

Population PK model and pharmacokinetic target attainment of micafungin in ICU patients

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Background

Micafungin is an echinocandin antifungal agent used as first-line therapy for the treatment of invasive candidiasis in critically ill (ICU) patients[1,2]. Micafungin is administered intravenous at a daily dose of 100 mg. In case the response is inadequate, maintenance dose may increased to 200 mg QD. The pharmacokinetics (PK) of many drugs are altered in ICU patients[3-5]. The PK of micafungin have been well studied in a wide population of non-ICU patients but there is only limited knowledge on the causes of PK variability and therapy failure in ICU patients[3]. PK of micafungin is correlated with treatment outcome: the ratio of the area under the concentration time curve over the minimal inhibitory concentration (AUC/MIC) of ≥ 3000 is associated with favorable response (85.1%)[6]. **The objectives of this work were (i)** to develop a population PK model to identify sources of PK variability of micafungin in ICU patients and **(ii)** to evaluate *in silico* the probability of target attainment in this population following various dosing regimens. The results of a non-compartmental analysis of this study were published previously[3].

METHODS

Study design and population[3]

- Open-label, multi-centre, multiple dose, observational trial.
- ICU patients with suspected/proven fungal infection.
- Micafungin treatment: 100mg QD.

Pharmacokinetic sampling

- 2 PK curves on days 3 and 7.
- Time points day 3: t=0 (pre-dose) 0.5, 1, 2, 4, 6, 8, 12, 18 and 24 hours post infusion; time points day 7: t=0 (pre-dose), 1, 4, 8, 12, and 24 hours post infusion.
- Additional trough samples on all other study days.
- PK sampling was limited to a maximum of 14 days with an additional 3 days after stopping micafungin.

Population PK modelling

- NONMEM version 7.3 (ICON Development solutions, Ellicott City, MA, USA); Perl-Speaks-NONMEM (version 4.2.0); Xpose (version 4.5.3); R; Piraña interface.
- First order conditional estimation method with interaction.
- The covariance step was used to obtain parameter precision

Covariate analysis

- Based on an a priori screening on physiologically plausibility, the following covariates were selected for analysis;
- The effect of albumin was assessed on V and CL, both linearly, exponentially and with a power function.
- Different thetas were estimated to assess the effect of CVVH (categorical covariate) on V.
- SOFA score (categorical covariate) was assessed linearly on CL and V. Scores were divided into low (score <10) and high (score ≥ 10).
- Forward inclusion criterion $p < 0.05$ (OFV decrease ≥ 3.84 , χ^2 , 1df).
- BW was incorporated a priori on CL (allometrically with a power exponent of 0.75) and on V (power exponent of 1) and standardized to a 70 kg patient.

Monte Carlo simulations of alternative dosing regimens

Monte Carlo simulations were performed also propagating parameter uncertainty, with the TNPRI function in NONMEM, using priors from our final pharmacokinetic model. Five dosing regimens were simulated in a cohort of 1000 hypothetical patients, with an average BW of 70 kg and a 20% CV. (Table 1). Exposure to micafungin in terms of AUC_{0-24h} was assessed on days 3 and 14 of therapy. Differences in exposure were statistically tested with Wilcoxon Rank Sum test.

Table 1 Dosing regimens for simulations. Regimens I and II are licensed [1].

	Loading dose	Maintenance dose
Regimen I	100 mg	100 mg
Regimen II	100 mg	From day 5: 200 mg
Regimen III	200 mg	From day 2: 100 mg
Regimen IV	200 mg	From day 2: 150 mg
Regimen V	200 mg	From day 2: 200 mg

Pharmacokinetic target attainment (PTA)

Target attainment based on a preclinical PK target ($AUC/MIC \geq 3000$) for *Candida* species was assessed on day 14 for relevant MICs (0.002, 0.004, 0.008, 0.016, 0.032, 0.064, 0.125, 0.25, 0.5, 1.0)[6].

