An integrated population pharmacokinetic analysis for posaconazole oral suspension, delayed-release tablet, and intravenous infusion in healthy volunteers

Chen, L.; Krekels, E.H.J.; Heijnen A.R.; Knibbe, C.A.J.; Brüggemann, R.J.

Drugs (2023) 83:75–86
https://doi.org/10.1007/s40265-022-01819-8

ORIGINAL RESEARCH ARTICLE

An Integrated Population Pharmacokinetic Analysis for Posaconazole Oral Suspension, Delayed-Release Tablet, and Intravenous Infusion in Healthy Volunteers

Lu Chen[1] · Elke H. J. Krekels[1] · Anne R. Heijnen[1] · Catherijne A. J. Knibbe[1,2] · Roger J. Brüggemann[3,4]

Accepted: 22 November 2023 / Published online: 6 January 2023

Abstract

Background Posaconazole is widely used for the prophylaxis and treatment of invasive fungal diseases. Because of the limited and variable absorption of the initially available oral suspension, a delayed-release tablet and intravenous formulation were developed.

Objective This study aimed to characterize the pharmacokinetics, including the absolute oral bioavailability, of all posaconazole formulations in healthy volunteers.

Methods Data from 182 healthy volunteers with 3898 densely sampled posaconazole concentrations were pooled from eight phase I clinical studies on the three formulations of various single and multiple dosage regimens between 50 and 400 mg. Analysis and simulations were performed using NONMEM 7.5.0. In the covariate analysis, the influence of food (fed vs fasted), nonlinearity, and for the delayed-release tablet, comedication (antacid, ranitidine, esomeprazole, and metoclopramide) were tested.

Results A two-compartment model with respectively, four and eight absorption transit compartments, best described the profiles of the oral suspension and delayed-release tablet. For the suspension, both a food effect and a dose-dependent nonlinear bioavailability were quantified, resulting in lower bioavailability when fasted or at a higher dose. The typical bioavailability of the suspension at 100 mg and 400 mg was derived to be respectively, 17.1% and 10.1% under fasted conditions and 59.1% and 49.2% under fed conditions. The absolute bioavailability of the delayed-release tablet was 58.8% (95% confidence interval 33.2–80.4) under fasted conditions and approached complete absorption under fed conditions for dosages up to 300 mg. Food intake reduced the absorption rate constant of the suspension by 52.2% (confidence interval 45.2–59.2). The impact of comedication on the absorption of the delayed-release tablet was not statistically significant. Model-based simulations indicate that under fed conditions, the licensed dosages of the three formulations yield a steady-state trough concentration $\geq$ 0.7 mg/L in over 90% of healthy volunteers. About 35% of healthy volunteers who receive the licensed 300-mg delayed-release tablet under fasted conditions do not achieve this target, while for the suspension this percentage varies between 55 and 85%, depending on the dose.

Conclusions For both oral posaconazole formulations, we quantified bioavailability and absorption rate, including food effects, in healthy volunteers. The pharmacokinetic superiority of the delayed-release tablet was demonstrated under both fed and fasted conditions, compared with the oral suspension. The impact of food on the bioavailability of the delayed-release tablet was larger than anticipated, suggesting that administering the delayed-release tablet with food enhances absorption.

1 Introduction

Posaconazole is a triazole antifungal agent and is widely used for preventing and treating invasive fungal diseases (IFDs) [1–3]. Posaconazole is available in three formulations, namely oral suspension, delayed-release (DR) tablet, and intravenous (IV) infusion [1, 3]. Erratic absorption, both in terms of rate of absorption and extent of absorption (i.e., bioavailability [F]) was widely reported for the oral suspension [4, 5] with the exposure of this formulation also being sensitive to food intake and other gastrointestinal conditions, such as pH and motility [6, 7]. A DR tablet was subsequently developed, which proved to be less sensitive to these factors and yielded a higher average exposure in patients compared with the oral suspension [4, 8–10]. Shortly after, an

Extended author information available on the last page of the article

Key Points

In healthy volunteers receiving the posaconazole oral suspension, bioavailability decreases with increasing dose in a sigmoidal manner, while food increases bioavailability, yielding a typical bioavailability at 100 mg versus 400 mg of 17.1% versus 10.1% under fasted conditions, and 59.1% versus 49.2% under fed conditions.

The dose-dependent nonlinear bioavailability for the oral suspension supports the common practice of dividing the same daily suspension dose into smaller doses as this would increase the bioavailability, thereby the exposure.

Linear bioavailability was found for the posaconazole delayed-release tablet within a dose range of 100–400 mg, with typical absolute bioavailability being 58.8% under fasted conditions and complete under fed conditions.

Simulations illustrate that around 80% of the healthy volunteers do not achieve a trough concentration ≥ 0.7 mg/L when the posaconazole oral suspension is given fasted at the recommended prophylactic dose and 35% do not achieve this target when the delayed-release tablet is given fasted at the recommended dose.

The pharmacokinetic superiority of the posaconazole delayed-release tablet compared with the oral suspension is demonstrated under both fed and fasted conditions. Extrapolating these findings to patients suggests that the delayed-release tablet should be advocated over the oral suspension to ensure sufficient exposure.

IV formulation was released for patients who are unable to take oral formulations.

Prophylactic failure against *Aspergillus* infections was reported to be associated with low exposure. A trough concentration (C_{trough}) ≥ 0.7 mg/L is included in the label as a target for preventing IFDs [11–13]. A treatment target of C_{trough} ≥ 1.0 mg/L or ≥ 1.25 mg/L was recommended in international guidelines [2, 14]. Both target concentrations for prophylaxis and therapy have, however, been subject to debate and it has been advocated to use pathogen susceptibility-dependent target concentrations [2].

