Pharmacokinetics and probability of target attainment of micafungin in normal-weight and morbidly obese adults

Running title: Pharmacokinetics of micafungin in obese adults

Roeland E. WASMANN[1,2,*], Cornelis SMIT[3,4], Rob TER HEINE [1], Simon E. KOELE[1], Eric P. H. VAN DONGEN[5], René M. J. WIEZER[6], David M. BURGER[1], Catherijne A. J.KNIBBE[3,4], Roger J. M. BRÜGGEMANN[1,2]

1) Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands;
2) Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands;
3) Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands;
4) Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands;
5) Department of Anesthesiology, Intensive Care and Pain Management, St. Antonius Hospital, Nieuwegein, The Netherlands
6) Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

* Address correspondence to Roeland E. Wasmann, roeland.wasmann@radboudumc.nl
Geert-Grooteplein-Zuid 10; 6500HB Nijmegen, The Netherlands

Principal Investigator: Roger. J. Brüggemann

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ABSTRACT

Objectives. The rising pandemic of obesity makes that more obese patients with serious infections require antimicrobial therapy. Micafungin is an echinocandin drug frequently used as therapy or prophylaxis of fungal infections, predominantly with *Candida* species. In order to maximize efficacy of micafungin in obese patients, the dose that corresponds with optimal exposure for each obese individual needs to be identified.

Methods. We performed a prospective study in sixteen obese and eight normal-weight healthy subjects with a weight ranging 61.5 to 184 kg (ClinicalTrials.gov Identifier: NCT03102658). A population pharmacokinetic model was developed and used to simulate several dosing regimens to evaluate the PTA for relevant MICs to define the optimal dose using the PK-PD target of an AUC/MIC ratio above 5,000.

Results. Total body weight was found to be most predictive for clearance and volume of distribution. Simulations show that a 100 mg dose results in a PTA above 90% in patients up to 125 kg with an MIC of 0.016 mg/L. The maintenance dose should be increased to 200 mg in patients above 125 kg infected with a *Candida* species with an MIC of 0.016 mg/L. At an MIC of 0.032 mg/L, a 300 mg maintenance dose is recommended above 125 kg weight. Furthermore, we demonstrate that patients can benefit from a loading dose (i.e. twice the maintenance dose).

Conclusions. We present easy-to-use dose recommendations for obese patients based on both weight and target MIC that results in adequate exposure in patients with body weights up to 190 kg.

INTRODUCTION

Since 1975, global prevalence of morbid obesity – a BMI above 40 kg/m^2 increased from 0.0% and 0.3% to 0.8% and 1.8% in men and women, respectively. In 2016, the United States of America had a prevalence of obesity (BMI above 30 kg/m^2) reaching 37% while continental Europe had a prevalence of 24%, both regions showing an alarming increase in prevalence.[1] Obesity is a major risk factor for diabetes, cancer and also results in a higher risk of nosocomial infections.[2-4] The rising pandemic of obesity combined with an increased morbidity risk makes that physicians in daily practice will be increasingly confronted with obese patients requiring antimicrobial therapy. Despite this, guidance on optimal dosing of antimicrobial agents is often lacking and this knowledge gap needs to be addressed.

Micafungin is an echinocandin indicated for the treatment of invasive and oesophageal candidiasis, and prophylaxis of *Candida* infections in patients undergoing allogeneic haematopoietic stem cell transplantation. The standard dose for invasive candidiasis is 100 mg per day which can be increased to 200 mg per day if the response is inadequate. Micafungin exhibits linear pharmacokinetics and is metabolized by arylsulfatase, catechol-*O*-methyltransferase and several cytochrome P450 (CYP) isoenzymes: CYP3A4, CYP1A2, CYP2B6 and CYP2C.[5]

Pharmacokinetic (PK)-Pharmacodynamic (PD) targets for micafungin have been defined in patients with invasive candidiasis or candidemia based on the AUC over the MIC. For all *Candida* species excluding C. *parapsilosis* a breakpoint between 5,000 and 12,000 showed a 98% success rate in response versus 87% if patients had an AUC/MIC ratio below 5,000.[6]

A previous report in obese and morbidly obese subjects showed that clearance increased with increasing weight, although this pharmacokinetic model still contained significant unexplained variability in clearance across body weights.[7] The authors present a dosing algorithm suitable for fully susceptible pathogens. In case of severe infections with *Candida*

species with higher MICs additional information is needed. This is nowadays highly relevant with the emergence of echinocandin resistance in *Candida* species due to mutations in the FKS genes, which can be as frequent as 12.3%.[8, 9] Also, the influence of obesity on volume of distribution and the potential need for a loading dose to shorten the time to reach (effective) steady state concentration still remains to be quantified.[7] Therefore, we investigated the effect of body weight in obese subjects with the objective to propose dosing guidelines of micafungin that incorporate both the effects of obesity and relevant MICs.

METHODS

Ethics. This study was approved by the Ethics Committee of the Radboud University Medical Center. It was conducted in accordance with the Declaration of Helsinki and good clinical practice regulations (ClinicalTrials.gov Identifier: NCT03102658). All subjects gave written informed consent before inclusion.