RESULTS

Patients

- 20 patients (12 female) with a total of 356 PK observations.
- Median age 68 years (range 20-84); median BW 77 kg (range 50-134).
- All patients had pronounced hypoalbuminemia (serum albumin ≤ 34 g/L).

Pop PK model

A two-compartment disposition model with first-order elimination from the central compartment and a proportional residual error model fitted the data best. An OMEGA covariance block (CL&V1) further improved the model. No covariates were identified significantly improving the model based on both OFV and GOF. Parameter estimates with bootstrap derived precisions of the final model are shown in Table 2. Basic GOF plots are shown in Figure 1 and the VPC of the final model is shown in Figure 2. Numerical predictive checks showed that 0.9% (95%CI 0-6.8%) of observations fell below 95%PI and 2.0% (0-8.0%) fell above 95%PI. Condition nr was 1979 and correlations between theta's and eta's did not exceed 0.95. High IOV on V was observed indicating important variation in V from day to day within this population.

Table 2 Parameter estimates of the final model of micafungin in ICU patients

	Parameter estimates [RSE] (Shrinkage)	Bootstrap parameter estimates (n=841/1000) Mean (95%CI) [RSE]
CL (L/h)	1.10 [8%]	1.10 (0.92-1.32) [8.8%]
V1 (L)	17.6 [14%]	16.8 (12.53-21.54) [12.7%]
Q (L/h)	0.363 [20%]	0.363 (0.30-3.82) [26.2%]
V2 (L)	3.63 [8%]	3.85 (3.20-7.77) [30.9%]
IIV CL (CV%)	40.1 [23.2%] (1.2%)	38.5 (28-47) [23%]
IIV V1 (CV%)	73.2 [62.7%] (41%)	72.1 (32-119) [53%]
IOV V1 (CV%)	37.0 [77.5%] (25-70%)	35.8 (14-60) [60%]
Proportional residual error	17% [24%]	17% (14-20%) [20%]

