J Antimicrob Chemother
https://doi.org/10.1093/jac/dkae160

Journal of Antimicrobial Chemotherapy

Dosing of IV posaconazole to treat critically ill patients with invasive pulmonary aspergillosis: a population pharmacokinetics modelling and simulation study

Omar Elkayal [1], Beatrijs Mertens [1,2], Joost Wauters [3,4], Yves Debaveye [5,6], Bart Rijnders [7], Paul E. Verweij [8], Roger J. Brüggemann [9], Isabel Spriet [1,2]† and Erwin Dreesen [1]*†

[1]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; [2]Pharmacy Department, UZ Leuven, Leuven, Belgium; [3]Medical Intensive Care Unit, UZ Leuven, Leuven, Belgium; [4]Laboratory for Clinical Infectious and Inflammatory Disorders, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium; [5]Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium; [6]Department of Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium; [7]Department of Internal Medicine, Section of Infectious Diseases and Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands; [8]Department of Medical Microbiology and Radboudumc, CWZ Center of Expertise for Mycology, Radboud University Medical Center, Nijmegen, The Netherlands; [9]Department of Pharmacy and Radboud Institute for Medical Innovation, Radboud University Medical Center, Nijmegen and Radboudumc, CWZ Center of Expertise for Mycology, Radboud University Medical Center, Nijmegen, The Netherlands

*Corresponding author. E-mail: erwin.dreesen@kuleuven.be
†Shared co-senior authorship.

Received 29 February 2024; accepted 3 May 2024

Background: Posaconazole is used for the prophylaxis and treatment of invasive fungal infections in critically ill patients. Standard dosing was shown to result in adequate attainment of the prophylaxis C_{min} target (0.7 mg/L) but not of the treatment C_{min} target (1.0 mg/L).

Objectives: To provide an optimized posaconazole dosing regimen for IV treatment of patients with invasive pulmonary aspergillosis in the ICU.

Methods: A population pharmacokinetics (popPK) model was developed using data from the POSA-FLU PK substudy (NCT03378479). Monte Carlo simulations were performed to assess treatment C_{min} and AUC_{0-24} PTA. PTA ≥90% was deemed clinically acceptable. PopPK modelling and simulation were performed using NONMEM 7.5.

Results: Thirty-one patients with intensive PK sampling were included in the PK substudy, contributing 532 posaconazole plasma concentrations. The popPK of IV posaconazole was best described by a two-compartment model with linear elimination. Interindividual variability was estimated on clearance and volume of distribution in central and peripheral compartments. Posaconazole peripheral volume of distribution increased with bodyweight. An optimized loading regimen of 300 mg q12h and 300 mg q8h in the first two treatment days achieved acceptable PTA by Day 3 in patients <100 kg and ≥100 kg, respectively. A maintenance regimen of 400 mg q24h ensured ≥90% C_{min} PTA, whereas the standard 300 mg q24h was sufficient to achieve the AUC_{0-24} target throughout 14 days, irrespective of bodyweight.

Conclusions: We have defined a convenient, optimized IV posaconazole dosing regimen that was predicted to attain the treatment target in critically ill patients with invasive aspergillosis.

Introduction

Invasive pulmonary aspergillosis (IPA) is commonly observed in immunocompromised patients, such as neutropenic patients or haematopoietic stem cell recipients. However, it was shown that patients in the ICU admitted with severe influenza and coronavirus disease 2019 (COVID-19) also have a high risk of developing IPA.[1] The incidence of this fungal-viral coinfection in critically ill patients has been reported to be up to 20% for influenza-associated pulmonary aspergillosis (IAPA) and 15% for COVID-19-associated pulmonary aspergillosis (CAPA).[2,3] The associated mortality rates are as high as 50%.[2]

Posaconazole is a broad-spectrum triazole antifungal used for prophylaxis and treatment of invasive aspergillosis.[4] It inhibits the lanosterol 14α-demethylase enzyme, thereby blocking the biosynthesis of ergosterol, a key component in the fungal cell wall.[5] Posaconazole mainly circulates as its parent compound in plasma and is highly protein-bound (>98%).[6] Most of the circulating metabolites are formed by glucuronidation by uridine diphosphate glucuronosyltransferase-1A4. Metabolites account for approximately 17% of the drug excreted in urine and faeces.[6]

The primary pharmacokinetic-pharmacodynamic (PKPD) target of posaconazole is the ratio of the AUC_{0-24} to the MIC. Based on preclinical data, an AUC_{0-24}/MIC of 167–178 is associated with a half-maximal antifungal effect against *Aspergillus* spp., which is often rounded to an AUC_{0-24}/MIC target of approximately 200 for treatment.[7–9] This corresponds with an AUC_{0-24} target of 25 mg h/L using the 0.125 mg/L EUCAST clinical breakpoint for susceptibility for *Aspergillus fumigatus* and *Aspergillus terreus*.[10] However, based on clinical data in the trial by Walsh *et al.*,[11] an AUC_{0-24} treatment target of 30 mg h/L and a C_{min} treatment target of 1 mg/L are used. Quartile analysis of these data revealed that an average concentration (C_{avg}) of 1.25 mg/L, which corresponds to an AUC_{0-24} of 30 mg h/L, was associated with a successful clinical response in 75% of the patients.[11] For prophylaxis, a C_{min} of 0.7 mg/L or higher is targeted as most breakthrough invasive fungal infections were observed in patients with C_{min} <0.7 mg/L.[12] As large interindividual variability in exposure and poor target attainment are observed, therapeutic drug monitoring (TDM) is often applied in daily clinical practice.[13]

Posaconazole has been shown to be effective in the prophylaxis against IPA in patients with haematological malignancies.[12,14] Besides, it is also found to be non-inferior to voriconazole in the primary treatment of IPA in the same patient setting.[14] A favourable safety profile, availability as an IV infusion, and residual activity against azole-resistant *A. fumigatus* make it a suitable candidate for prophylaxis against and treatment of IPA, also for patients admitted to the ICU.[14] However, there is limited knowledge about the PK characteristics of posaconazole in critically ill patients. Recently, in a PK analysis of the randomized, open-label POSA-FLU clinical trial of IV posaconazole for prevention of IPA in critically ill influenza patients, the current standard dosing regimen (i.e. 300 mg q12h for the first day as a loading dose and 300 mg q24h as a maintenance dose) was shown to result in adequate attainment of the prophylaxis C_{min} target but not of the treatment C_{min} target.[15] These results emphasize the need for dose optimization of IV posaconazole for treatment in critically ill patients.

We used data from the POSA-FLU study (i) to develop a population PK (popPK) model of IV posaconazole in critically ill patients admitted to the ICU, (ii) to identify covariates with a clinically relevant impact on posaconazole C_{min} and AUC_{0-24} target attainment under standard dosing, and (iii) to provide an optimized loading and maintenance dosing regimen that ensures adequate treatment target attainment in critically ill patients with invasive aspergillosis.

Patients and methods

Data

Data were obtained from the POSA-FLU trial (NCT03378479). Patients were enrolled in this prospective multicentre, randomized, open-label study to assess the efficacy of IV posaconazole as a prophylactic agent for IAPA.[16] The study was performed in 12 centres in the Netherlands, Belgium and France between December 2017 and March 2020. The exploratory PK study was conducted only in Belgian sites and was performed under the POSA-FLU study protocol (Ethics Committee Research UZ/KU Leuven; S60744). Written informed consent was obtained from each patient or their legal representative before enrolment.

