**Dosing of intravenous posaconazole in the intensive care unit:  
A population pharmacokinetics modeling and simulation study**

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# List of abbreviations

AUC0-24: area under the concentration-time curve for 24 hours; FOCE-I: first-order conditional estimation with interaction; CAPA: COVID-19 associated pulmonary aspergillosis; Cmin: trough concentration; CL: clearance; COVID-19: coronavirus disease 2019; IAPA: influenza-associated pulmonary aspergillosis; ICU: Intensive Care Unit; IIV: interindividual variability; IPA: invasive pulmonary aspergillosis; IV: intravenous; MIC: minimal inhibitory concentration; PK: pharmacokinetics; PKPD: pharmacokinetic-pharmacodynamic; PopPK: population pharmacokinetics; PTA: probability of target attainment; Q12h: every 12 hours; Q24h: every 24 hours; Q8h: every 8 hours; ROC: receiver operating characteristics; TDM: therapeutic drug monitoring; Vc: central volume of distribution; Vp: peripheral volume of distribution.

# Abstract

**Introduction**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 trough concentration (Cmin) target (0.7 mg/L) but not of the treatment Cmin target (1.0 mg/L). We aimed to provide an optimized posaconazole dosing regimen for intravenous (IV) treatment of patients with invasive pulmonary aspergillosis in the ICU.

**Patients and methods** A population pharmacokinetics (popPK) model was developed using data from the POSA-FLU PK sub-study (NCT03378479). Monte Carlo simulations were performed to assess treatment Cmin probability of target attainment (PTA). PTA ≥90% was deemed clinically acceptable. PopPK modeling and simulation were performed using NONMEM 7.5.

**Results** Thirty-one patients with intensive PK sampling were included in the PK sub-study, contributing 532 posaconazole plasma concentrations. The popPK of IV posaconazole was best described by a two-compartment popPK model with linear elimination. Interindividual variability was estimated on clearance and volume of distribution in central and peripheral compartments. The posaconazole peripheral volume of distribution increased with bodyweight.  
An optimized loading regimen of 300 mg every 12 hours (q12h) and 300 mg q8h in the first two treatment days resulted in acceptable PTA by day 3 in patients <100 kg and ≥100 kg, respectively. A maintenance regimen of 400 mg q24h assured ≥90% PTA throughout 14 days, irrespective of bodyweight.

**Conclusions** We have defined a convenient, optimized IV posaconazole dosing regimen that guarantees acceptable treatment Cmin PTA in critically ill patients with invasive aspergillosis.

**Keywords** Intravenous posaconazole, critically ill patients, invasive aspergillosis, antifungal, population pharmacokinetics, modeling and simulation, dose optimization

# Introduction

Invasive pulmonary aspergillosis (IPA) is commonly observed in immunocompromised patients, such as neutropenic patients or hematopoietic stem cell recipients. However, it was shown that patients in the intensive care unit (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 co-infection has been reported in critically ill patients up to 20% for influenza-associated pulmonary aspergillosis (IAPA) and 15% for COVID-19-associated pulmonary aspergillosis (CAPA). 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[3]. Its primary pharmacokinetic-pharmacodynamic (PKPD) target is the ratio of the 24-hour area under the concentration-time curve (AUC0-24) to the minimal inhibitory concentration (MIC). Based on clinical data of Walsh *et al.*, an AUC0-24 treatment target of 30 mg×h/L and a trough concentration (Cmin) treatmenttarget of 1 mg/L are used [4]. For prophylaxis, a Cmin of 0.7 mg/L is targeted [5]. As PK variability is large, therapeutic drug monitoring (TDM) is often applied in daily clinical practice [6].

Posaconazole has been shown to be effective in the prophylaxis against IPA in patients with hematological malignancies [5,7]. A favorable safety profile, the availability as an IV infusion, and residual activity against azole-resistant *Aspergillus fumigatus* make it a suitable candidate for prophylaxis against and treatment of IPA, also for patients admitted to the ICU [7]. However, there is limited knowledge about the PK characteristics of posaconazole in critically ill patients. In the POSA-FLU trial, critically ill influenza receiving standard dose IV posaconazole for prevention of IPA showed adequate attainment of the prophylaxis Cmin target but not of the treatment Cmin target, emphasizing the need for dose optimization of IV posaconazole for treatment of critically ill patients [8].