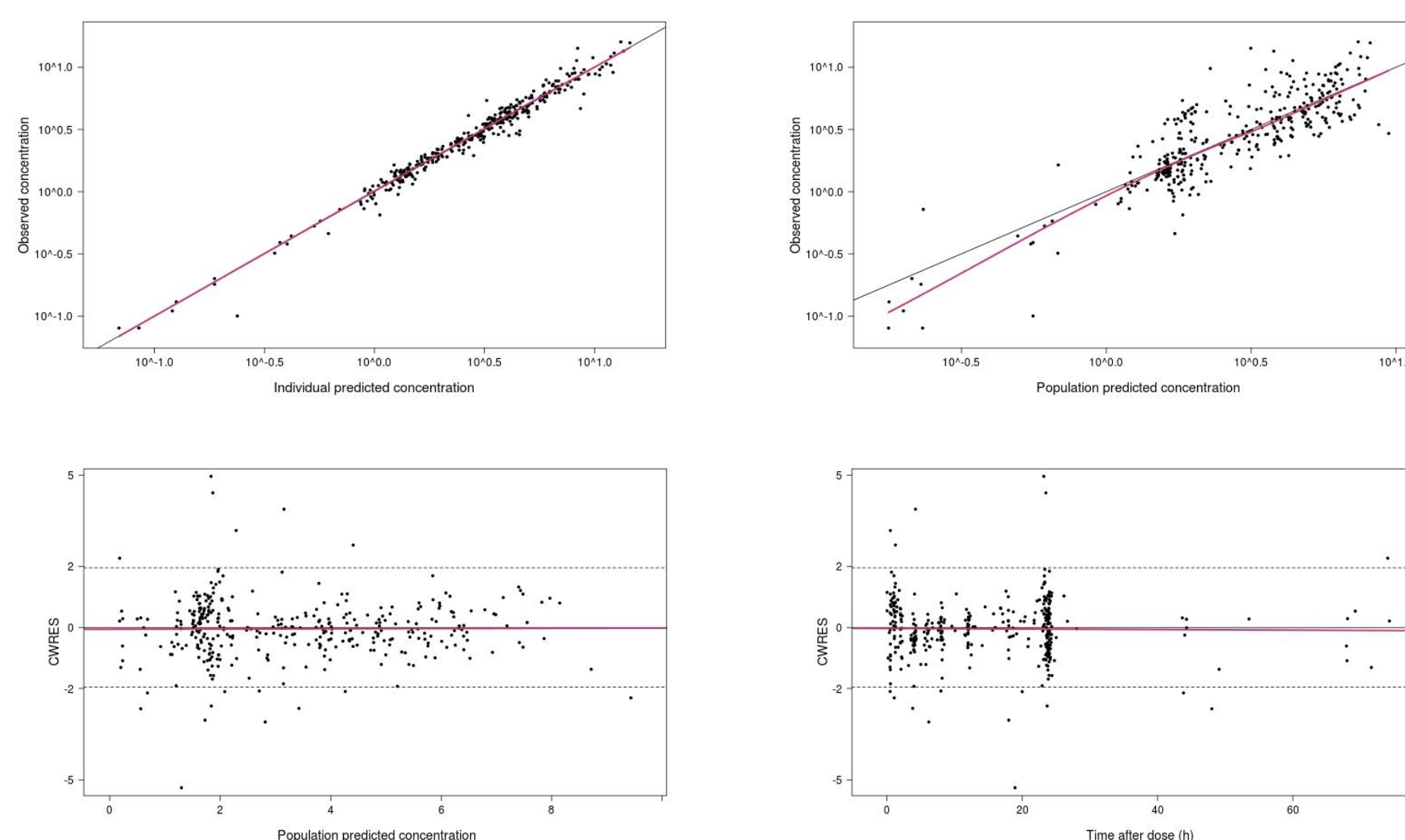


Figure 1 Goodness-of-fit plots for the final PK model of micafungin. CWRES= conditional weighted residuals. The thin black lines indicate unit line or the line of identity. The thick lines (purple) are smooth lines showing the trend in the observations.