Information on drug prescriptions, sampling times and covariates was retrieved from the electronic health records. Standard 300 mg IV posaconazole infusions over 90 min q12h on the first day as a loading dose and q24h on the following days as a maintenance dose were administered as prophylaxis for 7 days. Blood samples were collected during a 24 h dosing interval on an early day (Day 2 or 3) and a later day (≥Day 4) (see Supplementary methods, available as Supplementary data at *JAC* Online). A detailed description of the trial design and methodology can be found in Van Daele *et al.*[15] and Vanderbeke *et al.*[16]

Population PK modelling

A base popPK model was fitted to the total posaconazole concentration–time data. One-, two- and three-compartment models with linear and non-linear elimination processes were explored. Interindividual variability (IIV) and interoccasion variability (IOV; ≤Day 3 or >Day 3, corresponding to the early and late PK sampling design) were tested for different PK parameters. Additive, proportional and combined error models were explored to describe residual unexplained variability. Individual PK parameters were assumed to be log-normally distributed, which was achieved using an exponential function.

Parameter estimation was performed using first-order conditional estimation with interaction and differential equation solver ADVAN 13. The final base model was selected based on objective function value (OFV; calculated as −2×log-likelihood) comparisons (difference ≥3.84 points; $P \leq 0.050$), plausibility and precision of parameter estimates, and goodness-of-fit plots. A final model, including covariate effects, was built through stepwise covariate modelling, forward inclusion and backward deletion steps, using an OFV decrease of ≥3.84 ($P \leq 0.050$) and ≥6.63 ($P \leq 0.01$) for statistical significance, respectively. Linear, power and exponential functions were all tested to model the covariate effects (using parallel states). The tested covariates were sex, ICU admission baseline values for bodyweight and BMI, as well as time-varying serum albumin, bilirubin, serum creatinine, the estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation ($eGFR_{CKD-EPI}$),[17] AST, ALT, haemoglobin and haematocrit. Missing covariate values were imputed with the individual's median value calculated from available covariate values for that patient.

A prediction-corrected visual predictive check ($n = 1000$ simulated replicates of the original dataset) plot was used to evaluate the final model. A bootstrap ($n = 2000$ bootstraps) was performed to obtain non-parametric estimates of uncertainty in parameter estimates.

Dose-finding simulations

Monte Carlo simulations were performed using the final popPK model to evaluate seven posaconazole dosing regimens (Table S1). Target attainment was defined based on the C_{min} treatment target of 1 mg/L and the AUC_{0-24} target of 30 mg h/L. High posaconazole exposure was defined as C_{min} ≥3.75 mg/L.[18] The PTA was assessed at the end of Days 2, 7 and 14 of treatment. A PTA ≥90% was considered clinically acceptable as recommended by the EMA.[19]

First, simulations were performed to identify an optimized, inclusive dosing regimen that ensures a PTA ≥90% for each virtual patient. Virtual patients were defined by values of the covariates identified in the popPK model. Covariate values defining the virtual patients were confined within the range as observed in the modelling dataset (Table 1). For each virtual patient, 1000 simulations were conducted.

After an optimized, inclusive dosing regimen was identified, its impact at the population level was evaluated in terms of PTA, drug exposure and drug consumption (total amount in milligrams up to Day 14) in comparison with standard dosing. A virtual patient population ($n=1000$) was created by sampling covariates from the variance-covariance matrix created from the modelling dataset, bounded to the range as observed in the modelling dataset.

Receiver operating characteristic (ROC) analysis was used to evaluate the clinical relevance of covariates. An area under the ROC curve was used as a quantitative surrogate for clinical relevance.

Software

Dataset formatting and exploration were performed using R (v4.2.1; R Core Team, Vienna, Austria) using custom scripts based on packages including dplyr, ggplot and Xpose. PopPK analysis and simulations were performed using NONMEM (v7.5; ICON Development Solutions, Gaithersburg, MD, USA), with a GNU Fortran 95 compiler and the Perl-speaks-NONMEM (PsN; v5.2.6.) toolkit on the interface software Pirana (v2.9.7; Certara, Inc., Princeton, NJ, USA).

Results

Data

In 31 of the 88 patients enrolled in the POSA-FLU study, intensive PK sampling was performed, contributing a total of 532 posaconazole plasma samples, including 138 (26%) trough samples (Table 1, Figure S1). None of the total posaconazole plasma concentrations were below the assay limit of quantification. The standard IV posaconazole dosing regimen achieved clinically acceptable C_{min} prophylaxis target attainment rates of 94.2% and 97.7% on early and late days of therapy, respectively. However, C_{min} treatment target rates of 68.4% and 83.7% on the early and late days, respectively, were clinically unacceptable.

Population PK modelling

A two-compartment popPK model with linear elimination best described the posaconazole total concentration–time data (Figures 1, S2, S3, S4, S5 and S6). IIV was estimated on CL and volume of distribution in the central and peripheral compartments (V_c and V_p). IOV was estimated on CL and V_c. Bodyweight was retained as the only statistically significant covariate in the final model (Table 2, Figure S7). Equation 1 describes how V_p of posaconazole for patient i increases with increasing bodyweight:

$$V_{p(i)} = 230\ \text{L} \times \left(\frac{\text{Bodyweight}_i}{75\ \text{kg}}\right)^{1.6} \times e^{\eta_i} \text{ with } \eta_i \sim N(0,\ 0.0525) \quad (1)$$

Posaconazole V_p increases from 144.1 L (56 kg; min.) to 624.4 L (140 kg; max.), resulting in an increase in elimination half-life from 42 to 120 h.

The NONMEM control stream is available in the Supplementary material.

Table 1. Summary of patient characteristics

Parameter	Value
Demographics	
Patients, *n*	31
Age, y, median [range]	60 [26–90]
Sex, male, *n* (%)	18 [58]
Bodyweight at baseline, kg, median [range], (% missing)	75 [56–140] (0)
BMI at baseline, kg/m^2, median [range], (% missing)	26.8 [18.5–40.9] (0)
APACHE II score at baseline, median [range], (% missing)	19 [8–34] (13)
SOFA score, median [range], (% missing)	7 [2–19] (38)
Albumin concentration, g/L, median [range], (% missing)	32.5 [21.1–51.2] (24)
Bilirubin, mg/dL, median [range], (% missing)	0.68 [0.2–3.69] (15)
ALT, U/L, median [range], (% missing)	38 [9–1206] (15)
AST, U/L, median [range], (% missing)	49 [19–3245] (15)
Serum creatinine, mg/dL, median [range], (% missing)	0.93 [0.43–5.34] (14)
$eGFR_{CKD\text{-}EPI}$, mL/min/1.73 m^2, median [range], (% missing)	77.5 [10.0–125.0] (16)
Haemoglobin, g/dL, median [range], (% missing)	10.1 [6.4–17.0] (13)
Haematocrit, median [range], (% missing)	31 [18.6–51.8] (12)
Sampling information	
Number of plasma samples, *n*	536
At trough, *n* (%)	138 [25.7]
24 h-sampling days, *n*	35
24 h-sampling days per patient, median [range]	2 [1–2]
Posaconazole measurements	
C_{max} concentration, mg/L, median [range]	2.8 [1.21–8.9]
C_{min} concentration, mg/L, median [range]	1.5 [0.4–4.2]