We used POSA-FLU data to develop a population PK (popPK) model of IV posaconazole in critically ill patients admitted to the ICU. Simulations were performed to provide an optimized loading and maintenance dosing regimen that ensures adequate treatment target attainment.

# Patients and methods

## 2.1. Data

Data were obtained from the POSA-FLU trial (NCT03378479). Patients enrolled in this prospective multicenter, randomized, open-label study to assess the efficacy of IV posaconazole as a prophylactic agent for IAPA [9]. The study was performed in nine centers in The Netherlands, Belgium, and France between December 2017 and March 2020. Ethics committees approved the study and 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 minutes every 12 hours (q12h) on the first day as a loading dose and q24h on the following days as a maintenance dose were administered as prophylaxis for seven days. Blood samples were collected during a 24-hour dosing interval on an early day (day 2 or 3) and a later day (≥day 4) (**Supplementary Methods**). A detailed description of the trial design and methodology can be found in Vanderbeke *et al*. and Van Daele *et al*. [8,9].

## 2.2. Population pharmacokinetics modeling

A base popPK model was fit to the posaconazole concentration-time data. Parameter estimation was performed using first-order conditional estimation with interaction (FOCE-I) and differential equation solver ADVAN 13. Details on popPK model building and evaluation can be found in the **Supplementary Methods**.

## 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 Cmin treatment target of 1 mg/L and the AUC0-24 target of 30 mg×h/L. High posaconazole exposure was defined as Cmin ≥3.75 mg/L [10]. A total of 1,000 simulations were carried out per virtual patient. The probability of target attainment (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 European Medicines Agency [11].

First, simulations were performed to identify an optimized inclusive dosing regimen (*i.e.*, a dosing regimen that ensures a PTA ≥90% for each patient along the range of covariate values; 1,000 simulations per covariate value). Next, population-level PTA, drug exposure, and drug consumption (total amount in mg up to day 14) were compared between the standard dosing and the optimized inclusive dosing regimen identified in the previous simulation step. Covariates were sampled from a distribution fitted to the POSA-FLU dataset, bounded to a predetermined clinically relevant range. A population of 1,000 virtual patients was created and 1,000 simulations were performed for each virtual patient.

Receiver operating characteristics (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.

# Results

## 3.1. 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 S2**). None of the plasma concentrations were below the assay limit of quantification. The standard IV posaconazole dosing regimen achieved clinically acceptable Cmin prophylaxis target attainment rates of 94.2% and 97.7% on early and late days of therapy, respectively. However, Cmin treatment target rates of 68.4% and 83.7% on the early and late days, respectively, were clinically unacceptable.

## 3.2. Population pharmacokinetics modeling

A two-compartment popPK model with linear elimination best described the posaconazole concentration-time data (**Figure S1**, **Figure S2**, and **Figure S3**). Interindividual variability (IIV) was estimated on clearance (CL) and volume of distribution in the central and peripheral compartments (Vc and Vp). Interoccasion variability was estimated on CL and Vc. Bodyweight was retained as the only statistically significant covariate in the final model (**Table 1**, **Figure S4**). Equation 1 describes how Vp of posaconazole for patient *i* increases with increasing bodyweight.

with (Eq. 1)

Posaconazole Vp 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 h to 120 h.

The NONMEM control stream is available in the **Supplementary Code**.

## Dose finding simulations

### Identification of an optimized inclusive loading regimen

Standard dosing resulted in clinically unacceptable PTA at the end of day 2 across the entire bodyweight range (50-150 kg) (**Figure 1A**). A loading regimen of 300 mg q12h for two instead of one day resulted in clinically acceptable PTA at the end of day 2 for patients with bodyweight below 100 kg. A 300 mg q8h loading regimen for the first two days resulted in clinically acceptable PTA in patients with a bodyweight of 100 kg or higher (**Table S3**).

### Identification of an optimized inclusive maintenance regimen

Standard 300 mg q24h maintenance dosing resulted in clinically unacceptable PTA on days 7 and 14 across the entire bodyweight range. Increasing the maintenance dose from 300 mg to 400 mg q24h resulted in clinically acceptable PTA across the entire bodyweight range (**Figure 1B**, **Figure 1C**, and **Table S3**).

