect on each of CL, V1, Q, and V2 was modeled as a representative random effect on CL, and parameter-specific random effects were added for V1, Q, and V2 (Fig. 1). It was also confirmed that differences in the number of concentration data points obtained for each patient did not have a significant impact on individual PK parameters. There was no apparent trend between the number of data points and post hoc CL, and no significant difference in post hoc CL in patients with profiling data compared with those with trough data only (data not shown).

All population modeling was performed using the nonlinear mixed-effect modeling software NONMEM version 7.1.0 (ICON plc, Dublin, Ireland). An Intel Visual Fortran compiler version 11.1 was used. The first-order conditional estimation method with interaction option (FOCE-I) was employed for all runs.
Covariate model building. The effects of covariates obtained at the initial study visit on the PK of micafungin were estimated. Covariates included age, age group, sex, and baseline values of albumin (ALB), platelet (PLT), red blood cell (RBC), serum creatinine (CRE), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. The use of concomitant medications was not assessed as a covariate as the individual covariates. The impact of covariates on the PK was obtained from individual patients from the base model for micafungin (3).

The potential impact of the selected covariates on the population PK was explored by plotting Bayesian post hoc estimates for the CL and V1 obtained from individual patients from the base model for micafungin and the individual covariates. The impact of covariates on the PK was explored and modeled using the following equations for continuous and binary variables, respectively:

\[ \text{CL}_{\text{pop}}(X_j) = \text{CL}_{\text{pop}}(1) \times \exp(\theta_{\text{power}} \times \ln(\text{X}_j/\text{X}_{\text{pop}})) \]

\[ \text{CL}_{\text{pop}}(Z_j) = \text{CL}_{\text{pop}}(1) \times \theta_{\text{ratio}} \]

where \( \text{X}_j \) and \( Z_j \) are continuous or binary variables, respectively, for the \( j \)th patient, and \( \theta_{\text{power}} \) and \( \theta_{\text{ratio}} \) are fixed parameters describing the magnitude of the covariate effect. \( \text{X}_{\text{pop}} \) is a representative value of \( \text{X} \) in the population close to the mean, and \( Z_j \) carries a value of 0 or 1 when the binary variable is absent or present in the \( j \)th individual, respectively.

The impact of these covariates on the PK of micafungin was explored using a stepwise forward addition and backward deletion strategy within NONMEM. The significance of the covariates was judged on the basis of a log-likelihood ratio test, with acceptance values of 0.05 and 0.01 for the NONMEM. The final models of micafungin, M1, and M5 were converged for the final models of micafungin, M1, and M5, respectively. Measures of central tendency and dispersion and the 95% confidence interval (CI) for each parameter value were calculated and compared with the original parameter value’s estimates.

Simulations and identification of regimens for children resulting in comparable drug exposure to adults. Earlier studies have suggested that the PK of micafungin are linear (5) and supported by the use of linear structural models (6, 7). In this analysis, the pediatric dose for invasive candidiasis was initially investigated before extrapolation to regimens for prophylaxis and esophageal candidiasis (which were assumed to be 50% and 150%, respectively, of the estimated dose for invasive candidiasis).

The efficacy of micafungin 100 mg/day in adults with invasive candidiasis was established in clinical trials (03-0-192 [NCT00105144] [2] and FG463-21-08 [9]). Similarly, the PK of micafungin in adult patients are well characterized (14). Adult steady-state area under the concentration-time curve at 24 hours (AUC24) data were obtained from studies FG-463-21-08 (micafungin for invasive candidiasis) (13) and FG-463-21-09 (micafungin for esophageal candidiasis). Noncompartmental techniques were used to define the AUC24 in each of the 40 patients who participated in these studies and received micafungin 100 mg/day. The 10th and 90th percentiles of the distribution of AUC24 were determined, and the interindividual range was used to define the drug exposure target used to explore and define pediatric micafungin regimens. This range was selected to ensure that the majority (80%) of the population was included, while maintaining sufficient power to detect potential differences in exposure distribution.