$eGFR_{CKD\text{-}EPI}$, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

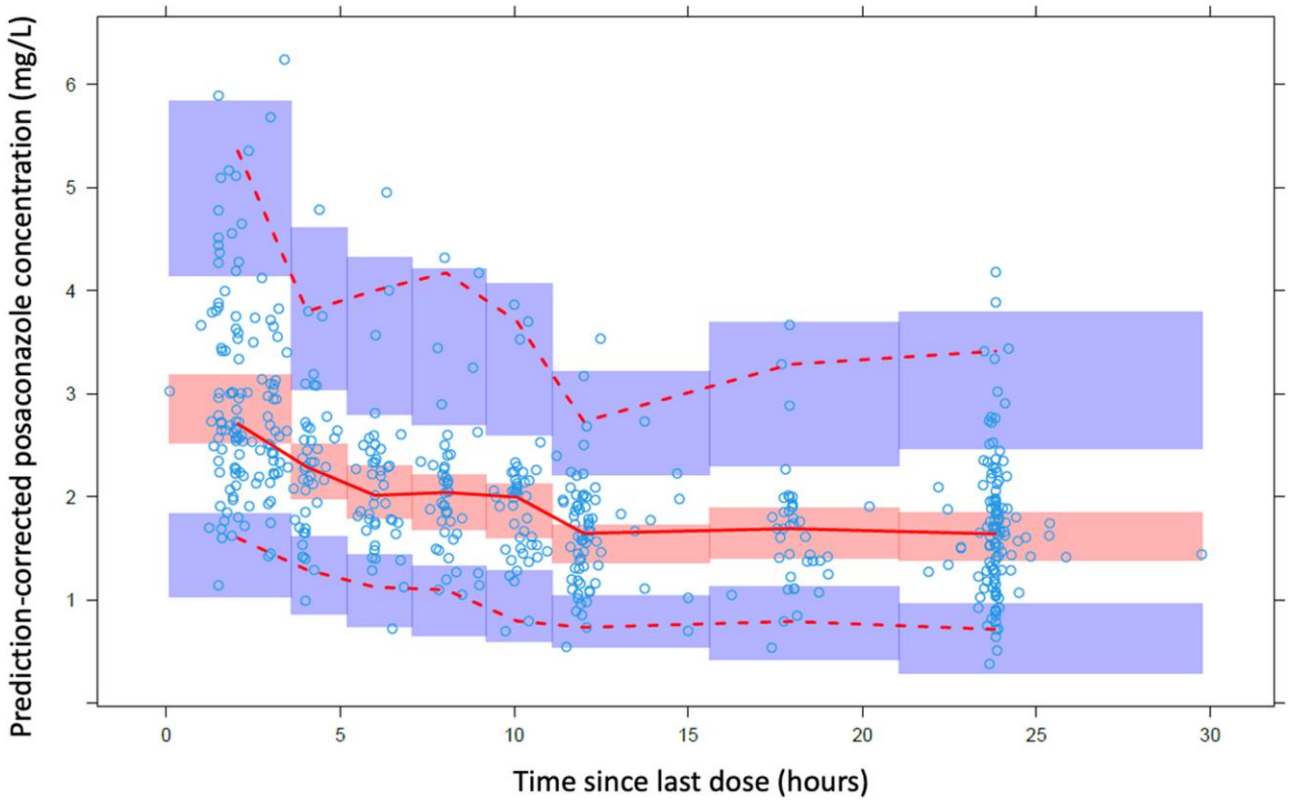

Figure 1. Prediction-corrected visual predictive check of the final popPK model. Open circles represent the prediction-corrected observed posaconazole concentrations. The solid line is the median of the observed data. The dashed lines are the 5th and 95th percentiles of the observed data. The red and blue shaded areas indicate the 90% prediction intervals of the median and 5th and 95th percentiles, respectively, of the simulated data ($n = 1000$). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Dose-finding simulations

Identification of an optimized inclusive loading regimen

Standard dosing resulted in clinically unacceptable C_{min} and AUC_{0-24} PTA at the end of Day 2 across the entire bodyweight range (50–150 kg) (Figures 2a and 3a). A loading regimen of 300 mg q12h for 2 days instead of 1 day resulted in clinically acceptable C_{min} and AUC_{0-24} PTA at the end of Day 2 for patients with bodyweight below 100 kg. A 300 mg q8h loading regimen for the first 2 days resulted in clinically acceptable C_{min} and AUC_{0-24} PTA in patients with a bodyweight of 100 kg or higher (Figures 2a and 3a; Table 3).

Identification of an optimized inclusive maintenance regimen

Standard 300 mg q24h maintenance dosing resulted in clinically unacceptable C_{min} PTA on Days 7 and 14 across the entire bodyweight range. Increasing the maintenance dose from 300 to 400 mg q24h resulted in clinically acceptable C_{min} PTA across the entire bodyweight range (Figure 2b and 2c; Table 3). Conversely, the standard 300 mg q24h maintenance dosing resulted in clinically acceptable AUC_{0-24} PTA throughout the remaining treatment period, eliminating the need for maintenance dose modification when targeting the AUC_{0-24} target (Figure 3b and 3c; Tables 3 and S2).

Comparison of AUC_{0-24} and C_{min} targets

Dose-finding simulations demonstrated higher PTA of the 30 mg h/L AUC_{0-24} target than of the 1.0 mg/L C_{min} treatment target (Figures 3–5). Although, the loading dose regimen recommendation remains the same for both targets, attainment of the AUC_{0-24} target requires no optimization of the maintenance dose, unlike the recommended increased maintenance dose when targeting C_{min}. An AUC_{0-24} of 37 mg h/L corresponds to a C_{min} of 1.0 mg/L, and an AUC_{0-24} of 30 mg h/L corresponds to a C_{min} of 6.8 mg/L, challenging the previously assumed equivalence of the AUC_{0-24} of 30 mg h/L and the C_{min} of 1 mg/L (Figure S8). Given the discrepancies between the two targets, we decided to perform our population-level simulations using the optimized posaconazole dosing regimen based on the C_{min} target as this approach ensures that both the C_{min} and AUC_{0-24} targets are adequately achieved.

Impact of the optimized inclusive dosing regimen on the patient population

The standard dosing regimen resulted in clinically unacceptable C_{min} PTA throughout the 2 week treatment period (Figure 4a, Table 4), and a clinically unacceptable AUC_{0-24} PTA at Day 2 (Figure 4b, Table 4). The optimized inclusive dosing regimen resulted in clinically acceptable PTA as early as Day 2 until Day 14

Table 2. Population pharmacokinetics model parameter estimates

Parameter	Base model estimates (% RSE) [% shrinkage] (OFV = −746.9, CN = 13.2)	Final model estimates (% RSE) [% shrinkage] (OFV = −764.2, CN = 22.6)	Bootstrap median (95% CI)
Typical values			
CL, L/h	4.9 (8.4)	4.7 (10.0)	4.7 (3.9–5.6)
V_c, L	131.0 (10.3)	130.0 (12.2)	129.5 (99.6–159.8)
Q, L/h	41.1 (5.5)	41.4 (5.6)	42.0 (37.9–48.9)
V_p, L	234.0 (8)	230.0 (14.5)	230.9 (198.4–263.8)
Covariate effects[a]			
BW on V_p		1.6 (14.5)	1.6 (1.1–2.1)
Interindividual variability[b]			
on CL (%CV)	47.8 (14.2) [12]	50.4 (14.6) [11]	49.0 (31.6–65.2)
on V_c (%CV)	63.9 (24.1) [16]	62.3 (24.7) [15]	59.5 (24.0–96.4)
on V_p (%CV)	39.9 (18.2) [19]	23.2 (27.0) [33]	21.9 (7.7–34.8)
Interoccasion variability			
on CL (%CV)	20.0 (21.1) [46]	20.8 (23.6) [44]	20.9 (11.1–31.7)
on V_c (%CV)	41.8 (22.5) [30]	40.1 (22.5) [31]	39.2 (21.7–56.2)
Residual variability			
Proportional error (%CV)	11.7 (12.0) [10]	11.7 (11.9) [24]	11.5 (8.9–14.4)

CN, condition number; CV, coefficient of variation calculated as $\sqrt{\exp(\omega^2)-1}\times 100\%$; OFV, objective function value; Q, intercompartmental clearance; RSE, relative standard error (for random effects and residual variability reported on the approximate SD scale; 100 × (standard error of estimate)/(estimate); V_c, volume of distribution in the central compartment; V_p, volume of distribution in the peripheral compartment.

[a]Covariates were tested on CL, V_c and V_p because eta-shrinkages of the interindividual variabilities in the base model did not exceed 20%. A total of 1853 out of 2000 bootstrap runs (92.6%) were successful.

[b]Interoccasion variability was defined as early (Days 1–3) versus late (Days 4–6) occasion.