Study Population. We included morbidly obese subjects (BMI above 40 kg/m^2) undergoing laparoscopic gastric bypass or sleeve gastroectomy surgery from March to July 2017 in the St. Antonius Hospital (Nieuwegein, The Netherlands). Normal-weight subjects (BMI between 18.5 and 25 kg/m^2) were included from January to March 2017 in the Radboud University Medical Center (Nijmegen, The Netherlands). Subjects were eligible if they had a BMI within the specified range at the time of screening and were aged between 18 and 65 years. Subjects were excluded when pregnant or breastfeeding, had documented history of echinocandin sensitivity, a history of abuse of drugs, alcohol or solvents, were unable to understand trial procedures or when using medication with a known interaction with micafungin.

Study Procedures. This was an open-label, single-dose, multicenter, multi-dose level, pharmacokinetic study in healthy volunteers. Morbidly obese subjects were randomized to receive either 100 mg or 200 mg micafungin intravenous (iv) prior to the bariatric surgery while normal-weight subjects all received 100 mg micafungin iv, all infused in 60 minutes. Patient demographics, clinical characteristics, medical history and concomitant medication were recorded. Blood samples were collected in lithium-heparin tubes at predefined times of 0.5, 0.95, 1.25, 1.5, 2, 4, 8, 12 and 24 hours after the start of infusion (n= 9 per individual). An additional sample at 48 hours after infusion was drawn in all normal-weight individuals and in obese individuals that were still admitted at that time. Samples were centrifuged at 1900 g for 5 minutes and immediately stored at -80° C. A study design evaluation can be found in the supplemental material.

Analytical Assay. Micafungin plasma concentrations were quantified using a validated ultra performance liquid chromatography with fluorescence detection and a range in plasma of 0.01 to 32.40 mg/L. This assay has been used for previous reports on micafungin PK [10-12]. Before injection, proteins were precipitated using 50% acetonitrile, 50% methanol, and 0.1% formic acid. The accuracy ranged from 97.6% to 101.6% (n=15). Intraday and interday precision ranged from 1.4% to 5.2% (n=5) and from 0.7% to 2.2% (n=15), respectively. Stability analysis showed that micafungin was stable for 7 days in whole blood at 4° C and for a minimum of 11.5 months in plasma at -80° C.

Pharmacokinetic Analysis. First, the observed area under the concentration-time curve ($AUC_{0\text{-}24h}$) was calculated using the linear-up log-down trapezoidal rule using Phoenix 64 WinNonlin 7.0 (Pharsight Corp, Mountain View, CA, USA). Hereafter, the concentration data were analyzed using non-linear mixed effects software package NONMEM version 7.4.0 (Icon Development Solutions, Ellicott City, MD) and Perl-Speaks-NONMEM (PsN) version 4.7.0, with PiranaJS version 1.3 interface.[13] Graphical processing of the data and NONMEM output was done in R version 3.4.1 with R Studio interface version 1.0.143.[14] In NONMEM, the first-order conditional estimation method with interaction was used for all model runs. One-, two-, and three-compartment models were considered to describe micafungin plasma concentrations. Inter-individual variability and residual variability were assumed to be log-normally distributed. Residual variability was evaluated using additive, proportional and combined (additive and proportional) models. Structural model selection was based on goodness-of-fit (GOF) scatter plots, objective function value (OFV) corresponding to minus 2 log-likelihood decrease with a significance level of $p = 0.05$ (a 3.84 decrease with 1 degree of freedom from the chi-squared distribution) and physiological plausibility. In addition, root squared error (based on the covariance step in NONMEM), shrinkage and parameter correlation were assessed.

After developing the structural model, the relationships between individual empirical Bayes estimates and weight derived parameters were examined in scatter plots. We investigated the predictive value of the following covariates: total body weight (weight), lean body weight (LBW),[15] BMI, ideal body weight, age, and sex. Linear and power functions were investigated and standardized for a typical 70 kg male with a height of 1.8 m. Covariates were included one at a time based on physiological plausibility and if it resulted in an OFV decrease of at least 10.8 points (Chi-squared distribution, p=0.001). Models were evaluated using GOF scatter plots and the performance of the final model was assessed by prediction-corrected visual predictive check (pcVPC) based on 1000 Monte-Carlo simulations. Parameter precision and model robustness was evaluated by non-parametric bootstrap (n = 1000).

Simulations. The final model was used to perform simulations for five typical subjects with empirical chosen weights of 60, 90, 120, 150 and 180 kg to visualize the changes in pharmacokinetics as a result of weight. We also performed Monte-Carlo simulations to calculate the PTA in a population of 9,450 virtual subjects with a uniform weight distribution between 60 and 190 kg (in 5 kg increments resulting in 27 weight groups each consisting of 350 subjects). Simulations with parameter uncertainty were performed through the stochastic simulation and estimation functionality in PsN utilizing the non-parametric bootstrap results as model input (n = 500 models). For this purpose, various dosing regimens were selected (100, 200 and 300 mg) at the discretion of the investigators. Also, we simulated the dosing formula reported by Pasipanodya *et al.* ("dose (mg) = weight + 42").[16] For every simulation, the $AUC_{0\text{-}24h}$ was calculated on day seven. In addition, we simulated the effect of a loading dose (i.e. twice the maintenance dose) up to 400 mg on the $AUC_{0\text{-}24h}$ on day one.

Probability of Target Attainment. The PK-PD target of an AUC/MIC ratio of >5,000 for infections with all *Candida* species excluding C. *parapsilosis*, associated with a 97.8%

156 mycological response rate, was used to calculate the probability of target attainment (PTA).[6]
157 The PTA on day one and seven were calculated using clinical relevant MIC values of 0.008,
158 0.016, 0.032, and 0.064 mg/L, as determined by the CLSI reference method.[17]

RESULTS

Data for Analysis. Twenty-four subjects (all Caucasian; 50% female), evenly distributed over all three groups, were included. Subject characteristics are summarized in Table 1. In total, 223 plasma samples were obtained for analysis throughout a 24h interval. For one individual a blood sample was drawn at 48h. Two samples from the obese subjects were excluded due to sampling errors. Figure 1 shows the observed mean plasma concentrations for each group.