In the clinical setting, switching from a DR tablet to an oral suspension is sometimes needed in patients with dysphagia or in patients with a nasogastric tube when solid intake is not possible. Switching from the IV dosing to an oral formulation is usually necessary as step-down therapy for long-term therapy in an outpatient setting. To gain knowledge on the exposure being obtained with each formulation and to ensure equivalent exposure when switching formulations, it is important to understand and quantify the differences in the pharmacokinetics for all formulations.

Many studies have investigated the pharmacokinetics of one or two of the three marketed posaconazole formulations, but an integrated analysis comparing the pharmacokinetics of all three formulations simultaneously is still lacking. This study uses a population pharmacokinetic modeling approach to quantify the pharmacokinetics of all currently available posaconazole formulations, including the absolute oral *F* of the oral suspension and DR tablet, and the impact of food intake and comedication on absorption in healthy volunteers. Model-based simulations were used to illustrate our findings.

2 Methods

2.1 Data for Analysis

In total, 3898 posaconazole concentrations (including 299 [7.7%] concentrations below the limit of quantification) densely sampled up to 168 h from 182 healthy volunteers pooled from eight clinical studies, with different formulations, dosages (range from 50 to 400 mg), and dosing schedules (i.e., single dose and multiple dose at different intervals), were included in the analysis. Six studies were performed by Merck & Co., Inc., i.e., P04975 [15], P07691 [16], P07764 [10], P07783 [16], P04985 [17], and P06356 [18], and two studies in the Radboud University Medical Center, Nijmegen, the Netherlands [19, 20]. In a crossover study P04975, 16 healthy volunteers received the oral suspension under both fasting and fed conditions with one subject dropping out and only being included under fasting conditions [15]. In this latter study, on two occasions, subjects were considered as separate individuals because individual identifying information was not available in the accessible data. Data characteristics per formulation and per study are summarized in Table 1 and Table S1 of the Electronic Supplementary Material (ESM), respectively.

Dosing scenarios for the oral suspension were limited to 100 mg under fed and fasted conditions and 400 mg only under fed conditions. To better describe the nonlinear saturable *F* based on the prior knowledge [5, 7, 21], the data were enriched with meta-data from the literature. We searched PubMed for clinical trials that investigated the effect of high-fat food on the *F* or area under the concentration–time curve (AUC) under a single dose of 100 mg and 400 mg in healthy volunteers. In cases that multiple studies met the criteria, studies with a longer sampling duration and a higher number of participants were selected. A value of 2.85 [15] and 4.91 [7] for the ratio of

F between the fed and fasted condition at 100 mg and 400 mg, respectively, with the value at 100 mg being based on a previous non-compartmental analysis on one of the datasets (P04975 [15]), were included in our analysis. Moreover, given that not all combinations of dose and food status were available to assess the saturable *F* of the oral suspension, reported literature values on the AUC and food effect from other pharmacokinetic studies were used during the model evaluation [6, 7, 15, 16, 19].

2.2 Population Pharmacokinetic Model

The population pharmacokinetic model was developed using the nonlinear mixed-effects modeling software NONMEM version 7.5.0 (ICON Development Solutions, Hanover, MD, USA) supported by Perl-speaks-NONMEM (version 5.2.6) with the Pirana interface (version 3.0.0; Certara USA, Inc., Princeton, NJ, USA) [22]. Data processing and visualization were performed with R 4.1.1 and RStudio 1.4.1717. Because of the long run times, the M1 method for which observations below the quantification limit are discarded was applied during model development after establishing that the estimation results were similar between the M1 and M3 methods for the base model. The M3 method, in which the likelihood is maximized for all the data and below the quantification limit concentrations are treated as censored, was used to fit the final model [23]. The first-order conditional estimation method with interaction and LAPLACIAN in combination with the stochastic approximation expectation maximization method were adopted for models using the M1 and M3 methods, respectively.

One-, two-, and three-compartmental disposition models were evaluated. Various approaches were assessed to describe absorption for each oral formulation, including first-order absorption with and without absorption lag time, transit compartment models [24, 25], mixed zero-order and first-order absorption [26, 27], and a Weibull absorption function [27]. Separate values for *F* and absorption rate were estimated for the oral suspension and DR tablet. Inter-individual variability (IIV) was assumed to be log-normally distributed, except for *F* for which a logit transformation was applied and a normal distribution for IIV was incorporated in the logit domain. Proportional, additive, and combined additive and proportional error models were assessed for residual unexplained variability. The structural and stochastic model selection was based on the difference in objective function value (OFV, i.e., − 2 log-likelihood) with an OFV reduction of > 3.84 ($p < 0.05$) for nested models being considered statistically significant, on the physiological plausibility of the parameter estimates, on the relative standard error of parameter estimates being <50%, and on the goodness-of-fit plots stratified by formulation and study.

Concentration nonlinearity on clearance (CL) was tested to investigate possible saturation of the elimination of posaconazole [18]. Dose nonlinearity on *F* was tested to investigate possible saturation of the absorption for the DR tablet. Dose nonlinearity on *F* was included for the oral suspension with decreasing sigmoidal functions, with different values for the maximum *F* of the suspension ($F_{sus,max}$) and for the oral suspension dose that could achieve half of the $F_{sus,max}$ ($D_{50,sus}$) under fed and fasted conditions (see Eq. 1).