Using the final model of micafungin and the post hoc PK parameters obtained from individual pediatric patients (\( n = 229 \)), the steady-state AUC24 under various micafungin regimens was simulated in order to determine the most appropriate weight-based micafungin dosage (mg/kg) for pediatric patients. In this process, the pediatric regimens were chosen to maximize the proportions of simulated AUC24 that were within the 10th and 90th percentile of the AUCs for adults receiving 100 mg/day (i.e., 75 to 139 μg · h/ml). Pediatric dosages of 0.5, 0.75, 1.0, 1.25, 2.5, 3.5, 4, 4.5, and 5 mg/kg/day were explored. Based on observations made in previous work in this pediatric population (5), the patients were grouped by age (4 months to <2 years, 2 to 5 years, 6 to 11 years, and 12 to 16 years), and exposures simulated for each age group were assessed for each dosage to explore the impact of body size on drug exposure.

In addition, the weight cutoff at which pediatric dosing (mg/kg/day) transitions to a standard adult dose (mg/day) was examined. This is important because adolescents weighing >50 kg have the potential to receive more than the currently licensed adult dosage of 100 mg/day for the treatment of invasive candidiasis. Therefore, a number of cutoffs were investigated: (i) none, i.e., all patients received 2 mg/kg regardless of the fact that the absolute dose administered may be >100 mg/day; (ii) 40 kg, the current cutoff approved by the EMA and used for dosing in Europe; and (iii) 50 kg, a “natural” cutoff if a dose of 2 mg/kg is chosen for children, in conjunction with an adult dosage of 100 mg/day.

Analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA), S-Plus version 6.2J (Mathematical Systems, Inc., Tokyo, Japan), and Excel 2007 (Microsoft Corporation, Redmond, WA, USA).

RESULTS
Micafungin base model and final model. The demographic details of the patients enrolled in these studies are summarized in Table 1. The parameter estimates and the associated estimation

TABLE 1 Demographics and clinical characteristics of patients

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Data (mean ± SD) for age group:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 mo to &lt;2 yrs (( n = 29 ))</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>7.9 ± 1.7</td>
</tr>
<tr>
<td>Albumin (g/liter)</td>
<td>32.6 ± 6.9</td>
</tr>
<tr>
<td>Platelets (10^9/liter)</td>
<td>189.8 ± 161.8</td>
</tr>
<tr>
<td>Red blood cells (10^12/liter)</td>
<td>3.53 ± 0.55</td>
</tr>
<tr>
<td>Creatinine (μmol/liter)</td>
<td>28.2 ± 22.2</td>
</tr>
<tr>
<td>ALT (U/liter)</td>
<td>60.7 ± 49.5</td>
</tr>
<tr>
<td>AST (U/liter)</td>
<td>52.9 ± 39.6</td>
</tr>
<tr>
<td>Total bilirubin (μmol/liter)</td>
<td>15.0 ± 27.2</td>
</tr>
</tbody>
</table>

\(^a\) ALT, alanine aminotransferase; AST, aspartate aminotransferase.

\(^b\) Except albumin (\( n = 26 \)) and ALT, AST, and total bilirubin (\( n = 27 \)).

\(^c\) Except albumin (\( n = 71 \)), ALT and AST (\( n = 73 \)), and total bilirubin (\( n = 70 \)).

\(^d\) Except albumin (\( n = 67 \)), platelets and ALT (\( n = 72 \)), and AST and total bilirubin (\( n = 71 \)).
errors obtained using the base model are summarized in Table 2. The estimate for the allometric scaling exponent for the base model was 0.790, which closely approximates the value of 0.75 that is often empirically used.

In the process of forward addition of covariates, AST, ALT, and bilirubin had the strongest effect on clearance ($P = 0.002, 0.004, and 0.007$, respectively). None of the other covariates met the prespecified significance threshold of 0.05. In the second step of the process of forward addition, AST and ALT were added to the model together. However, the effect of ALT plus AST on clearance was not statistically significant ($P = 0.28$), suggesting that ALT and AST may be interchangeable. In contrast, the effect of AST plus bilirubin on clearance was statistically significant ($P = 0.005$).

In the backward deletion process, both AST and bilirubin were statistically significant covariates of micafungin CL in addition to weight. Incorporation of ALT plus total bilirubin into the model was also tested and yielded a comparable, but slightly lower, improvement in object function value. Therefore, AST and total bilirubin were included in the final model.