Pharmacokinetic analysis. The observed geometric mean [range] $AUC_{0\text{-}24h}$ in normal-weight versus obese subjects receiving 100 mg micafungin was 96.9 mg*h/L [80.8-119.0] versus 55.5 mg*h/L [39.9-74.1] ($p < 0.05$), respectively. Obese subjects receiving 200 mg had an $AUC_{0\text{-}24h}$ of 114 mg*h-L [97.7-139] which seems in accordance with the exposure observed in normal-weight subjects receiving 100 mg micafungin.

For the population pharmacokinetic analysis, the data were best described using a two-compartment model with first-order elimination from the central compartment, a proportional residual error model and inter-individual variability on clearance and the central compartment (V_c). Parameter estimates of the structural model are presented in Table 2. The addition of body weight as a covariate on clearance using a power function with an estimated exponent of 0.74 [95% CI 0.64-0.83] best described the variability between subjects. Inter-individual variability decreased from 28.6% [95% CI 21.7-34.3] to 8.1% [95% CI 4.80-10.47] upon inclusion of this covariate function. Also, weight best described the variability between subjects of V_c using a power function with an estimated exponent of 1.17 [0.89-1.45]. Inter-individual variability on V_c decreased from 69% [95% CI 42.5-91.9] to 12.8% [95% CI 7.76-16.45]. Finally, weight was added to the peripheral compartment (V_p) using a power function with an estimated exponent of 0.71 [95% CI 0.56-0.86] resulting in a further OFV decrease of 86.8 ($p < 0.0001$). Adding age or sex to the model did not result in model improvement. Parameter estimates and their uncertainty based on 1000 bootstraps are shown in Table 2.

Goodness-of-fit plots (Figure S1) show that the (structural) model is appropriate for the data. The population and individual predicted concentrations are in concordance with the observed concentrations, the discrepancy between predictions and observations is small. Furthermore, the conditional weighted residuals indicate no model misspecification, the distribution is homogeneous and the majority of the data lies within the [-2, 2] interval. The pcVPC of the final model shows that predictions were consistent with observations suggesting a good internal validity of the model to the data (Figure 2).

Simulations. Simulated pharmacokinetic curves for five typical subjects with weights of 60, 90, 120, 150 and 180 kg receiving daily 100 mg micafungin iv illustrate a significantly lower exposure and peak plasma concentration with increasing weight (Figure S2).

Probability of Target Attainment. The PTA on day one and day seven, based on the Monte-Carlo simulations, are shown in Figure 3. These show that a standard 100 mg dose gives a high (> 90%) probability of target attainment in patients up to 125 kg for *Candida* species with an MICs of 0.016 mg/L or lower. Patients above 125 kg and an MIC of 0.016 mg/L have a declining PTA and benefit from an augmented dose of 200 mg. When the MIC is 0.032 mg/L, patients should be treated with a 200 mg dose which will result in adequate target attainment up to a body weight of 125 kg, after which a dose increase to 300mg should be sufficient. Finally, an MIC of 0.064 mg/L and a dose of 300 mg might only be sufficient for patients up to 90 kg. For the previous published algorithm “dose (mg) = weight + 42”, Figure 3 shows that this algorithm results in adequate target attainment up to 190 kg for infections with an MIC of 0.016 mg/L. Above this MIC the algorithm does not result in adequate exposure for treatment.

The PTAs on day one indicate that patients with infections with *Candida* sp. with MICs of 0.016 mg/L and higher might benefit from a loading dose (i.e. twice the maintenance dose) on day one. The use of a loading dose at day one results in a similar target attainment at this day

compared to the target attainment on day seven. A proposed dose monogram based on these results is given in Figure 4.

DISCUSSION

In this study we show that obese subjects receiving the licensed 100 mg dose have a significantly lower exposure to micafungin compared to normal-weight subjects, i.e. 55.5 mg*h/L versus 96.9 mg*h/L, respectively. We described the pharmacokinetic parameters of micafungin in obese and normal-weight subjects with a weight range of 61.5 to 184 kg and show that clearance and volumes of distribution of the central and peripheral compartments increase substantially with weight. We visualized the impact of body weight on the concentration-time curve using five typical subjects to emphasize the need for a personalized dose incorporating body weight.

Based on the Monte-Carlo simulations we propose that patients with a body weight above 125 kg should be treated with 200 mg micafungin in the setting of infections with a *Candida* species with an MIC of 0.016 mg/L (as a conservative target for empirical therapy). In case of an MIC of 0.032 mg/L, an even higher daily dose of 300 mg in patients with more than 125 kg body weight is required to reach adequate exposure on day seven. A loading dose would further improve the target attainment for a certain MIC on the first day of therapy. A 400 mg loading dose results in an adequate exposure on day one when aiming for *Candida* species with an MIC of 0.032 mg/L.