Table 1 Summary of the pharmacokinetic data included in this analysis

Characteristics	Suspension [15, 16, 19]	DR tablet [10, 16]	IV infusion [16–18, 20]
No. of studies	3	3	4
No. of subjects	75	67	74
Dosage (mg)			
Single dose	100	100, 300, 400	50, 100, 200, 250, 300
Multiple dose	400 bid[a]	300 qd[b]	NA
Duration of sampling after the last dose (h)			
Single dose	168	168	48, 144, 168
Multiple dose	12	48	NA
No. of concentrations	1028	1924	946
No. of BQL concentrations (%)	141 (13.7%)	110 (5.7%)	48 (5.1%)
No. of concentrations per subject, median (range)	13 (11–16)	13 (2–65)	12 (10–20)
Available covariates	food status	Food status, comedications (antacid, ranitidine, esomeprazole, metoclopramide)	NA

bid twice daily, *BQL* below the quantification limit, *DR* delayed-release, *IV* intravenous, *NA* not available, *qd* once daily

[a]Posaconazole oral suspension 200 mg once daily on day 1, 200 twice daily on day 2, 400 mg twice daily from day 3 to day 10

[b]300 mg bid on the first day followed by 300 mg qd

$$F_{\text{sus,fed}} = F_{\text{sus,max,fed}} \times \left(1 - \frac{\text{Dose}}{\text{Dose} + D_{50,\text{sus,fed}}}\right). \quad (1)$$

In which $F_{\text{sus,fed}}$ represents the population value of F for the suspension under fed condition, $F_{\text{sus,max,fed}}$ represents the maximum F of the suspension under fed condition, *Dose* represents the suspension dose that was given, and $D_{50,\text{sus,fed}}$ represents the oral suspension dose that could achieve half of the $F_{\text{sus,max,fed}}$ under the fed condition. Assuming the literature value of 4.91 for the ratio of F between fed and fasted conditions at 400 mg [7] and assuming that the reported ratio of 2.85 at 100 mg is the same at the maximum F (e.g., F at the lowest possible dose), a correlation was deducted between the oral suspension dose that could achieve half of the maximum F under fasted condition ($D_{50,\text{sus,fasted}}$) and $D_{50,\text{sus,fed}}$ (see Eq. 2).

$$D_{50,\text{sus,fasted}} = \frac{3249 \times D_{50,\text{sus,fed}}}{5597.4 + 5.871 \times D_{50,\text{sus,fed}}}. \quad (2)$$

Among three studies administering the oral suspension under the fed condition, two were confirmed to be administered with high-fat food [15, 19], while the third unpublished study was also deduced to be administered with high-fat food as the concentration profiles overlapped with the profiles of the other study with high-fat food at the same dosage [16]. In addition to the assessment of dose nonlinearity and the impact of food intake for the oral suspension described above, food intake was also tested as a covariate on the absorption rate. For the DR tablet, food intake (fed or fasted) was also tested as a covariate on both the rate and extent (F) of absorption. In one study (P07764), the DR tablet was administered alone or with antacid, ranitidine, esomeprazole, and metoclopramide according to a cross-over design [10], which was used for an assessment of the influence of these comedications on the rate and extent (F) of absorption. Additionally, for these data, inter-occasion variability (IOV) for each chronological treatment period was tested on the absorption parameters. All these binary covariates were tested in a proportional relationship. A covariate analysis followed a forward inclusion and backward deletion step, using an OFV difference of > 3.84 ($p < 0.05$) and > 10.83 ($p < 0.001$) for statistical significance, respectively. Comparisons to values reported in the literature of simulated AUC values and the ratio of AUC values under different statuses of food intake were also used for the selection of the covariate models for the oral suspension [6, 7, 15, 16, 19].

The final model was validated using a normalized prediction distribution error analysis based on 1000 simulations and stratified by formulation. Stratified bootstrap ($n = 100$) was used to assess the model robustness and parameter precision of the final model.

2.3 Illustration of Model Findings

To illustrate the exposure differences for the three posaconazole formulations, concentration–time profiles after a single dose of a posaconazole 300-mg oral suspension (fed and fasted), DR tablet (fed and fasted), and IV formulation were simulated with the final model for a typical healthy individual. To evaluate the commonly used dosage regimens, simulations were performed for a typical healthy individual receiving the recommended dose for the prophylaxis of invasive fungal infections. Various commonly used dosing regimens were simulated. This included 200 mg three times daily (tid) for the oral suspension and a loading dose of 300 mg twice daily (bid) on the first day followed by a maintenance dose of 300 mg once daily (qd) for both the DR tablet and IV formulation [1, 3]. For the treatment of invasive fungal infections, the simulated recommended doses included 400 mg bid and 200 mg four times daily (qid) for the oral suspension, as well as the same dose as the recommended prophylactic dose for both the DR tablet and IV formulation [1–3]. Both fed and fasted conditions were simulated for each oral regimen to illustrate the influence of food intake on posaconazole exposure.

Stochastic simulations were performed to illustrate the distribution of the exposure at a population level. Each commonly used regimen was simulated 1000 times with IIV to predict posaconazole concentration–time profiles and the 24-h AUC.

3 Results

3.1 Population Pharmacokinetic Model

A two-compartment disposition model with first-order elimination and a combined proportional and additive residual error model best described the data from all formulations. For the oral suspension and DR tablet, the absorption profile was best described by respectively, four and eight absorption transit compartment models (Fig. S1 of the ESM). Inter-individual variability was included on F, the first-order rate constant between absorption transit compartments (k_{tr}), CL, and volume of distribution of the central compartment.