(Figure 4a and 4b; Table 4). The total posaconazole dose for a 2 week treatment course increased from 4500 mg per patient to 6055 mg per patient and resulted in a significant increase in PTA% on Days 2 (from 75% to 97%), 7 (88% to 94%) and 14 (88% to 94%). The optimized dosing regimen resulted in higher exposure compared with the standard regimen (Figures 5 and S9; Table 4). The median C_{min} (IQR) was higher for the optimized dosing regimen than the standard regimen on Days 2, 7 and 14, with values of 1.97 (1.56–2.42) mg/L, 2.59 (1.91–3.50) mg/L, and 2.92 (1.97–4.19) mg/L compared with 1.26 (0.97–1.65) mg/L, 1.90 (1.34–2.56) mg/L, and 2.13 (1.37–3.13) mg/L, respectively. The percentage of patients with high posaconazole exposure (C_{min} >3.75 mg/L) while using the optimized dosing regimen was 1.7%, 19.0% and 30.5% on Days 2, 7 and 14, respectively, compared with 0.1%, 4.8% and 14.5% of patients on standard dosing (Figure S9). Bodyweight was confirmed to lose its clinically relevant impact on end of Day 2 PTA when using the optimized instead of the standard dosing regimen (Figure 4c and 4d).

Discussion

By using data from the POSA-FLU trial, we studied the popPK of posaconazole in critically ill patients, a population for which PK data are scarce. Our modelling and simulation results showed that the standard IV dosing regimen resulted in clinically unacceptable C_{min} and AUC_{0-24} target attainment when used in a treatment setting. We proposed a pragmatic and easy-to-implement optimized dosing regimen leading to >90% PTA from Day 2 of treatment and throughout a 2 week treatment course.

Unlike the standard dosing regimen, which is characterized by poor target attainment, the optimized dosing regimen would no longer require TDM to guarantee target attainment. TDM of posaconazole is often applied, especially in the treatment setting and in special patient populations such as critically ill patients or obese patients. The primary objective of TDM of posaconazole is to verify exposure to warrant efficacy. However, posaconazole bioassays are not available in every clinical centre, especially not in limited-resource settings. In centres where it is available, turnaround times are not always ideal, and TDM is also associated with a cost. Besides, traditional TDM services, in which dose adjustments are carried out based on the clinician's or pharmacist's experience (and not on popPK models), are not always very successful in terms of improvement of target attainment.[20] Therefore, we propose an easy-to-implement weight-based stratified loading dose and flat maintenance dose, leading to >90% PTA from Day 2 onwards, making TDM no longer necessary to ensure adequate exposure. However, TDM might still be needed to ensure safety and monitor drug–drug interactions.

For critically ill patients suffering from IPA, it is imperative to achieve the treatment target as quickly as possible to improve patient outcomes.[21] Our simulations demonstrated that the standard 1 day loading regimen of IV posaconazole fails to achieve clinically acceptable C_{min} PTA in the early days of treatment and that bodyweight should be considered in loading dose optimization. Early target attainment is ensured with a 2 day loading regimen of 300 mg q12h and 300 mg q8h for

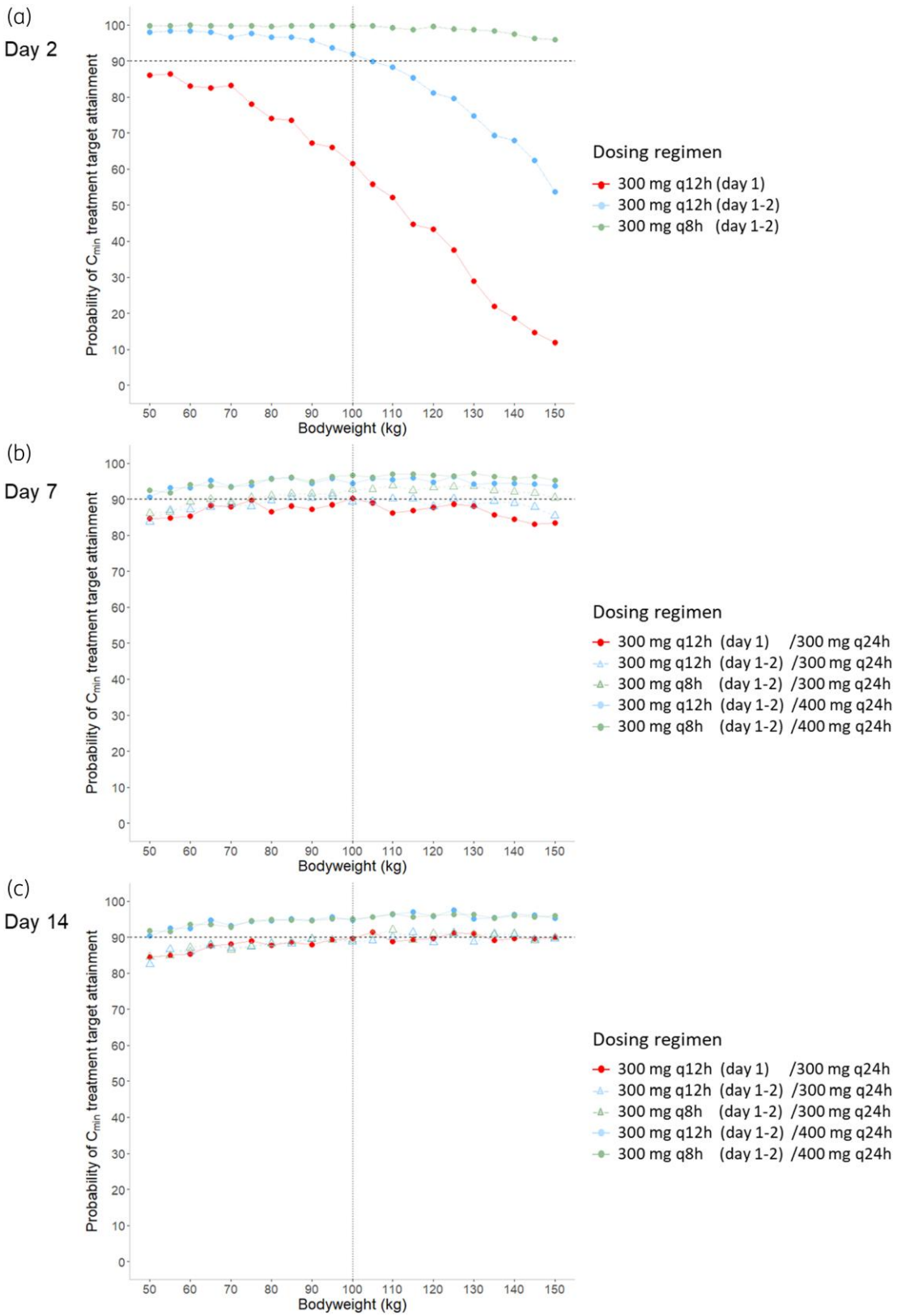

Figure 2. The probability of posaconazole C_{min} treatment target (≥1 mg/L) attainment versus bodyweight at (a) Day 2, (b) Day7 and (c) Day 14 of treatment. Simulations were performed over a bodyweight range from 50 to 150 kg in steps of 5 kg. Each patient was simulated 1000 times. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