A two-compartment model with first order elimination best described the micafungin plasma concentrations, which is in line with previous reports.[5, 12, 18-20] In our study, body weight was the size descriptor best explaining the inter-individual variability in clearance, where individual clearance (in L/h) is predicted using the power function $0.69 * (\text{weight} / 70)^{0.74}$. This relation is supported by previously reported clearances in normal-weight healthy subjects.[21-24] For example, in a study by Hebert et al. in 2005 in a population with a mean weight of 71.7 kg, a mean clearance of 0.72 L/h was reported,[23] where our model would predict a similar clearance of 0.70 L/h. A recent report in obese and normal-weight critically

ill patients also showed a similar relationship between clearance with weight but the authors also added a strong age-related effect on clearance which we could not confirm in our population.[19] We speculate that the increase in clearance with body weight can be explained by an increased cardiac output, liver blood flow, and liver size but might also due to possible upregulation of arylsulfatase. As arylsulfatase is mainly involved in the metabolism of sulphate-containing lipids it is possible that this enzyme is more abundant in obese individuals.

An increased clearance results in a decreased exposure to micafungin which makes that obese patients are at risk for suboptimal therapy. Therefore, we propose a dosing nomogram (Figure 4) based on both the patients and the pathogens characteristics. Since MIC values are typically not available at therapy initiation dose selection should be based on local epidemiology, possibly followed by dose adaption when MIC values are available. Using local or national MIC data to determine the cumulative fraction of response of your patient population would be most beneficial. In addition, we evaluated the previously proposed dosing algorithm, "daily dose (mg) = weight + 42". This algorithm results in a probability of target attainment of 100% in patients with weights from 60 to 190 kg in *Candida* species with MICs up to 0.016 mg/L (Figure 3).[16] However, one in four *Candida* species excluding C. *parapsilosis*, have an MIC above 0.016 mg/L making that this algorithm is not expected to result in optimal therapy for one out of four patients when employed empirically.[17]

Additional factors contributing to a lower exposure must be taken into account as well, such as critical illness in case of admission to an intensive care unit. These patients show an increased micafungin clearance and an augmented dose of 200 mg has been proposed previously.[12, 20] In obese critically ill patients, a significant lower probability of target attainment was reported compared to normal-weight critically ill patients.[19] Although a 300

mg dose was not investigated in this study, this should be considered in critically ill obese patients, if possible under the guidance of therapeutic drug monitoring.

There are some limitations to our study that should be considered. First, we investigated the pharmacokinetics in obese subjects undergoing a minor surgical procedure which might influence pharmacokinetic parameters. Although it is a short (< 1 hour) laparoscopic procedure with minor blood loss) there might be additional variability due to administration of fluids and concomitant medication. We expect this to be of minimal impact. Second, we studied a relatively small group of 24 relatively young healthy subjects as a representation of obese patients. Although we had a very wide weight range (61.5 to 184 kg) and our results are in line with previous reports, a relatively small study population results in uncertainty of the comparability between populations. For the proposed dose nomogram, we therefore used the most conservative target of an AUC/MIC ratio of 5,000. In addition, we took parameter uncertainty into account in the Monte-Carlo simulations and selected the lower limit of the PTA as a cut-off value for dose increase. This probably results in an underestimation of the PTA but since micafungin is a drug with relatively few side effects we emphasize that this approach is most beneficial for patients.[25]

The augmented maintenance dose and addition of a loading dose can be considered for two reasons: 1) the safety of high dose micafungin has been established in a maximum tolerated dose study up to 900 mg per day,[26] and in several cases up to a single 1200 mg dose summarized by Gumbo *et al.* and; [27] 2) the volume of distribution and clearance increase with weight resulting in a decreased peak plasma concentration and decreased AUC (Figure S2). The above is demonstrated in our study by direct comparison between normal-weight subjects receiving 100 mg versus morbid obese subjects receiving 200 mg (Figure 1). Therefore, we expect that risks of toxicity in obese patients receiving higher doses are in line with the risks of normal-weight patients receiving an approved 100 or 200 mg daily dose.

In conclusion, we found that the maintenance dose should be increased to 200 mg in patients above 125 kg infected with a *Candida* species with an MIC of 0.016 mg/L. At an MIC of 0.032 mg/L, a 300 mg maintenance dose is recommended above 125 kg weight. We demonstrated that patients could benefit from a loading dose (i.e. twice the maintenance dose on the first day) to achieve optimal exposure at start of therapy in the setting of a high frequency of reduced *Candida* susceptibility. Finally, we offer an easy-to-implement dosing nomogram that enables a personalized therapy that can be tailored to the local MIC distribution for obese and morbidly obese patients.

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R.E.W., participated in study design, data collection, analysis of the data and writing of the article. C.S. participated in data collection, analysis of the data and writing of the article. R.H., C.K. and R.B. participated in study design, analysis of the data and writing of the article.

E.D., R.M.W. and S.K. participated in data collection and writing of the article. D.B. participated in writing of the article.