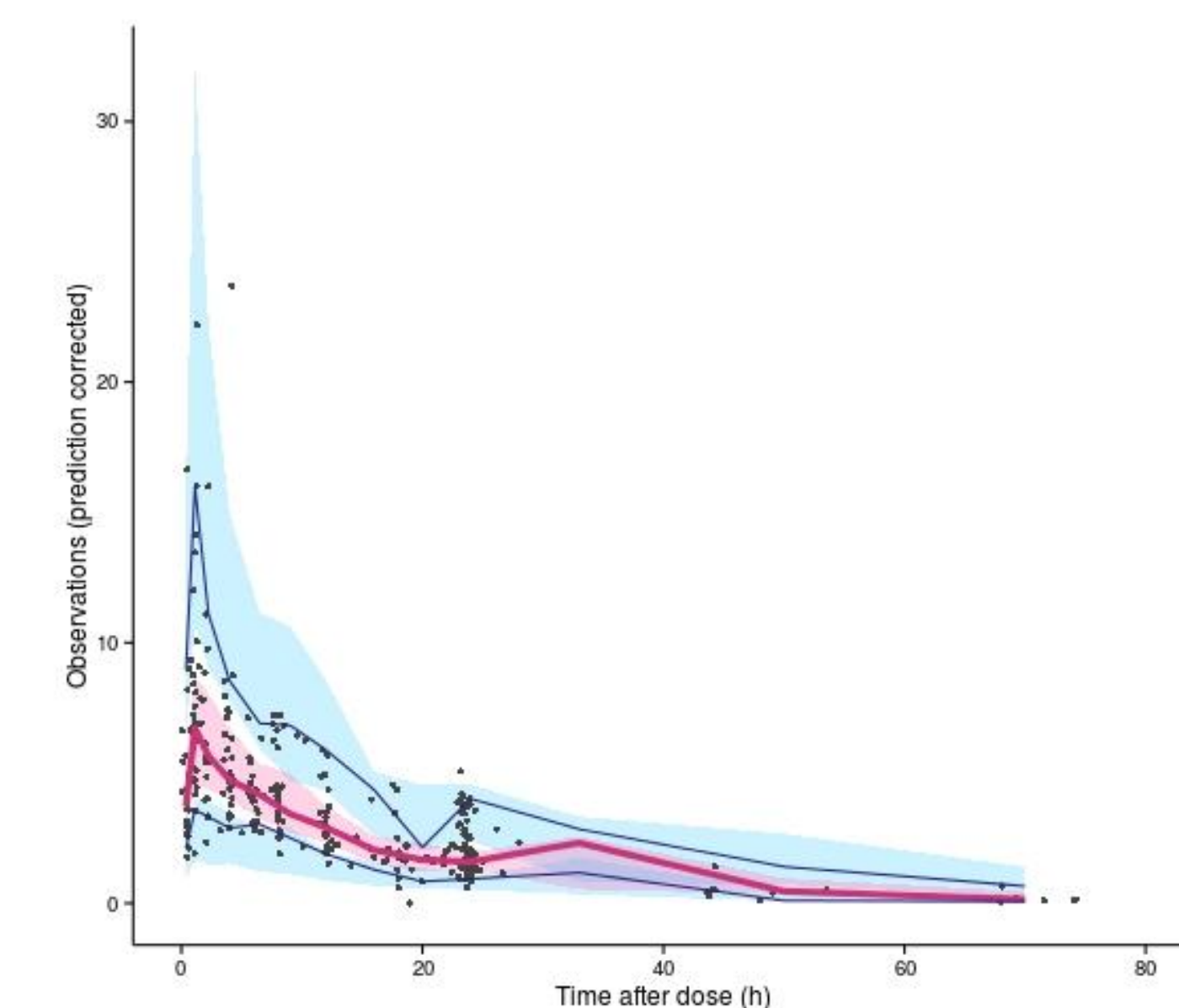


Figure 2 Visual predictive check for the final PK model of micafungin, based on n=1000 simulations. Prediction-corrected simulated (areas) and observed (points and lines) micafungin concentrations versus time after dose (hours). The thick pink line connects the observed median values per bin. The solid thinner blue lines connect the 5th and 95th percentiles of the observations. The blue areas are the 95th percentiles of the observations. The pink area indicates the CI of the median.

References

- [1] European Medicines agency; Mycamine EPAR; 08-05-2008; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000734/WC500031075.pdf [2] Pappas et al. Mycoses 2012; 55 (Suppl. 1), 8–12 [3] Lempers et al. AAC 2015 Aug;59(8):4403-9. [4] Martial et al. Clin Pharmacokinetics. 2015 Dec 9. [Epub ahead of print] [5] Roberts et al. Lancet Infect Dis. 2014;14(6):498-509 [6] Andes et al. AAC 2011 May;55(5):2113-21. [7] Pfaller et al. J Clin Microbiol 2010. Jan;48(1): 52–56.

RESULTS (CONTINUED)

Monte Carlo simulations of alternative dosing regimens

Daily exposure (AUC_{0-24h}) on day 14 achieved by different dosing regimens (Table 1) is shown in Figure 3. >75% of patients on regimen I and III (100 mg maintenance) showed an AUC_{0-24h} lower than 135 (AUC_{0-24h} often encountered in health volunteers[3]). AUC_{0-24h} on day 14 were significantly different between all treatment regimens, except for regimen 1 vs 3 and 2 vs 5. Concentration time curves are shown in Figure 4. A loading dose resulted in higher earlier exposure (regimen III and IV).