The parameter values for the final model are shown in Table 2, and the diagnostic plots are shown in Fig. 2. The allometric scaling exponent was 0.787, which was comparable with the estimate from the base model. Based on the final model for micafungin, clearance of the $j$th individual (CL$_{j}$) is given by:

$$\text{CL}_j = \frac{\text{weight}_j \times 0.356 \times (\text{AST}_j/21.5)^{0.787} \times (\text{bilirubin}_j/12)^{0.0492}}{0.00443 \times (\text{weight}_j/21.5)^{0.787} \times (\text{AST}_j/21.5)^{0.787} \times (\text{bilirubin}_j/12)^{0.0492}}$$

where weight$_j$, AST$_j$, and bilirubin$_j$ are the body weight, AST, and bilirubin values at baseline, respectively, of the $j$th individual. In particular, 0.356 liter/h is the population mean CL for a typical patient weighing 21.5 kg, with an AST value of 50 U/liter and a bilirubin value of 12 μmol/liter.

**Validation of the micafungin model.** The final micafungin model was validated using a nonparametric bootstrap. A random resampling technique was used to replace 300 data sets from the final data set. The final micafungin model was successfully fitted to 243 data sets. The bootstrap means and 95% CIs for each parameter closely approximated the estimates obtained from the final model (Table 3), indicating that the parameter estimates from the final model were robust and stable.
Estimation of micafungin exposure in children versus adults. The pooled mean AUC$_{24}$ (± standard deviation) values for the 40 adults in trials FG-463-21-08 (13) and FG-463-21-09 who received micafungin 100 mg/day was 106.2 ± 28.2 μg · h/ml. The 10th and 90th AUC$_{24}$ percentiles were 75 and 139 μg · h/ml, respectively; this was used as the reference range in subsequent analyses. The simulated mean AUC$_{24}$ of all 229 children was 119.8 ± 36.5 μg · h/ml. The simulated mean AUC$_{24}$ values for children weighing <40 kg receiving micafungin 2 mg/kg and those weighing >40 kg receiving 100 mg/day in the age groups 4 months to <2 years, 2 to 5 years, 6 to 11 years, and 12 to 16 years were 108 ± 38.0 μg · h/ml, 107.6 ± 30.6 μg · h/ml, 129.0 ± 36.4 μg · h/ml, and 130.9 ± 37.2 μg · h/ml, respectively.

A pediatric dosage of 2 mg/kg/day (without a transition to adult dosing) maximized the proportion of patients across a range of age groups within the predefined drug exposure target range (Fig. 3). As many of the older children weighed >50 kg, they had exposures higher than the 90th percentile because they received >100 mg/day micafungin as an absolute dosage and because of the nonlinear relationship between body weight and clearance. The percentage of all patients in the AUC$_{24}$ target range was highest with the 2-mg/kg dose but was achieved at the cost of a significant proportion of older children having an AUC$_{24}$ value of >139 μg · h/ml.

The potential for exposures in older, heavier young patients to be in excess of those typically observed in adults suggested that a weight cutoff for dosing was required. The effect of employing either the 40- or 50-kg cutoff as opposed to universal dosing with 2 mg/kg resulted in fewer patients with AUC$_{24}$ values of >139 μg · h/ml. The use of a 40-kg dosing cutoff resulted in 65.4% of patients in the 12- to 16-year age group in the AUC$_{24}$ target range, whereas the use of a 50-kg cutoff resulted in 71.1% of patients in this age group falling within the desired range (Fig. 4).

Population PK of micafungin metabolites. The structural model adequately accounted for the micafungin and the M1 and M5 metabolite data, as evidenced by the small estimation errors of the model parameters (Table 4). For M1, there was a relatively minor, albeit statistically significant, impact of the albumin concentration with the parameter KP. In contrast, for M5, there was a relationship between KP and age, which was especially apparent for patients <4 years of age. Moreover, there was a significant effect of total bilirubin concentration on the KP of M5. The parameter estimates were stable and robust following bootstrapping (data not shown).