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386 TABLES AND FIGURES

387 Table 1. Summary of subject characteristics. [a]

		100 mg iv		200 mg iv
		Normal-weight	Obese	Obese
Sex (no.(%))	Male	4 (50)	3 (37.5)	5 (62.5)
	Female	4 (50)	5 (62.5)	3 (37.5)
Age (years)	Median [range]	31 [22-56]	51 [35-61]	46 [24-54]
Weight (kg)	Median [range]	70.8 [61.5-81.5]	156 [112-184]	141 [126-180]
BMI (kg/m^2)	Median [range]	22.5 [21.4-24.9]	44.4 [38.9-63.6]	43.5 [40.3-55.7]
LBW (kg)	Median [range]	46.3 [40.0-52.8]	65.21 [55.1-76.6]	65.2 [60.1-74.8]

[a] iv, intravenous; LBW, lean body weight, according to Janmahasatian et al.[15]

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390 Table 2. Pharmacokinetic parameter estimates of the structural and final model. [a]

Parameter		Structural model (RSE %) [95% CI]	Final model (RSE %) [95% CI]
Typical Value			
CL (L/h)		1.00 (5.9) [0.89-1.12]	-
$\mathbf{CL_{70kg}} \times \left(\frac{TBW}{70}\right)^{\theta 1}$			
	CL_{70kg} (L/h)	-	0.690 (2.9) [0.66-0.72]
	θ_1	-	0.74 (6.9) [0.64-0.83]
Q (L/h)		6.72 (7.7) [5.53-7.90]	7.15 (8.9) [5.62-8.68]
V_c (L)		10.2 (14.1) [7.9-12.6]	-
$\mathbf{V_{c;70kg}} \times \left(\frac{TBW}{70}\right)^{\theta 2}$			
	$V_{c;70kg}$ (L)	-	5.84 (10.1) [4.40-7.27]
	θ_2	-	1.17 (9.4) [0.89-1.45]
V_p (L)		8.54 (4.8) [7.1-10.0]	-
$\mathbf{V_{p;70kg}} \times \left(\frac{TBW}{70}\right)^{\theta 3}$			
	$V_{p;70kg}$ (L)	-	6.96 (6.8) [5.84-8.07]
	θ_3	-	0.71 (10.0) [0.56-0.86]
Inter-individual variability (%) [c]			
CL [b]		28.6 (14.8) [21.7-34.3]	8.1 (17.4) [4.80-10.47]
V_c [b]		69.0 (17.4) [42.5-91.9]	12.8 (18.1) [7.76-16.45]
Residual error (%)			
σ_{prop} [b]		7.76 (6.3) [4.9-9.9]	5.0 (6.3) [4.00-5.84]
OFV		-28.684	-271.991

[a] Abbreviations: CL, clearance; V_c, volume of distribution of central compartment; V_p, volume of distribution of peripheral compartment; Q, inter-compartmental clearance between V_c and V_p; σ_{prop}, proportional residual error; RSE, relative standard error based on covariance step in NONMEM; 95% CI, 95% confidence interval obtained from non-parametric bootstrap (n=1000).

[b] Eta and epsilon shrinkage of inter-individual variability for CL, V_c and residual error are below 15%.

[c] Calculated by $\sqrt{\left(e^{\omega^2} - 1\right)}$

391

392

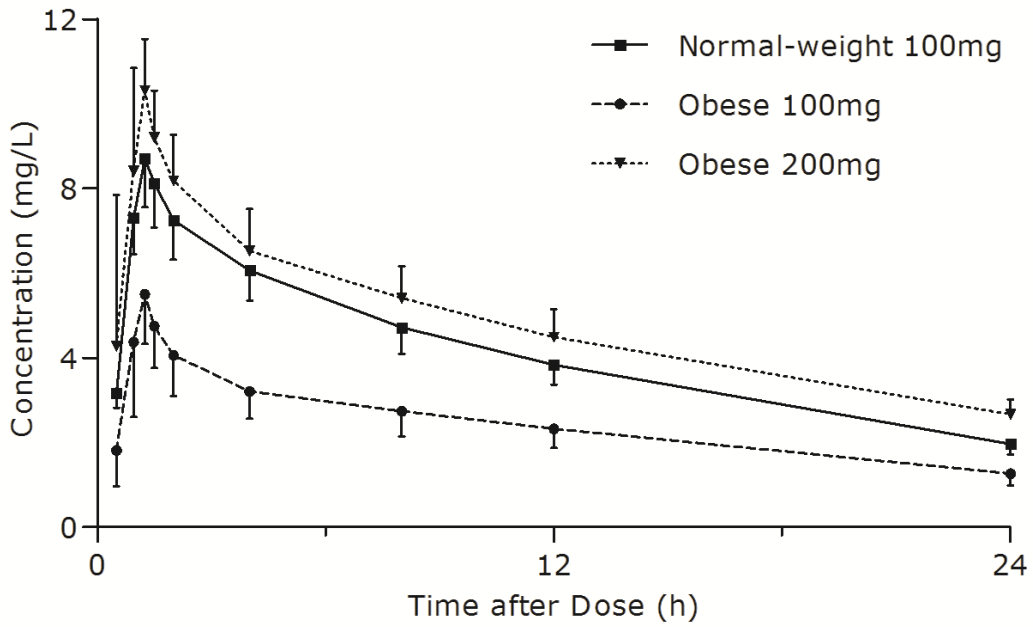

Figure 1. Observed mean (SD) micafungin plasma concentrations.