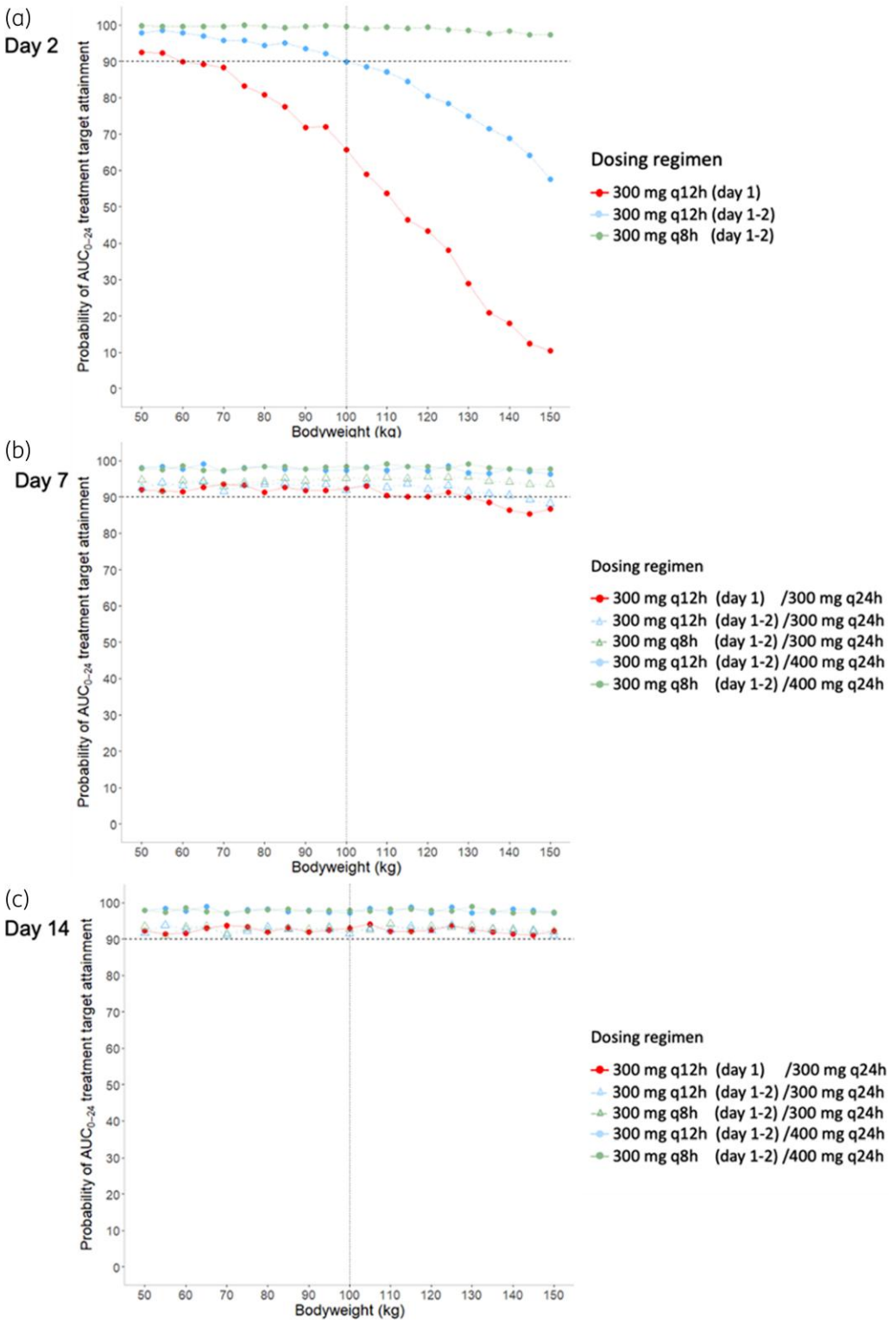

Figure 3. Probability of posaconazole AUC_{0-24} treatment target (≥30mg h/L) attainment versus bodyweight at (a) Day 2, (b) Day 7 and (c) Day 14 of treatment. Simulations were performed with bodyweights from 50 to 150 kg in steps of 5 kg. Each patient was simulated 1000 times. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

patients <100 kg and ≥100 kg, respectively. The standard maintenance regimen of 300 mg q24h fails to achieve clinically acceptable C_{min} PTA on Days 7 and 14. A flat maintenance dose of 400 mg q24h (irrespective of bodyweight) is needed to attain the C_{min} treatment target. This optimized dosing regimen guaranteeing target attainment also in higher bodyweight patients is relevant for treating CAPA, as patients admitted to the ICU with COVID-19 often have higher bodyweight.[22]

The optimized posaconazole dosing regimen that we recommend increases the overall posaconazole exposure. Theoretically, this might increase the risk of toxicity (e.g. liver injury and pseudohyperaldosteronism), as suggested in some small or retrospective studies.[23,24] However, a clear relation between exposure and toxicity has thus far not been documented in larger clinical trials.[25–27] Consequently, no upper limit for C_{min}, corresponding to a higher risk for toxicity, has been defined for posaconazole, unlike for voriconazole.[13] Therefore, the EMA recommended using 3.75 mg/L as a surrogate C_{min} target for toxicity during development of the new tablet and IV formulation.[18] The safety of our optimized posaconazole dosing regimen should be further assessed in a prospective clinical trial; yet, considering the high mortality of invasive aspergillosis in critically ill patients, we believe that the benefit of early target attainment is clinically more desirable compared with the small risk of increased toxicity.

The PK of posaconazole in critically ill patients was best described by a two-compartment model with first-order elimination. Bodyweight significantly impacted IIV of V_p, but not of V_c. This observation may be attributed to the drug's high lipophilicity, which causes its accumulation in the peripheral volume, and its sensitivity to bodyweight (as a surrogate for peripheral fat). Previously conducted posaconazole popPK studies have primarily focused on the oral suspension or tablet formulation.[28–38] The extended absorption phase that follows oral administration

Table 3. Optimized dosing regimen

Patient bodyweight	Loading dose (first 2 days)	Maintenance dose
<100 kg	300 mg q12h	400 mg q24h
≥100 kg	300 mg q8h	400 mg q24h