### Impact of the optimized inclusive dosing regimen on the patient population

The standard dosing regimen resulted in clinically unacceptable PTA throughout the two-week treatment period (**Figure 2A**, **Table S4**). The optimized inclusive dosing regimen resulted in clinically acceptable PTA as fast as day 2 until day 14 (**Figure 2A**, **Table S4**). The total posaconazole dose for a two-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 to the standard regimen (**Figure S5**, **Figure S6**, and **Table S4)**. The median Cmin (interquartile range) 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 to 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 (Cmin >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 to 0.1%, 4.8%, and 14.5% of patients on standard dosing. 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 2B**).

# 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 modeling and simulation results showed that the standard IV dosing regimen resulted in clinically unacceptable Cmin target attainment in when used in a treatment setting. We proposed a pragmatic and easy-to-implement optimized dosing regimen leading to >90% PTA from day two of treatment and throughout a two-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 when it is used in the treatment setting and when it is used 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 center, especially not in limited resource settings. In centers where it is available, turnaround times are not always ideal, and TDM is also associated with a cost. 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.

For critically ill patients suffering from IPA, it is imperative to achieve the treatment target as quickly as possible to improve patient outcomes [12]. Our simulations demonstrated that the standard one-day loading regimen of IV posaconazole fails to achieve clinically acceptable PTA in the early days of treatment and that bodyweight should be considered in loading dose optimization. Early target attainment is ensured with an two-day loading regimen of 300 mg q12h and 300 mg q8h for patients <100 kg and ≥100 kg, respectively. The standard maintenance regimen of 300 mg q24h fails to achieve clinically acceptable PTA on days 7 and 14. A flat maintenance dose of 400 mg q24h (irrespective of bodyweight) is needed to attain the Cmin 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 [13].

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 pseudo-hyperaldosteronism), as suggested in some small or retrospective studies [14,15]. However, a clear relation between exposure and toxicity has thus far not been documented in larger clinical trials [16–18]. Consequently, no upper limit for Cmin, corresponding to a higher risk for toxicity, has been defined for posaconazole, unlike for voriconazole [6]. Therefore, EMA recommended using 3.75 mg/L as a surrogate Cmin target for toxicity during development of the new tablet and IV formulation [10]. 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 Vp, but not of Vc. 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). The PK of a single IV posaconazole dose was recently investigated in patients with normal to obese bodyweights [19]. Similar to our model, a two-compartment model with bodyweight impacting Vp was identified, 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 [20].

Our study aligns with the recommendation of a 400 mg maintenance dose for IV posaconazole, as suggested by previous research [19]. 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 (diluted) solution of posaconazole is stable for at least 24 hours if stored between 2°C and 8°C, vials can be fractionated with keeping the remaining undiluted solution for the next administration (stability of the undiluted solution confirmed by Merck, personal communication, March 2023). We did not evaluate q12h maintenance dosing as q24h dosing is more practical, requires fewer manipulations, and occupies the catheter line for less time.

This is the first popPK modeling 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 modeling, 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. In other words, the generalizability of our findings enables the extrapolation of dosing recommendations to a broad population of patients admitted to the ICU with invasive aspergillosis. Second, only four patients in our modeling dataset weighing over 100 kg. A prospective clinical study is ultimately needed to confirm the impact of the optimized bodyweight-based stratified loading regimen and the flat maintenance dose on Cmin treatment target attainment, safety, and (cost-)effectiveness in critically ill patients with invasive aspergillosis.

# Conclusion

We have identified an optimized weight-based loading regimen and a flat maintenance dose for IV posaconazole that guarantees attainment of the Cmin treatment target in critically ill patients with invasive aspergillosis from the second treatment day onwards.

# Declarations

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## Conflicts of interest

OE and BM have nothing to disclose.

JW reports investigator-initiated grants from Pfizer, Gilead, and MSD; consulting fees from Pfizer and Gilead; speakers’ fees from Pfizer, Gilead, and MSD; travel fees from Pfizer, Gilead, and MSD; participation in advisory boards of Pfizer and Gilead; receipt of study drugs from MSD; outside the submitted work.

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## Ethics approval and consent to participate

This project is a secondary use of clinical trial data (POSA-FLU), All of this study procedures were performed in compliance with the principles of the Declaration of Helsinki, the principles of good clinical practice and in accordance with all applicable regulatory requirements. The study protocol was approved by the ethical committee of all participating centers in Belgium and France and by the independent ethical committee Arnhem-Nijmegen for all five participating Dutch sites (CMO 2018-4041).

## Consent of publication

Not applicable

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