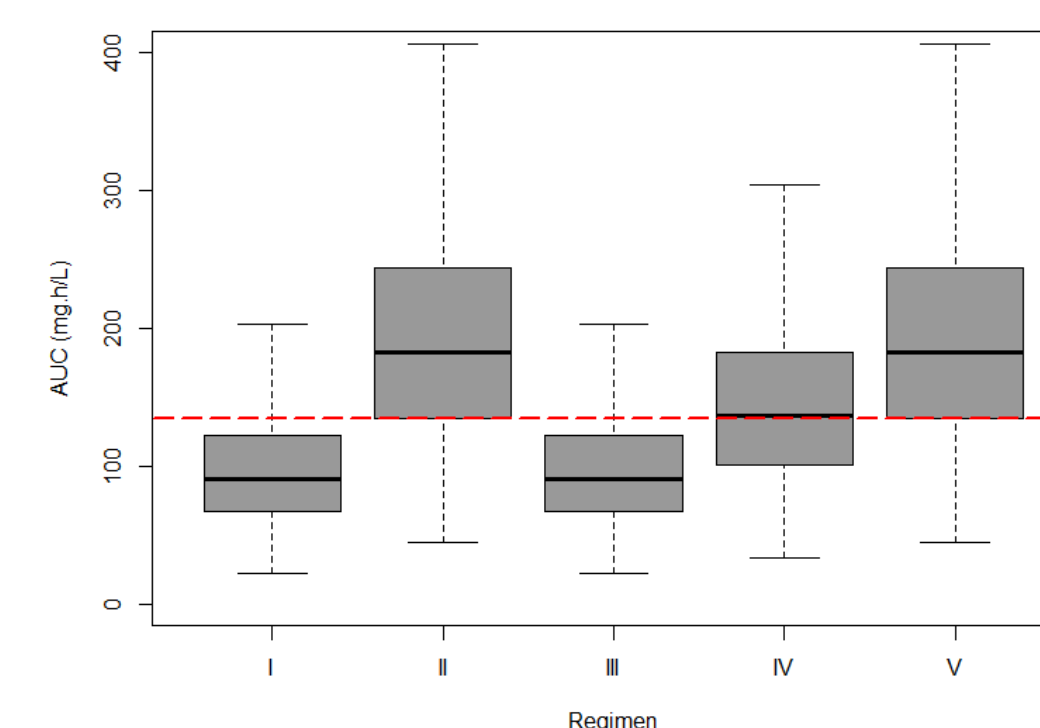


Figure 3 AUC_{0-24h} on day 14 for the hypothetical cohort. >75% of patients on regimen I and III (100 mg maintenance) showed an AUC_{0-24h} lower than 135 (AUC_{0-24h} often encountered in health volunteers[3], red line), risking therapeutic failure. (I) 100mg QD; (II) 100mg QD followed by 200mg QD from day 5; (III) 200 mg loading dose with 100mg maintenance; (IV) 200mg loading dose with 150mg maintenance and (V) 200mg QD.