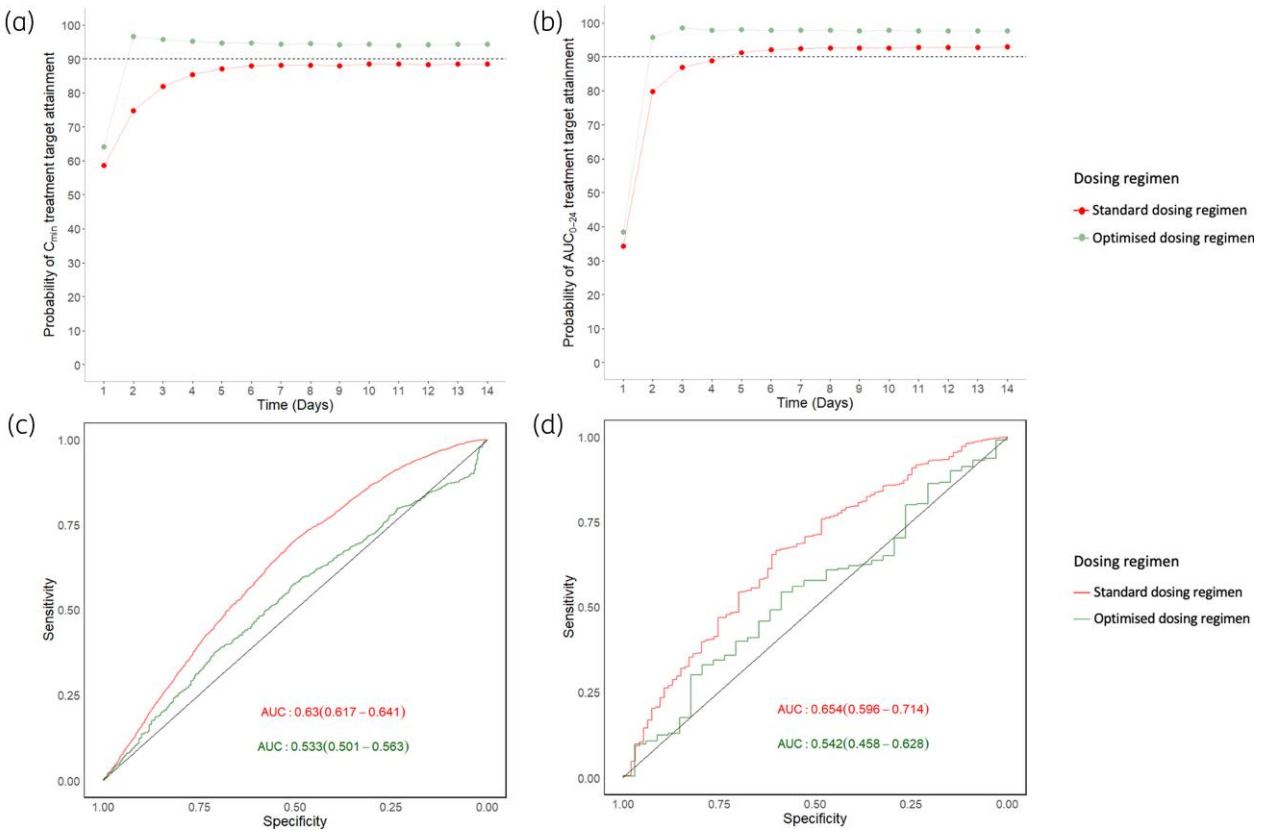

Figure 4. (a) The probability of C_{min} target (≥1 mg/L) attainment versus days of treatment on a population level. (b) The probability of AUC_{0-24} (≥30 mg h/L) target attainment versus days of treatment. (c) Receiver operating characteristic plots for investigating the clinical relevance of bodyweight on posaconazole probability of attaining the C_{min} treatment target on Day 2. (d) Receiver operating characteristic plots representing the clinical relevance of bodyweight on posaconazole probability of attaining the AUC_{0-24} treatment target at Day 2. The red line represents the standard dosing regimen of 300 mg q12h on the first treatment day followed by 300 mg q24h. The green line represents the optimized dosing regimen of 300 mg q12h and 300 mg q8h on the first two treatment days in patients <100 kg and ≥100 kg, respectively, followed by 400 mg q24h. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

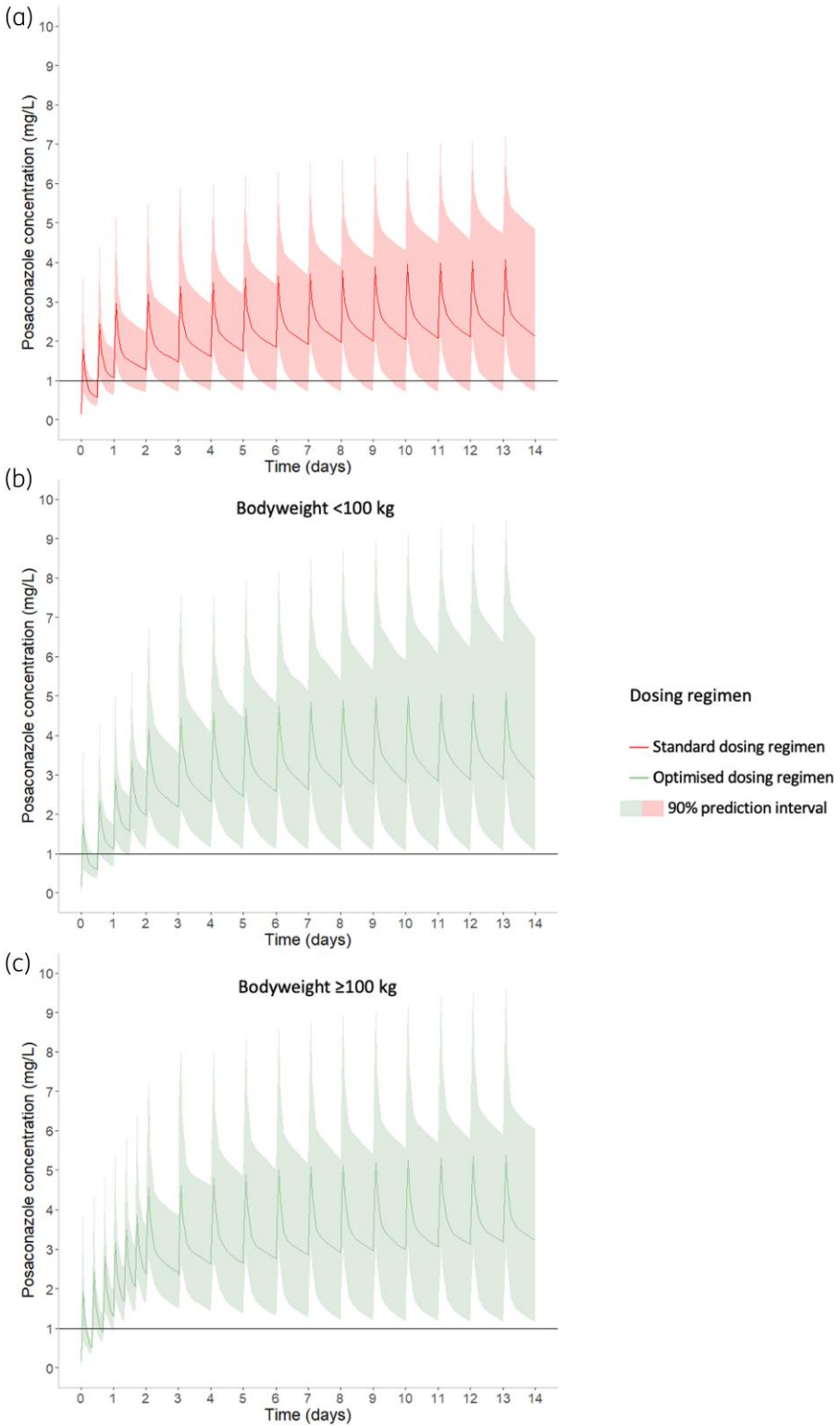

Figure 5. Posaconazole concentration, plotted against time in days using population-level simulations. (a) Patients receiving the standard posaconazole standard regimen. (b) Patients <100 kg receiving the optimized posaconazole dosing regimen. (c) Patients ≥100 kg receiving the optimized posaconazole dosing regimen. The red colour represents the standard dosing regimen of 300 mg q12h on the first treatment day followed by 300 mg q24h. The green colour represents the optimized inclusive dosing of 300 mg q12h and 300 mg q8h in the first two treatment days in patients <100 kg and ≥100 kg, respectively, followed by 400 mg q24h. The shaded area represents the 90% prediction interval. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 4. Population-level target attainment

Day	Dosing regimen	% PTA C_{min} ≥1 mg/L	% PTA AUC_{0-24} ≥30 mg h/L	% Patients C_{min} ≥3.75 mg/L
2	Standard dosing	75	80	0.1
2	Optimized dosing	97	96	1.7
7	Standard dosing	88	92	4.8
7	Optimized dosing	94	98	19.0
14	Standard dosing	88	92	14.5
14	Optimized dosing	94	98	30.5

of posaconazole may have hindered the identification of the distribution phase, possibly explaining why one-compartment models have been used to describe oral posaconazole data in previous literature. Only one popPK study of the oral formulations based on rich Phase 1 trial data captured a two-compartment model.[39] The PK of a single IV posaconazole dose was recently investigated in patients with normal to obese bodyweights.[40] Similar to our model, a two-compartment model was identified where increased bodyweight leads to an increase in V_p, suggesting the need to increase posaconazole dosing for patients with higher bodyweights. Our study is the first popPK study to investigate multiple day IV posaconazole dosing in critically ill patients. The only previous popPK study in critically ill patients was in a single-dose setting identifying another bodyweight metric (BMI) as a significant covariate on the volume of distribution.[41]

Our study aligns with the recommendation of a 400 mg maintenance dose for IV posaconazole, as suggested by previous research.[40] Nevertheless, we are aware that this recommendation implies some practical and economic challenges. The IV formulation is marketed as vials containing only 300 mg of posaconazole, aligning with the standard loading and maintenance dose. With our proposed optimized maintenance dose of 400 mg q24h, two vials per dose would be needed, resulting in a potential waste of 200 mg per dose. However, as the solution of posaconazole is stable for at least 24 h if stored between 2°C and 8°C, vials can be fractionated and the remaining undiluted solution retained for the next administration.[18] We did not evaluate q12h maintenance dosing as q24h dosing is more practical, requires fewer manipulations, and occupies the catheter line for less time.