Including nonlinear CL decreased OFV significantly compared with the linear CL, but the goodness-of-fit plots did not show an improvement where it would be expected. For this reason, a linear CL was retained for all formulations. Incorporating dose nonlinearity on *F* of the DR tablet did not significantly improve the model ($p > 0.05$) and therefore was not included in the model.

Food intake was found to reduce the k_{tr} of the oral suspension by 52.2% (95% confidence interval of the estimate [CI] 45.2–59.2). Based on prior knowledge and improvement in the predicted AUC values compared to literature reports, the dose-dependent decreasing sigmoidal functions for *F* were incorporated for the oral suspension under fed and fasted conditions, even though no statistical significance was found in our dataset compared to a dose-independent F. In addition to the dose dependency, *F* of the oral suspension depends on food intake, with higher doses being associated with a larger food effect. From these covariate functions, the typical value of *F* at 400 mg of the oral suspension under fed and fasted conditions could be derived to be respectively, 49.2% and 10.1%, and they are increased to 59.1% and 17.1%, respectively, at a dose of 100 mg. The *F* at other doses can be calculated using the nonlinear equation of *F* in Table 2. The typical value of *F* of the DR tablet was 58.8% (CI 54.4–63.2) under a fasted condition. When fed, the typical value of *F* in individuals receiving the DR tablet approached 100% and was fixed to 99.5% to avoid boundary issues.

The impact of comedication on the absorption of the DR tablet was not statistically significant, but introducing IOV on the *F* and k_{tr} of the DR tablet for the five-way crossover study that tested on each occasion coadministration of drugs known to interact with the absorption of the posaconazole oral suspension [7] significantly reduced the OFV and the IIV of *F* in the DR tablet, and improved goodness-of-fit plots. This was therefore retained in the model [10]. After inclusion of IOV and the food impact as a covariate, the IIV on *F* was still high for both the oral suspension and DR tablet, with a 95% distribution interval of 28.4–70.2% versus 4.40–21.3% for a 400-mg oral suspension under fed versus fasted conditions, and 33.2–80.4% for the DR tablet under the fasted condition. The IOVs were slightly higher than the IIVs in *F* (0.401 vs 0.290) and k_{tr} (31.5% vs 29.9%) for the DR tablet.

Parameter estimates of the final model are presented in Table 2 and the NONMEM control stream for the final model can be found in the ESM. Goodness-of-fit plots of the final model are included in Fig. S2 of the ESM and suggest that the model described the data well for each formulation. The normalized prediction distribution error results shown in Figs. S3A and S3B of the ESM indicate an accurate predictive performance of the final model regarding both the structural and stochastic model for each formulation. Figure S3C of the ESM suggests a good predictive performance of concentrations below the limit of quantification, with an acceptable agreement between observed data and model-simulated median and 95% CI. Model-predicted AUC values were in reasonable agreement with the reported AUC values from the literature with doses that ranged from 100 mg to 400 mg (Table S2 of the ESM). Furthermore, the final model also demonstrated good predictive performance of the food effect on the oral suspension at a dose of 100 mg, 200 mg, and 400 mg (Table S3 of the ESM). Bootstrap results in Table 2 indicate that the final model was robust and all model parameters were estimated with good precision.

3.2 Illustration of Model Findings

The distribution of *F* for both oral formulations under fed and fasted conditions is illustrated in Fig. 1. It can be seen that food intake increases *F* for both oral formulations, which is more pronounced for the suspension compared with the DR tablet. Moreover, the overall *F* for the oral suspension is lower than for the DR tablet, causing the median value for *F* of the oral suspension at 100 mg under fed conditions to be comparable to that of the DR tablet under the fasted condition.

Figure 2 illustrates exposure-time profiles in a typical healthy individual receiving a single dose of 300 mg for each formulation under fed and fasted conditions. The exposure of the oral suspension under fed conditions is similar to the exposure of the DR tablet under fasted conditions. The AUC of the oral suspension under the fasted condition yields approximately one-quarter of the exposure value of the oral suspension under the fed condition or the DR tablet under the fasted condition, and one-sixth of the exposure of the DR tablet under the fed condition or the IV formulation.

Figure 3 shows the simulated typical concentration–time profiles for healthy individuals over a week, for four commonly used posaconazole dosage regimens for the three posaconazole formulations. Owing to the use of loading doses, steady state is achieved after the first day for the regimen of the DR tablet and the IV infusion, but takes about 5 days to be reached for the regimen with the oral suspension. In typical healthy individuals receiving posaconazole under fed conditions, all simulated dosing scenarios achieve $C_{trough} \geq 1.25$ mg/L at steady state. However, under fasted conditions, the DR tablet regimen yields a prophylactic steady-state $C_{trough} \geq 0.7$ mg/L, but fails to achieve treatment values of ≥ 1 mg/L, while all three suspension regimens even fail to achieve the prophylactic target when fasted.