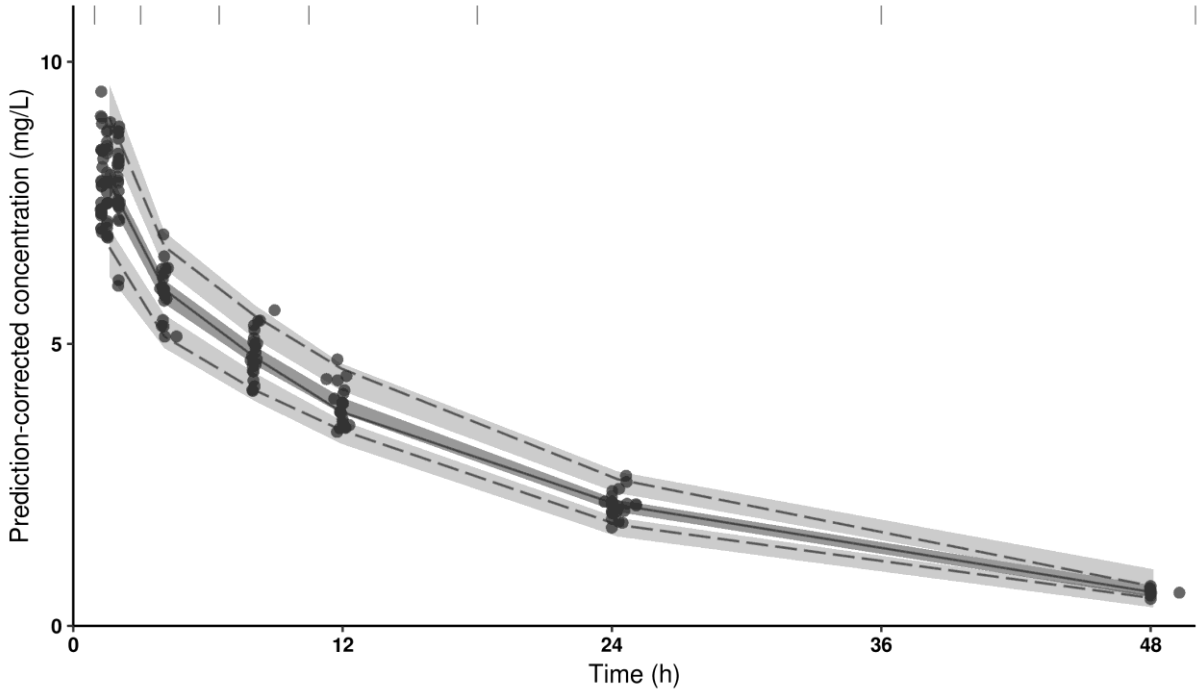

Figure 2. Prediction-corrected visual predictive check for the final pharmacokinetic model of micafungin, based on n = 1000 simulations. Prediction-corrected simulated (shaded areas) and observed (circles and lines) micafungin concentrations versus time after dose. The solid line connects the median values per bin. The outer dashed lines connect the 5th and 95th percentiles of the observations. The shaded areas are the 95% confidence interval of the 5th and 95th percentile, and the median. The vertical lines at the top of the graph indicate the placement of the bins.