To our knowledge, this is the first popPK modelling and simulation study for multiple day IV posaconazole dosing in critically ill patients. Our study included rich sampling data on two occasions for each patient, which allowed us to develop a two-compartment popPK model that adequately describes our data. Our findings are particularly relevant for the treatment of invasive aspergillosis, a common complication in critically ill patients with severe influenza and COVID-19 infections. Nevertheless, there are some limitations to our study. First, for popPK modelling, we relied on PK data from critically ill patients with influenza receiving posaconazole to prevent IPA. Although the clinical benefit of posaconazole prophylaxis is not established, the clinical benefit of posaconazole treatment is. The POSA-FLU data provide valuable insight into the PK of posaconazole in critically ill patients, allowing for reliable popPK simulations to inform dose optimization in the on-label treatment setting. Second, only four patients in our modelling dataset had a bodyweight over 100 kg (101, 103, 105 and 140 kg). This might limit the reliability of our simulations in patients with higher bodyweights. However, a previously published popPK model built on a population including 16 morbidly obese patients also suggested a similar increase in dosing.[40] Finally, our work relied on total posaconazole concentrations. Nevertheless, posaconazole exhibits high protein binding, estimated to be approximately 99%. However, reports show variability in the percentage of free posaconazole, ranging from 0.65% to 2.7%,[14,36,41] introducing uncertainty when defining a precise target based on free posaconazole concentrations and fraction unbound. Considering that our cohort consisted of critically ill patients, it is important to acknowledge that the modified physiology in these patients could affect plasma protein binding.[42,43] A prospective clinical study, including a wider patient bodyweight range, is ultimately needed to confirm the impact of the optimized bodyweight-based stratified loading regimen and the flat maintenance dose on posaconazole treatment target attainment in critically ill patients with invasive aspergillosis. Safety monitoring (including monitoring of the QT interval and hepatotoxicity) during this trial and a (cost-)effectiveness analysis will be essential.

Conclusion

We have identified an optimized weight-based loading regimen and a flat maintenance dose for IV posaconazole that was predicted to attain the C_{min} and AUC_{0-24} treatment target in critically ill patients with invasive aspergillosis from the second treatment day onwards.

Acknowledgements

We thank the patients, their families and the clinical trial teams at all participating centres for contributing data to the PK substudy. We also thank Lore Vanderbeke and Cato Jacobs for their contributions to the clinical trial. The resources and services used in this work were provided by the VSC (Flemish Supercomputer Centre), funded by the Research Foundation—Flanders (FWO) and the Flemish Government.

This study is based on data from the PK substudy of the POSA-FLU clinical trial, exclusively conducted in Belgian centres under the study protocol registered as S60744 with the Ethics Committee Research UZ/KU Leuven. All procedures conducted within this study were executed in strict adherence to the principles of the Declaration of Helsinki, as well as the principles of good clinical practice, and in accordance with all pertinent regulatory requirements.

Funding

This study was supported by internal funding.

Transparency declarations

O.E. and B.M. have nothing to disclose. J.W. reports investigator-initiated grants from Pfizer, Gilead and MSD; consulting fees from Pfizer and Gilead; speaker's fees from Pfizer, Gilead and MSD; travel fees from Pfizer, Gilead and MSD; participation in advisory boards of Pfizer and Gilead; and receipt of study drugs from MSD, outside the submitted work. Y.D. reports travel support from Pfizer and participation in advisory boards of Pfizer and MSD outside the submitted work. B.R. reports research grants from Gilead Sciences and F2G and is on the advisory board for F2G, outside the submitted work. P.E.V. reports research grants from Thermo Fisher, MSD, Gilead Sciences and EORTC, and speaker's honoraria for Gilead Sciences, Mundipharma and Pfizer, outside the submitted work. R.J.B. reports consultancy fees from Mundipharma, Cidara, Amplyx, F2G, Gilead, Pfizer and MSD, speaker's fees from Pfizer and Gilead; and grants from Pfizer, Gilead and MSD, outside the submitted work. I.S. is supported by the Clinical Research Fund of UZ Leuven and reports consulting fees from Pfizer and Cidara; speaker's fees from Pfizer; and travel support from Pfizer, outside the submitted work. E.D. received consultancy fees from argenx and Janssen (all honoraria/fees paid to the University) outside the submitted work.

Author contributions

O.E.: conceptualization; methodology; formal analysis; writing—original draft; visualization. B.M.: writing—review and editing. J.W.: data curation; writing—review and editing. Y.D.: data curation; writing—review and editing. B.R.: data curation; writing—review and editing. P.E.V.: data curation; writing—review and editing. R.J.B.: data curation; writing—review and editing. I.S.: conceptualization; writing—review and editing; supervision. E.D.: conceptualization; writing—review and editing; supervision.

Supplementary data

Figures S1 to S9 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

References

1 Schauwvlieghe AFAD, Rijnders BJA, Philips N *et al*. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. *Lancet Respir Med* 2018; **6**: 782–92. https://doi.org/10.1016/S2213-2600(18)30274-1

2 Feys S, Almyroudi MP, Braspenning R *et al*. A visual and comprehensive review on COVID-19-associated pulmonary aspergillosis (CAPA). *J Fungi* 2021; **7**: 1067. https://doi.org/10.3390/jof7121067

3 Fortarezza F, Boscolo A, Pezzuto F *et al*. Proven COVID-19-associated pulmonary aspergillosis in patients with severe respiratory failure. *Mycoses* 2021; **64**: 1223–9. https://doi.org/10.1111/myc.13342

4 Sun QN, Fothergill AW, McCarthy DI *et al*. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. *Antimicrob Agents Chemother* 2002; **46**: 1581–2. https://doi.org/10.1128/AAC.46.5.1581-1582.2002

5 Hof H. A new, broad-spectrum azole antifungal: posaconazole—mechanisms of action and resistance, spectrum of activity. *Mycoses* 2006; **49**: 2–6. https://doi.org/10.1111/j.1439-0507.2006.01295.x

6 Krieter P, Flannery B, Musick T *et al*. Disposition of posaconazole following single-dose oral administration in healthy subjects. *Antimicrob Agents Chemother* 2004; **48**: 3543. https://doi.org/10.1128/AAC.48.9.3543-3551.2004

7 Andes DR, Lepak AJ. In vivo infection models in the pre-clinical pharmacokinetic/pharmacodynamic evaluation of antimicrobial agents. *Curr Opin Pharmacol* 2017; **36**: 94–9. https://doi.org/10.1016/j.coph.2017.09.004

8 Howard SJ, Lestner JM, Sharp A *et al*. Pharmacokinetics and pharmacodynamics of posaconazole for invasive pulmonary aspergillosis: clinical implications for antifungal therapy. *J Infect Dis* 2011; **203**: 1324–32. https://doi.org/10.1093/infdis/jir023

9 Mavridou E, Brüggemann RJM, Melchers WJG *et al*. Efficacy of posaconazole against three clinical *Aspergillus fumigatus* isolates with mutations in the cyp51A gene. *Antimicrob Agents Chemother* 2010; **54**: 860–5. https://doi.org/10.1128/AAC.00931-09

10 Seyedmousavi S, Mouton JW, Melchers WJG *et al*. Posaconazole prophylaxis in experimental azole-resistant invasive pulmonary aspergillosis. *Antimicrob Agents Chemother* 2015; **59**: 1487–94. https://doi.org/10.1128/AAC.03850-14

11 Walsh TJ, Raad I, Patterson TF *et al*. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; **44**: 2–12. https://doi.org/10.1086/508774

12 Cornely OA, Maertens J, Winston DJ *et al*. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59. https://doi.org/10.1056/NEJMoa061094