The simulations in Fig. 4 were performed to present the distribution of posaconazole concentration and 24-h AUC versus time over 1 week in 1000 healthy individuals. With food intake, both recommended prophylactic posaconazole oral regimens of 200 mg tid of the oral suspension and 300

Table 2 Pharmacokinetic parameter estimates for the final posaconazole model

Parameters	Parameter estimates (RSE%) [%shrinkage]	Bootstrap[a] median (95% CI)
Population parameter values [units]		
$F_{\text{sus,fed}} = F_{\text{sus,max,fed}} \times \left(1 - \frac{\text{Dose}}{\text{Dose}+D_{50,\text{fed}}}\right)$		
$F_{\text{sus,fasted}} = \frac{F_{\text{sus,max,fed}}}{2.85} \times \left(1 - \frac{\text{Dose}}{\text{Dose}+\frac{3249\times D_{50,\text{fed}}}{5597.4+5.871\times D_{50,\text{fed}}}}\right)$		
$F_{\text{sus,max,fed}}$ [%]	63.3 (8.10)	63.8 (34.9–71.6)
$D_{50,\text{fed}}$ [mg]	1390 (60.5)	1017 (205–2217)
$F_{\text{tab,fed}}$ [%]	99.5 (fixed)	99.5 fixed
$F_{\text{tab,fasted}}$ [%]	58.8 (3.80)	58.6 (53.9–64.2)
$k_{\text{tr,sus,fed}} = k_{\text{tr,sus,fasted}} \times (1 - \theta_{\text{sus,fed,ktr}})$		
$k_{\text{tr,sus,fasted}}$ [h^{-1}]	2.20 (6.70)	2.2 (1.99–2.4)
$\theta_{\text{sus,fed, ktr}}$ [–]	0.522 (6.90)	0.525 (0.465–0.567)
$k_{\text{tr,tab}}$ [h^{-1}]	2.70 (5.60)	2.59 (2.44–2.72)
CL [L/h]	6.65 (2.70)	6.97 (6.65–7.18)
V_c [L]	152 (4.80)	153 (135–166)
V_P [L]	109 (4.40)	110 (98–122)
Q [L/h]	46.4 (9.10)	47.3 (40.5–55.1)
Inter-individual variability in %CV		
F_{sus}[b,c]	0.206 (25.1) [50.9]	0.210 (0.100–2.94)
F_{tab}[b,c]	0.290 (26.9) [52.1]	0.320 (0.180–0.570)
$k_{\text{tr,sus}}$	20.7 (12.3) [47.5]	20.3 (15.7–25.9)
$k_{\text{tr,tab}}$	29.9 (11.7) [46.1]	28.9 (22.2–33.8)
CL	31.3 (6.80) [7.60]	30.5 (27.2–34.3)
V_c	31.3 (10.0) [19.6]	32.7 (26.8–36.8)
Inter-occasion variability[d] in %CV		
F_{tab}[b]	0.401 (19.7) [67.0–76.3][e]	0.433 (0.290–0.612)
$k_{\text{tr,tab}}$	31.5 (6.20) [65.0–74.2][e]	31.8 (26.0–38.1)
Residual error		
σ_{prop}	18.8% (0.600)	18.7% (17.4–20.3)
σ_{addi} (mg/L)	0.0025 (4.50)	0.0023 (0.0008–0.0039)

σ_{addi} additive residual error, σ_{prop} proportional residual error, $\theta_{sus,fed,ktr}$ proportion of food influence on k_{tr} of the oral suspension, *CI* confidence interval, *CL* clearance, *CV* coefficient of variation, $D_{50,fed}$ oral suspension dose that could achieve half of the $F_{sus,max,fed}$ under fed condition, *DR tablet* delayed-release tablet, *F* absolute oral bioavailability, $F_{sus,fed}$ population value of *F* for the oral suspension under fed condition $F_{sus,max,fed}$ the maximum *F* of the oral suspension under fed condition, $F_{tab,fed}$ population value of *F* for DR tablet under fed condition, $F_{tab,fasted}$ population value of F for DR tablet under fasted condition, k_{tr} first-order absorption rate constant and the rate constant between absorption transit compartments, $k_{tr,sus,fasted}$ k_{tr} of the oral suspension under fasted condition, $k_{tr,sus}$ k_{tr} of the oral suspension, $k_{tr,sus,fed}$ k_{tr} of the oral suspension under fed condition, $k_{tr,tab}$ k_{tr} of the DR tablet regardless of food intake, *Q* intercompartment clearance between central and peripheral compartments, *RSE* relative standard error of the estimate, V_c volume of distribution of the central compartment, V_p volume of distribution of the peripheral compartment

[a]Bootstrap success rate was 63% for the final model using the M3 method ($n = 63$ out of 100)

[b]The variability of *F* was added within the logit domain and was presented as the variance

[c]A 95% distribution interval with the 2.5th and 97.5th percentiles calculated by $\left(\frac{e^{\ln\left(\frac{F}{1-F}-1.96\times\sqrt{\omega_F^2}\right)}}{1+e^{\ln\left(\frac{F}{1-F}-1.96\times\sqrt{\omega_F^2}\right)}}, \frac{e^{\ln\left(\frac{F}{1-F}+1.96\times\sqrt{\omega_F^2}\right)}}{1+e^{\ln\left(\frac{F}{1-F}+1.96\times\sqrt{\omega_F^2}\right)}}\right)$ was used to describe the inter-individual variability of F. The 95% distribution intervals for 200 mg of oral suspension under fed and fasted conditions were 33.7–75.1% and 6.2–28.0%, respectively. The 95% distribution intervals for 400 mg of oral suspension under fed and fasted conditions were 28.4–70.2% and 4.4–21.3%, respectively. The 95% distribution intervals for the DR tablet under fed and fasted conditions were 98.6–99.8% and 33.2–80.4%, respectively

[d]Inter-occasion variability was only incorporated in a five-way crossover study for the DR tablet (P07764)[10]

[e]Shrinkages for the inter-occasion variability of each occasion are different and therefore were summarized as a range