DISCUSSION
Micafungin is an echinocandin that has been extensively studied in premature infants, children, and adults (2, 4–10, 15, 16). The
efficacy and safety of this compound have been established in children and adults with invasive candidiasis. Micafungin also appears to have activity against Aspergillus spp. (10) and can be used for the prevention of invasive Candida infections in patients following hematopoietic stem cell transplantation (8). Micafungin was approved by the EMA for children, including neonates, in 2008 (1). At that time, the only available PK data were those from a single phase I PK and safety study in children aged 2 to 17 years (5), a PK and tolerability study in neonates (4), and a subset of pediatric patients from a phase III study in the treatment of invasive candidiasis (13). In the European Union, the currently approved dosages of micafungin for children weighing <40 kg are 1 and 2 mg/kg for the prevention and treatment of invasive candidiasis, respectively. The progressive accumulation of PK data in recent years provides an opportunity to further reflect on the adequacy of current dosage regimens for children and adolescents.

A reasonable approach, and one that is accepted by regulatory authorities, for designing appropriate antimicrobial regimens for children is to ensure that the drug exposure is equivalent to that observed in adults in whom definitive clinical trials have been performed (11). Such an approach is only valid if there are concomitant safety data and sufficient PK data and the disease entities are comparable. Specifically, while efficacy can often be extrapolated from adults to children for most infections, the safety and PK must be assessed separately (17).

The exposure-response relationships for micafungin for the treatment of esophageal candidiasis and invasive candidiasis in children and adults can reasonably be assumed to be the same. Importantly, however, the conclusions of the current study do not apply to neonates, principally because the PD of micafungin for neonatal hematogenous meningoencephalitis are distinct from the PD for other forms of invasive candidiasis (18). In this situation, a higher dose is required (10 mg/kg), and this was determined using a PK–PD bridging study with subsequent validation in a multicenter international clinical trial, which is currently enrolling patients (NCT00815516).

This analysis highlights some of the challenges of defining dosing regimens for children and adolescents. In an early study of micafungin PK in pediatric patients, an inverse relationship between age and weight-adjusted clearance was observed, i.e., weight-adjusted clearance was approximately 1.35-fold higher in patients aged 2 to 8 years than in patients aged ≥9 years (5). Subsequently, it was shown in a larger patient population that

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**TABLE 4 Parameter estimate of M1 and M5 base and final models**

<table>
<thead>
<tr>
<th>Parameter†</th>
<th>Base model</th>
<th>Final model</th>
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<tr>
<td><strong>M1</strong></td>
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<tr>
<td>Population mean</td>
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<tr>
<td>KP</td>
<td>0.104 4.9</td>
<td>0.107 3.4</td>
</tr>
<tr>
<td>$K_{\text{D}}$</td>
<td>0.0134 9.1</td>
<td>0.0134 6.4</td>
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<tr>
<td>Fixed-effect exponent of albumin</td>
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<td>NA</td>
</tr>
<tr>
<td>Intersubject variability</td>
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<tr>
<td>$\omega_{K_{\text{D}},2}$</td>
<td>0.0672 20.2</td>
<td>0.0627 19.3</td>
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<tr>
<td>$\omega_{\text{const},2}$</td>
<td>0.0783 29.1</td>
<td>0.0741 52.0</td>
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<td>Residual error</td>
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<td>$\varepsilon_{\text{prop},2}^{a}$</td>
<td>0.0199 33.8</td>
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<td>$\varepsilon_{\text{prop},2b}^{a}$</td>
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<td>$\varepsilon_{\text{const}}^{a}$</td>
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</tr>
<tr>
<td><strong>M5</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KP</td>
<td>0.117 3.8</td>
<td>0.0921 2.1</td>
</tr>
<tr>
<td>$K_{\text{D}}$</td>
<td>0.0668 11.3</td>
<td>0.0664 17.2</td>
</tr>
<tr>
<td>Fixed-effect exponent of age</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fixed-effect exponent of total bilirubin</td>
<td>NA</td>
<td>1.55 18.0</td>
</tr>
<tr>
<td>Intersubject variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\omega_{K_{\text{D}},2}$</td>
<td>0.411 11.9</td>
<td>0.292 21.7</td>
</tr>
<tr>
<td>$\omega_{\text{const},2}$</td>
<td>0.232 72.0</td>
<td>0.216 117.6</td>
</tr>
<tr>
<td>Residual error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\varepsilon_{\text{prop},2}^{a}$</td>
<td>0.0196 13.7</td>
<td>0.0196 18.7</td>
</tr>
<tr>
<td>$\varepsilon_{\text{prop},2b}^{a}$</td>
<td>0.0647 30.3</td>
<td>0.0648 29.9</td>
</tr>
<tr>
<td>$\varepsilon_{\text{const}}^{a}$</td>
<td>0.000956 27.9</td>
<td>0.000983 35.1</td>
</tr>
</tbody>
</table>