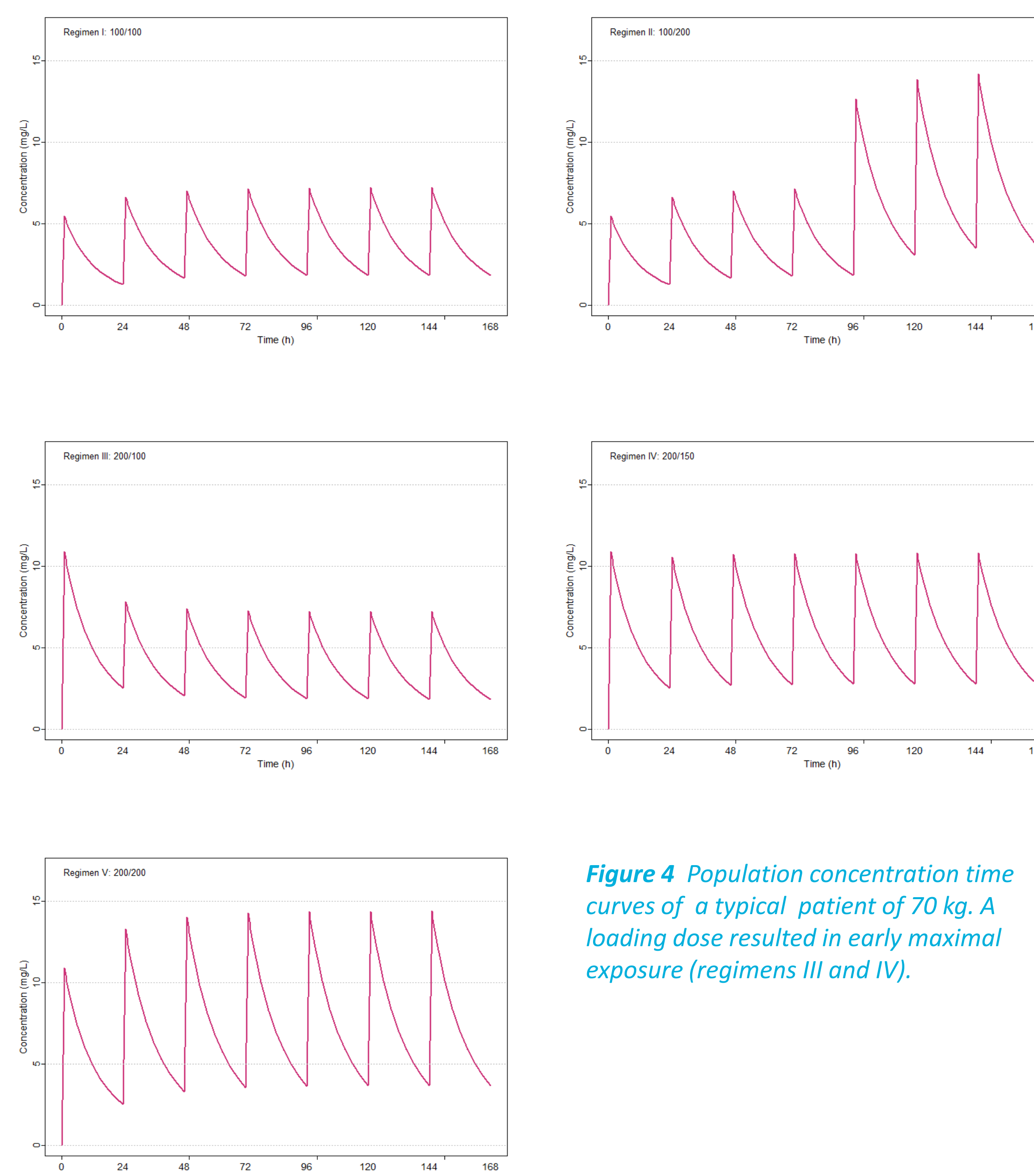


Figure 4 Population concentration time curves of a typical patient of 70 kg. A loading dose resulted in early maximal exposure (regimens III and IV).

Pharmacokinetic target attainment (PTA)

Target attainment (day 3) based on a hypothetical cohort (n=1000) treated with five regimens and based on different MIC values is shown in Figure 5. With an MIC ≥ 0.25 $\mu\text{g/mL}$ none of the regimens resulted in target attainment. Especially in case of an MIC of 0.032 $\mu\text{g/mL}$, higher maintenance dose resulted in increased PTA (44% versus >78%).