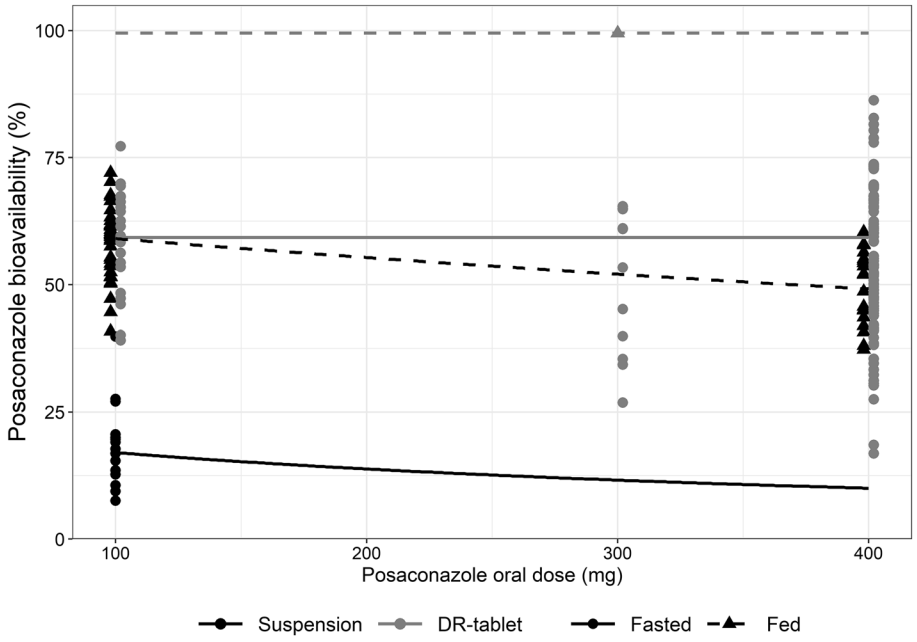

Fig. 1 Population prediction of posaconazole bioavailability (lines) and individually estimated bioavailability (symbols) versus dose for the oral suspension and the delayed-release tablet (DR-tablet) under fed and fasted conditions. At 100-mg and 400-mg, *symbols* were placed next to each other to allow a better visual comparison

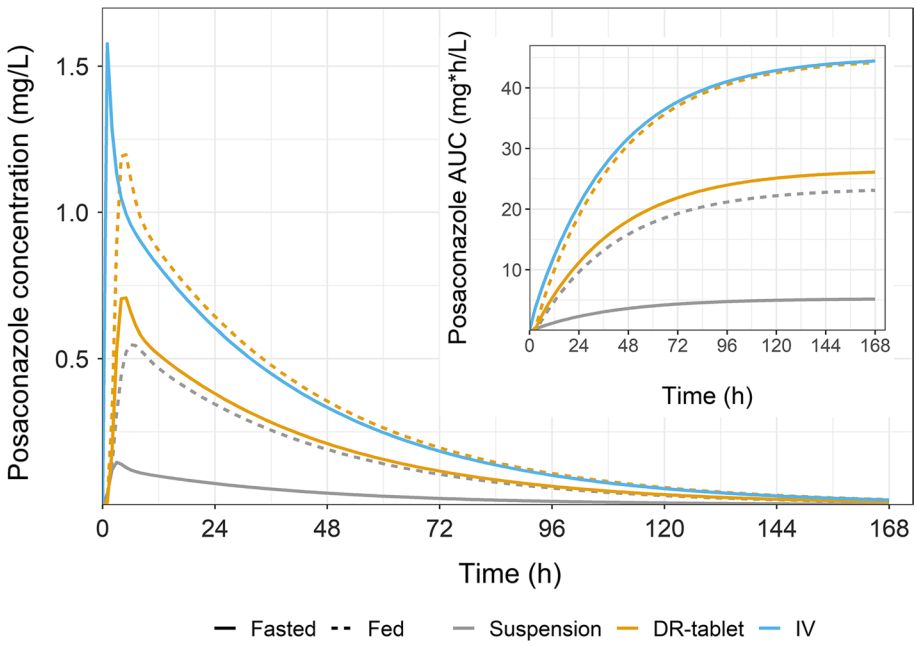

Fig. 2 Posaconazole concentration–time profiles in a typical healthy individual receiving a 300-mg single dose given as an oral suspension, delayed-release tablet (DR-tablet), or intravenous infusion (IV). Profiles for oral formulations were simulated under both fed and fasted conditions. The upper right insert exhibits the area under the concentration–time curve (AUC). *h* hours

mg bid on the first day followed by 300 mg qd thereafter of the DR tablet yield a $C_{trough} \geq 0.7$ mg/L in over 90% of healthy volunteers on day 7. However, once the same dose is given fasted, only 20% of healthy volunteers receiving the oral suspension, and 65% of the population receiving the DR tablet achieve this target. Under fed conditions, >90% of healthy volunteers receiving the three commonly used oral suspension regimens (i.e., 200 mg tid, 400 mg bid, 200 mg qid), and >80% of the population receiving the commonly used DR tablet regimen achieve a $C_{trough} \geq 1.0$ mg/L on day 7. The recommended IV regimen of 300 mg bid on the first day followed by 300 mg qd yields a steady-state $C_{trough} \geq 1.0$ mg/L in over 70% of the population.