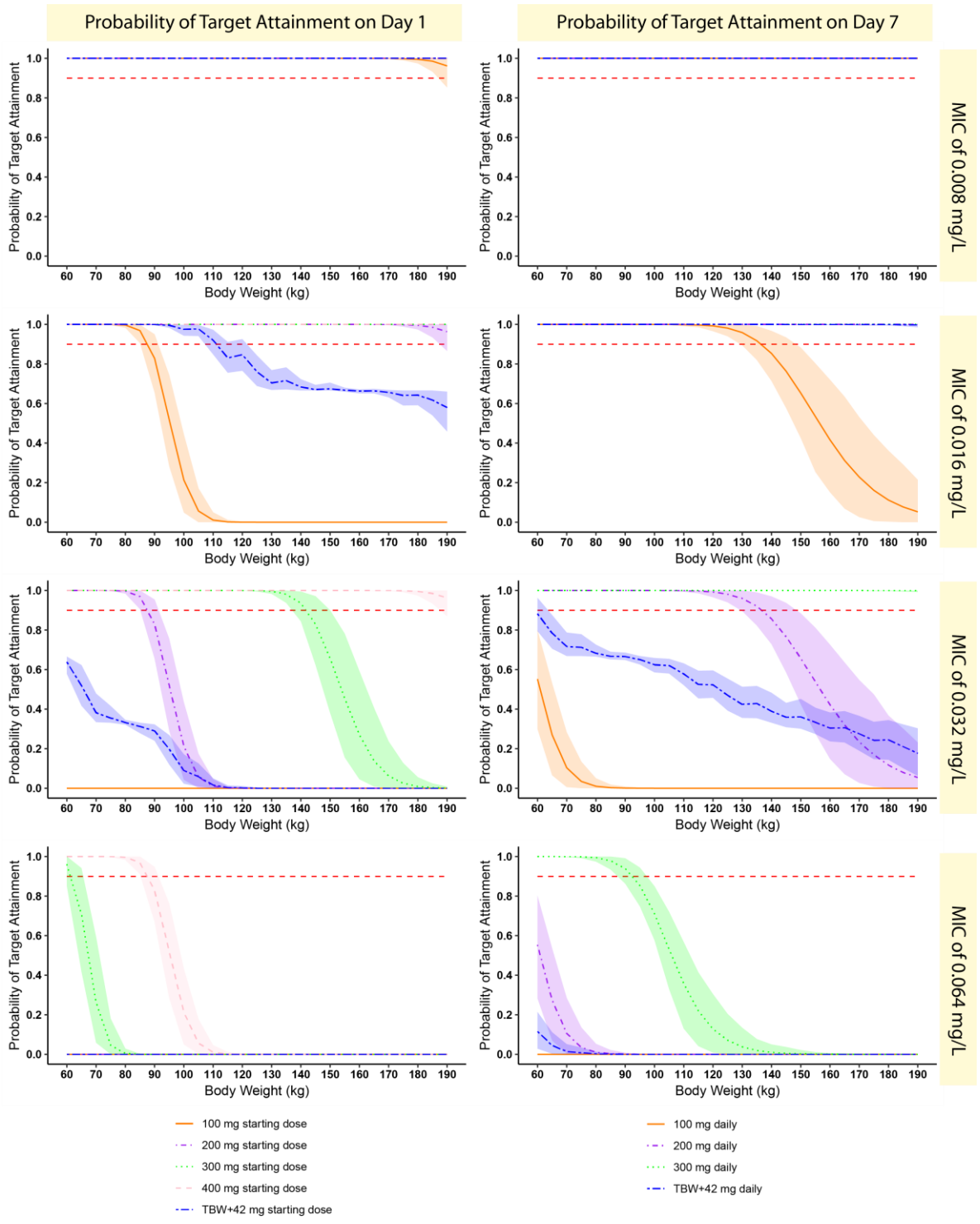

Figure 3. Probability of target attainment versus body weight on day one (left panel) and in steady state on day seven (right panel) for four different minimum inhibitory concentrations (MIC). The horizontal red dotted line represents a target attainment of 90%. The shade around the lines represents the 95% confidence interval of the prediction.

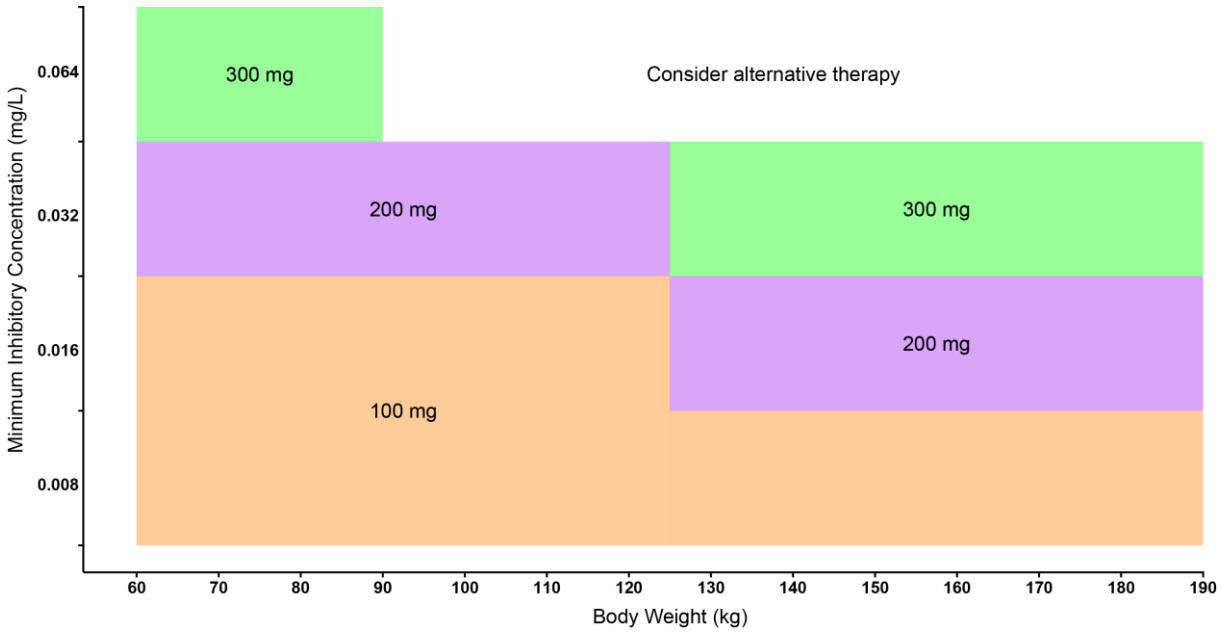

Figure 4. Recommendations for maintenance dose by body weight and minimum inhibitory concentrations. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