13 Ullmann AJ, Aguado JM, Arikan-Akdagli S *et al*. Diagnosis and management of aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect* 2018; **24**: e1–38. https://doi.org/10.1016/j.cmi.2018.01.002

14 Chen L, Krekels EHJ, Verweij PE *et al*. Pharmacokinetics and pharmacodynamics of posaconazole. *Drugs* 2020; **80**: 671–95. https://doi.org/10.1007/s40265-020-01306-y

15 Van Daele R, Wauters J, Dreesen E *et al*. Exposure to intravenous posaconazole in critically ill patients with influenza: a pharmacokinetic analysis of the POSA-FLU study. *Mycoses* 2022; **65**: 656–60. https://doi.org/10.1111/myc.13446

16 Vanderbeke L, Janssen NAF, Bergmans DCJJ *et al*. Posaconazole for prevention of invasive pulmonary aspergillosis in critically ill influenza patients (POSA-FLU): a randomised, open-label, proof-of-concept trial. *Intensive Care Med* 2021; **47**: 674–86. https://doi.org/10.1007/s00134-021-06431-0

17 Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006

18 European Medicines Agency. Noxafil-epar-product-information_en.pdf. https://www.ema.europa.eu/en/documents/product-information/noxafil-epar-product-information_en.pdf

19 European Medicines Agency. Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products. 2016. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-use-pharmacokinetics-pharmacodynamics-development-antimicrobial-medicinal-products_en.pdf

20 Wicha SG, Märtson A-G, Nielsen EI *et al*. From therapeutic drug monitoring to model-informed precision dosing for antibiotics. *Clin Pharmacol Ther* 2021; **109**: 928–41. https://doi.org/10.1002/cpt.2202

21 Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. *Curr Opin Crit Care* 2015; **21**: 412. https://doi.org/10.1097/MCC.0000000000000229

22 Greco M, De Corte T, Ercole A *et al*. Clinical and organizational factors associated with mortality during the peak of first COVID-19 wave: the

global UNITE-COVID study. *Intensive Care Med* 2022; **48**: 690–705. https://doi.org/10.1007/s00134-022-06705-1

23 Tverdek FP, Heo ST, Aitken SL *et al*. Real-life assessment of the safety and effectiveness of the new tablet and intravenous formulations of posaconazole in the prophylaxis of invasive fungal infections via analysis of 343 courses. *Antimicrob Agents Chemother* 2017; **61**: e00188-17. https://doi.org/10.1128/AAC.00188-17

24 Nguyen M-VH, Davis MR, Wittenberg R *et al*. Posaconazole serum drug levels associated with pseudohyperaldosteronism. *Clin Infect Dis* 2020; **70**: 2593–8. https://doi.org/10.1093/cid/ciz741

25 Cornely OA, Robertson MN, Haider S *et al*. Pharmacokinetics and safety results from the phase 3 randomized, open-label, study of intravenous posaconazole in patients at risk of invasive fungal disease. *J Antimicrob Chemother* 2017; **72**: 3406–13. https://doi.org/10.1093/jac/dkx263

26 Jia M, Zhang Q, Qin Z *et al*. Dose optimisation of posaconazole and therapeutic drug monitoring in pediatric patients. *Front Pharmacol* 2022; **13**: 833303. https://doi.org/10.3389/fphar.2022.833303

27 Sabatino DC, Lange NW, Salerno DM *et al*. Elevated posaconazole trough concentrations are not associated with increased risk for posaconazole toxicity in lung transplant recipients. *Clin Transplant* 2023; **37**: e14826. https://doi.org/10.1111/ctr.14826

28 van Iersel MLPS, Rossenu S, de Greef R *et al*. A population pharmacokinetic model for a solid oral tablet formulation of posaconazole. *Antimicrob Agents Chemother* 2018: **62**: e02465-17. https://doi.org/10.1128/AAC.02465-17

29 Vanstraelen K, Prattes J, Maertens J *et al*. Posaconazole plasma exposure correlated to intestinal mucositis in allogeneic stem cell transplant patients. *Eur J Clin Pharmacol* 2016; **72**: 953–63. https://doi.org/10.1007/s00228-016-2057-6

30 Boonsathorn S, Cheng I, Kloprogge F *et al*. Clinical pharmacokinetics and dose recommendations for posaconazole in infants and children. *Clin Pharmacokinet* 2019; **58**: 53–61. https://doi.org/10.1007/s40262-018-0658-1

31 AbuTarif MA, Krishna G, Statkevich P. Population pharmacokinetics of posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. *Curr Med Res Opin* 2010; **26**: 397–405. https://doi.org/10.1185/03007990903485056

32 Dolton MJ, Brüggemann RJM, Burger DM *et al*. Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis. *Antimicrob Agents Chemother* 2014; **58**: 6879–85. https://doi.org/10.1128/AAC.03777-14

33 Elkayal O, Spriet I, Uyttebroeck A *et al*. A population pharmacokinetic modeling and simulation study of posaconazole oral suspension in immunocompromised pediatric patients. *Ther Drug Monit* 2021; **43**: 512–8. https://doi.org/10.1097/FTD.0000000000000877

34 Petitcollin A, Boglione-Kerrien C, Tron C *et al*. Population pharmacokinetics of posaconazole tablets and monte carlo simulations to determine whether all patients should receive the same dose. *Antimicrob Agents Chemother* 2017; **61**: e01166-17. https://doi.org/10.1128/AAC.01166-17

35 Peña-Lorenzo D, Rebollo N, Sánchez-Hernández JG *et al*. Population pharmacokinetics of a posaconazole tablet formulation in transplant adult allogeneic stem cell recipients. *Eur J Pharm Sci* 2022; **168**: 106049. https://doi.org/10.1016/j.ejps.2021.106049

36 Jansen AME, Muilwijk EW, Velden WJFMVD *et al*. Posaconazole bioavailability of the solid oral tablet is reduced during severe intestinal mucositis. *Clin Microbiol Infect* 2022; **28**: 1003–9. https://doi.org/10.1016/j.cmi.2022.01.029

37 Vehreschild JJ, Müller C, Farowski F *et al*. Factors influencing the pharmacokinetics of prophylactic posaconazole oral suspension in patients with acute myeloid leukemia or myelodysplastic syndrome. *Eur J Clin Pharmacol* 2012; **68**: 987–95. https://doi.org/10.1007/s00228-012-1212-y

38 Störzinger D, Borghorst S, Hofer S *et al*. Plasma concentrations of posaconazole administered via nasogastric tube in patients in a surgical intensive care unit. *Antimicrob Agents Chemother* 2012; **56**: 4468–70. https://doi.org/10.1128/AAC.06167-11

39 Chen L, Krekels EHJ, Heijnen AR *et al*. An integrated population pharmacokinetic analysis for posaconazole oral suspension, delayed-release tablet, and intravenous infusion in healthy volunteers. *Drugs* 2023; **83**: 75–86. https://doi.org/10.1007/s40265-022-01819-8

40 Wasmann RE, Smit C, van Donselaar MH *et al*. Implications for IV posaconazole dosing in the era of obesity. *J Antimicrob Chemother* 2020; **75**: 1006–13. https://doi.org/10.1093/jac/dkz546

41 Sime FB, Byrne CJ, Parker S *et al*. Population pharmacokinetics of total and unbound concentrations of intravenous posaconazole in adult critically ill patients. *Crit Care* 2019; **23**: 205. https://doi.org/10.1186/s13054-019-2483-9

42 Abdul-Aziz MH, Alffenaar J-WC, Bassetti M *et al*. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper#. *Intensive Care Med* 2020; **46**: 1127–53. https://doi.org/10.1007/s00134-020-06050-1

43 Roberts JA, Pea F, Lipman J. The clinical relevance of plasma protein binding changes. *Clin Pharmacokinet* 2013; **52**: 1–8. https://doi.org/10.1007/s40262-012-0018-5