4 Discussion

This study integrates the quantification of the pharmacokinetics of all currently available pharmaceutical formulations of posaconazole. Furthermore, absolute *F* and oral

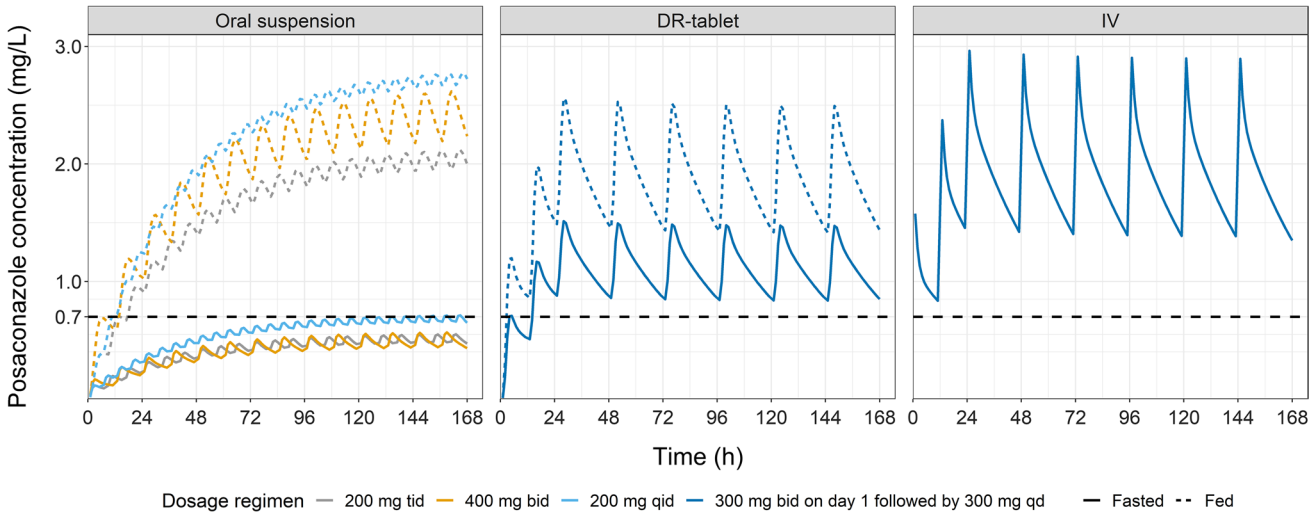

Fig. 3 Typical posaconazole concentration–time profiles in healthy volunteers receiving commonly used posaconazole doses for treatment and/or prophylaxis by oral suspension, delayed-release tablet (DR-tablet), and intravenous infusion (IV). Profiles for oral formulations were simulated under both fed and fasted conditions. The horizontal dashed line (0.7 mg/L) represents the trough concentration target for prophylaxis in patients. *bid* two times daily, *h* hours, *qd* once daily, *qid* four times daily, *tid* three times daily

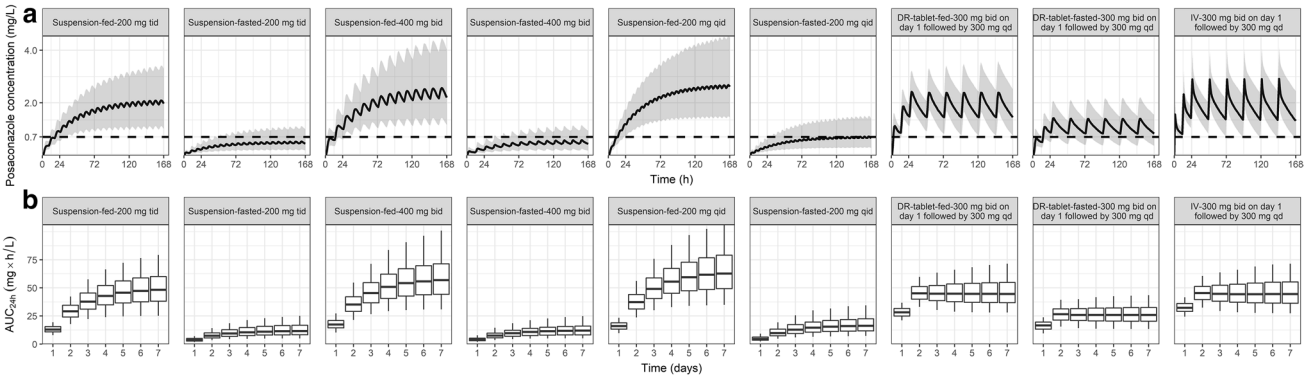

Fig. 4 Distribution of posaconazole concentration–time profiles (**a**) and distribution of the area under the curve per day (AUC_{24h}) (**b**) in 1000 simulated healthy volunteers receiving commonly prescribed posaconazole regimens for the oral suspension, delayed-release tablet (DR-tablet), and intravenous infusion (IV). Profiles for oral formulations were simulated under both fed and fasted conditions. In (**a**), the solid lines represent the median concentration, and the shaded areas represent the 90% prediction interval for the simulated individuals and the horizontal dashed line (0.7 mg/L) represents the concentration target for prophylaxis in patients. In (**b**), the *boxes* represent the 25th, 50th (median), and 75th percentiles, and the *whiskers* represent the 5th and 95th percentiles (i.e., 90% distribution interval). *bid* two times daily, *h* hours, *qd* once daily, *tid* three times daily

absorption rate were quantified including the influence of dose and food for both oral formulations in healthy volunteers. This study is the first to directly compare these formulations and quantify the dose-dependent nonlinear *F* for the oral suspension under fed and fasted conditions. One of the strengths of this study is the large amount of dense data for each formulation together with the novel application of available literature data during parameter estimation and covariate selection. Additionally, the potentially confounding influence of pathological and clinical factors was circumvented by focusing on healthy individuals, which allows for better clarification of the pharmacokinetic difference among the three formulations.