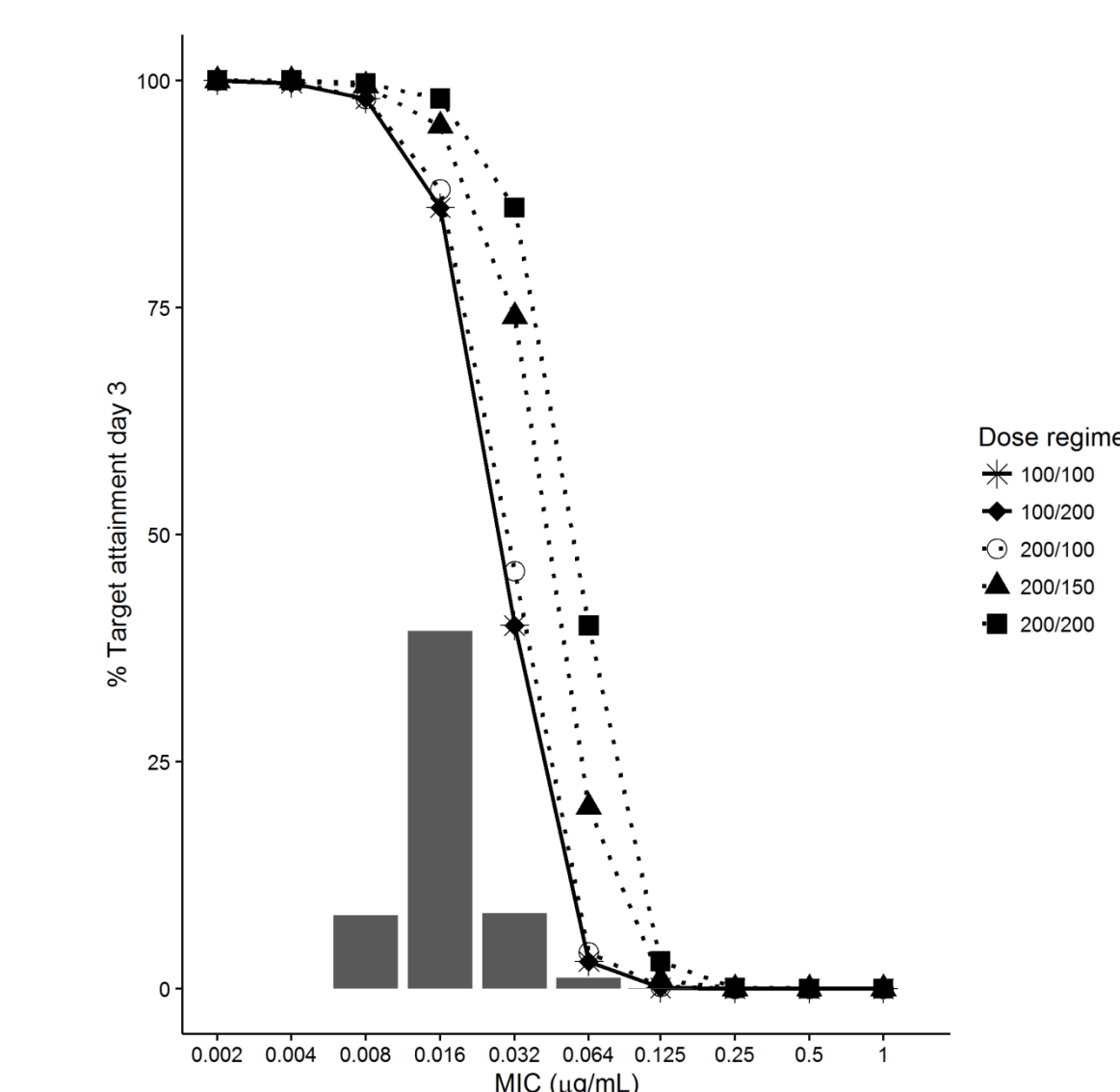


Figure 5 Target attainment at day 3 versus MIC for all five simulated regimens based on a clinical target AUC/MIC ratio of ≥ 3000 . Bars represent wild type population distribution of *C. Albicans* for micafungin, as measured by CLSI guidelines[7].

CONCLUSIONS

- A population PK model was developed describing the PK of micafungin in ICU patients.
- With the current regimens infections with wild type *Candida* species can be treated well, except for MIC's of 0.032 $\mu\text{g/mL}$ which may benefit from a dose increase to 200 mg QD.

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