Supplements

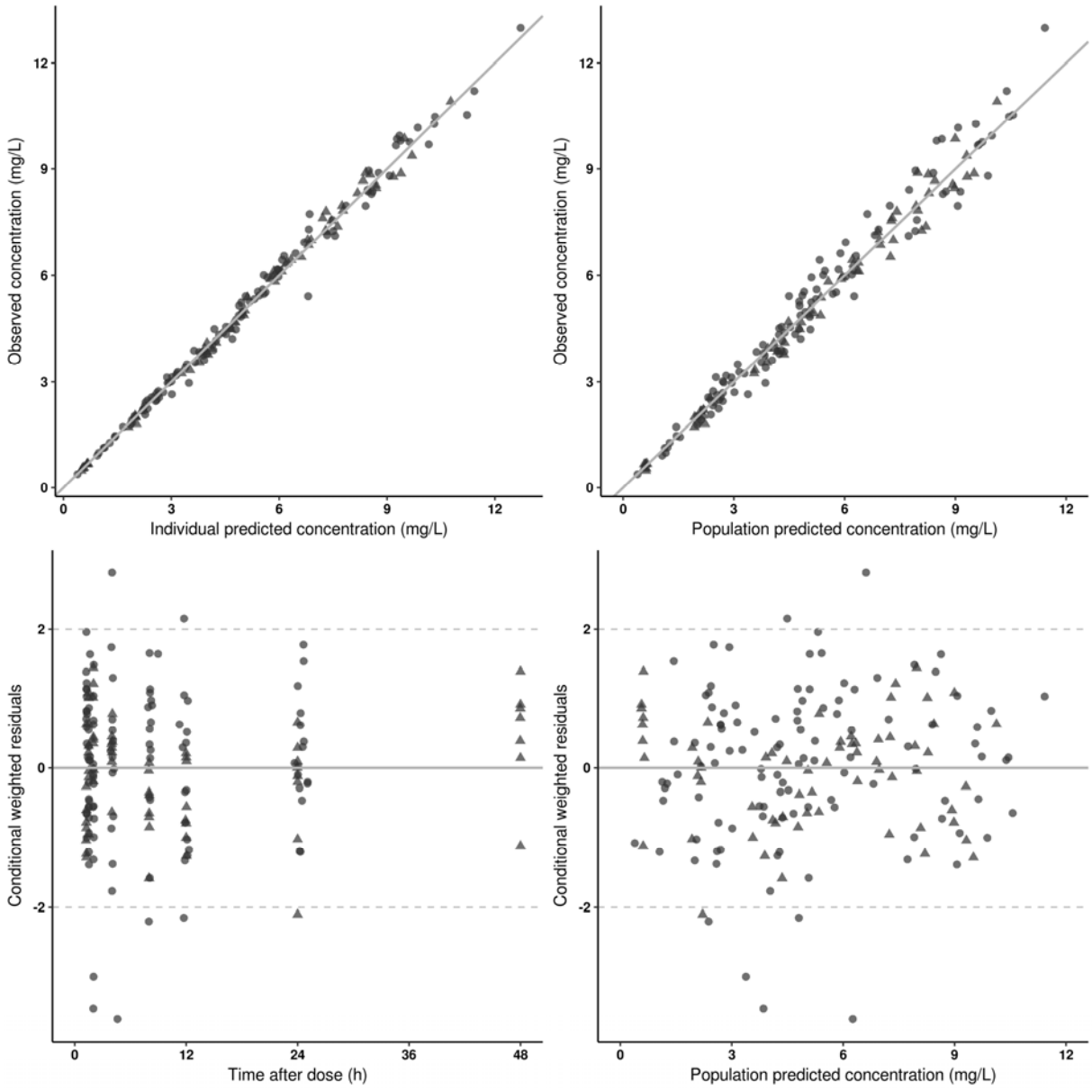

Figure S1. Goodness-of-fit diagnostics of the final population pharmacokinetic model of micafungin in normal-weight (triangles) and obese (circles) adult subjects.

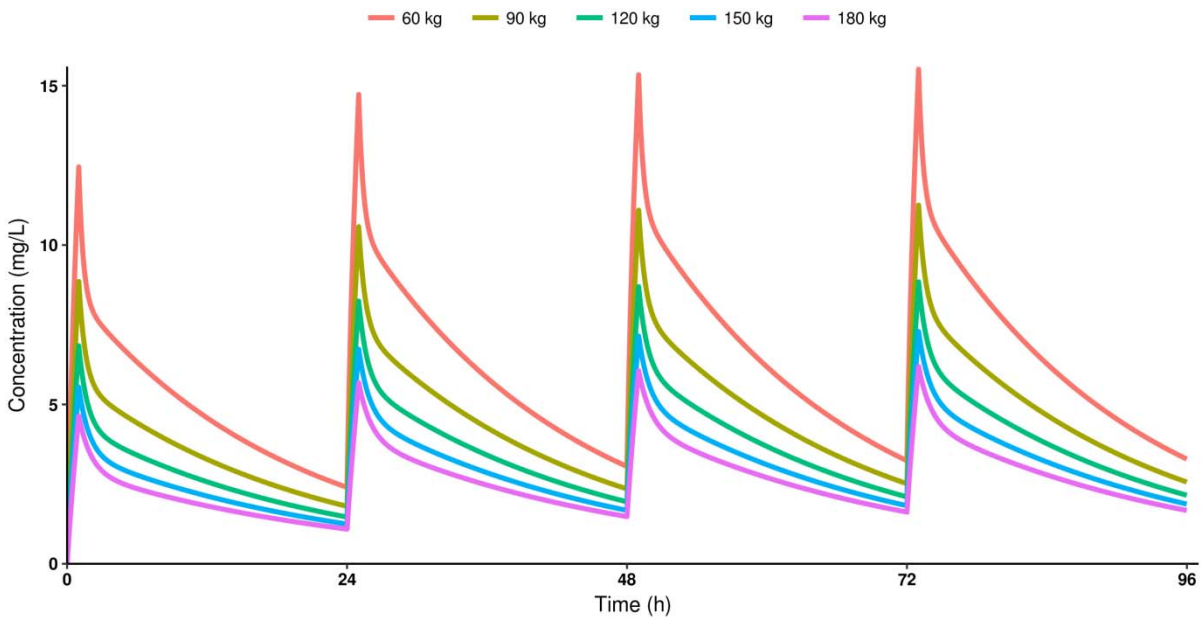

Figure S2. Simulated micafungin plasma concentrations in five typical patients (i.e. 60, 90, 120, 150 and 180 kg) receiving a daily 100 mg micafungin infusion over 4 days.

Study Design Evaluation. A design evaluation was performed to estimate parameter precision and accuracy by means of stochastic simulation and estimation (n=500 virtual trials), as implemented by Perl-Speaks-NONMEM. A previously reported 2-compartmental PK model was used as input with additional added inter-individual variability of 30% and a large proportional residual error of 30%.[7] A sample of 24 subjects (16 obese and 8 normal-weight) resulted in a bias and error below 15%, with the exception of a 24.6% error in inter-compartmental clearance. As inter-compartmental clearance does not impact systemic exposure this was considered acceptable.