†CV%, coefficient of variation; $K_{\text{D}}$, elimination rate constant; KP, exposure relative to micafungin exposure; $\varepsilon_{\text{prop}}$, proportional residual error; $\varepsilon_{\text{const}}$, constant residual error; $\omega$, variance of the intersubject variability of the specified parameter.

‡Different proportional error applied to patients (n = 25) in study 463-CL-2101 with highly variable trough screen data.

NA, not applicable.
there is a nonlinear relationship between size (a clinically relevant measure of which is body weight) and clearance. The reasons for this were recently articulated and summarized using micafungin as an example (11). This nonlinear relationship is most frequently described using a power function with an allometric scaling exponent. As size (or weight) increases, so does clearance. Importantly, however, the rate of increase is not linear, and larger children and adolescents have lower estimates for clearance than those expected from the data obtained from younger, smaller children, as the allometric scaling exponent on CL is <1. The corollary of this is that smaller children have higher weight-adjusted clearances than adolescents and adults. Consequently, if dosing is administered on a mg/kg basis, the resultant AUCtau in smaller children is lower than that observed in older, heavier children. Another challenge is in constructing regimens that are straightforward to use in the clinic. In this regard, there is a compromise between precision and unnecessarily complicated regimens that may lead to dosing errors. In this analysis, a dosage of 2 mg/kg/day resulted in a satisfactory proportion of patients predicted to have AUCtau values in a prespecified target range, especially for the youngest patients in the data set, who achieved an exposure range almost identical to the adult range. Moreover, the results of this study suggest that 40 or 50 kg are weights at which pediatric dosing (i.e., micafungin administered on a mg/kg basis) can safely transition to a fixed adult dosage of 100 mg/day.

This study is the first to describe the population PK of the metabolites of micafungin. The analyses described here suggest that the relative exposures of M1 and M5 are 10.7% and 9.2% of the parent drug, respectively. Neither M1 nor M2 has inherent antifungal activity, and the antifungal activity of M5 is 0.5/125 that of the parent compound (19). In addition, there do not appear to be any issues in terms of toxicity or other adverse effects when micafungin is administered at high doses (e.g., 15 mg/kg) (7, 16). The most interesting observation is that there is an association between M5 exposure and younger age, i.e., M5 exposure is higher in younger patients. The reason for this is not clear but is potentially related to the ontogeny of catechol-O-methyltransferase. Lower expression of this enzyme may favor oxidative metabolism of the parent drug via cytochrome P450 (CYP) pathways and thereby the generation of M5. In addition, high relative M5 exposure is also seen in adult patients with hepatic impairment, which is consistent with the fact that total bilirubin is the covariate of relative exposure of M5. The higher exposure in younger children has been investigated in a toxicology study that showed no relevant histopathological or toxicological findings.

In summary, this is the most comprehensive PK data set for micafungin in children and adolescents. Despite confirmation of the nonlinear relationship between weight and clearance, a dosage of 2 mg/kg for children and adolescents weighing up to 40 to 50 kg results in drug exposures that are equivalent to those observed in adults. Since the relationship between micafungin dosage and exposure is proportional, this conclusion can be extended to other clinical contexts. Dosages of 1 mg/kg and 3 mg/kg for children up to 40 to 50 kg can be used for the prevention of invasive fungal infections and the treatment of esophageal candidiasis, respectively. Children weighing >40 to 50 kg should receive a standard adult regimen.

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REFERENCES