Nonlinearity in posaconazole exposure with an increasing oral suspension dose is well known and attributed to solubility issues in the gastrointestinal tract, which can be partly counteracted with the coadministration of food [28, 29]. Moreover, it has been reported for healthy volunteers that the difference in posaconazole exposure between fed and fasted conditions varies for different doses, which could be explained by the fact that solubility issues are less for lower doses; therefore, the impact that food can have on

increasing the solubility is also less [7]. The available previous knowledge, including reported quantitative differences, was included in our model with separate sigmoidal functions describing the relationship between dose and *F* for the fed and fasted condition. Because of the known influence of dose and food on *F* for the oral suspension, it was already strongly advised to divide a daily posaconazole dose over multiple smaller doses and to take the doses with a full meal to enhance oral absorption and maximize exposure [1, 3]. This advice is supported by our findings as illustrated in Fig. 3.

However, it should be kept in mind that feeding status does not have a fixed binary impact on posaconazole absorption, which our model does suggest. Differences in the impact of coadministration of various amounts of nutritional supplements, non-fat meals, and high-fat meals on *F* have been reported (1.35-fold to 2.69-fold vs 2.68-fold vs. 4.91-fold, respectively) [6, 7, 30], with the value obtained in our study reflecting results obtained after high-fat meals. Additionally, in single-dose studies, 8–12 h of fasting can be achieved, but upon repeated dosing multiple times per day not all doses will be administered under the same fasting conditions. This may for instance explain the underprediction of exposure by our model, for which estimations of parameters under fasted conditions were based on single-dose studies, compared to the studies that report on qid and bid dosing under fasted conditions (Table S2 of the ESM).

For the DR tablet, an absolute *F* of 54% was reported previously in the literature for healthy volunteers [17], which is similar to our estimate of 58.8% under fasting conditions. Unexpectedly, we found that food intake considerably increased the *F* for the DR tablet as well, with absorption being near-maximal under fed conditions, which might be attributable to a longer gastric residence time. This is in line with the finding from another population pharmacokinetic analysis in which it is concluded that DR tablet administration with food results in similar exposure levels to the IV formulation [32]. As a result of the positive food effect, the recommended dosage regimen of the DR tablet in healthy volunteers yields a typical C_{trough} ≥1.25 mg/L under fed conditions, but fails to achieve a C_{trough} ≥ 1 mg/L under fasted conditions (Fig. 3) [2]. Similar to the oral suspension, the US Food and Drug Administration suggests administering the posaconazole DR tablet with food to increase the exposure, while the European Medicines Agency proposed that the tablet may be taken with or without food [1, 3]. Based on our findings, administering the DR tablet with food should be advocated to enhance oral absorption and ensure adequate exposure whenever possible.

Contrary to the oral suspension [7], concomitant use with an antacid, ranitidine, esomeprazole, and metoclopramide did not show a statistically significant impact on the absorption of the DR tablet. This is in agreement with a <10% difference in AUC reported by a model independent method [10]. The IIV in the pharmacokinetics of the oral suspension might be slightly underestimated because the 16 healthy volunteers in the crossover study P04975 were considered as separate individuals under both fasting and fed conditions. Even so, high IIV on *F* was found for both the oral suspension and DR tablet, which contributes to the high variability in exposure levels in Fig. 4. Moreover, it should be noted that the pharmacokinetic properties of the DR tablet result in this formulation being favored in the clinic and sometimes even being used in a crushed form for administration through enteral tubes [31]. The results of our analysis do however have no bearing on the exposure profile of the DR tablet when administered this way.

First-order [33–35], absorption lag time [36], or sequential zero first-order [37, 38] were adopted by published studies to describe the oral absorption of posaconazole. In our analysis, these methods did not outperform the transit compartment approach in describing the absorption profile for both oral formulations in our analysis. This discrepancy could result from the high-density data obtained during the absorption phase in our analysis, and from the healthy study population that avoids the interference of pathological factors on absorption. As expected, with the acid-resistant pH-sensitive film, the DR tablet showed a longer absorption delay versus the oral suspension under the fasted condition described by a mean transit time of 2.96 h versus 1.82 h, respectively. Under the fed condition, a longer mean transit time of 3.80 h was found for the oral suspension as a result of delayed gastric emptying [7], while this was not the case for the DR tablet.

The pharmacokinetics of posaconazole in patients has mainly been reported in separate studies for different formulations [33–40]. Trends between exposure upon administration of the different formulations as well as the impact of food appear to be similar to what we found for healthy volunteers, but an integrated approach will be needed to quantify the extent of these differences in patients as well. To achieve this, the current analysis needs to be enriched with data from patients. Additionally, the impact of coadministered drugs or pathological factors including (severe) mucositis and gastric motility dysfunction is known to reduce exposure and increase IIV in the exposure of posaconazole upon oral dosing in patients [36, 41]. Direct extrapolations from our model, which is based on healthy volunteers, to patients cannot be made, as our simulations can be expected to over-predict the exposure and under-predict the IIV that can be expected in patients. For instance, when >90% of the simulated healthy individuals achieve the prophylactic target of IFDs if the commonly used oral prophylactic regimens are administered under fed conditions, this percentage is expected to be lower in patients. More importantly, our simulation results based on healthy individuals already

indicate a risk of underexposure for preventing IFDs when using the recommended oral dosage regimens under fasted conditions. This is of particular importance considering that food intake is often not feasible in patients [42].

To achieve the reported total posaconazole AUC_{24h}/MIC target of 167–178, which is associated with the half-maximal antifungal effects for treating aspergillosis [43–45], a deduced minimum total AUC_{24h} of 22.3 mg*h/L is required, based on the susceptible clinical minimum inhibitory concentration breakpoints of *Aspergillus fumigatus* of 0.125 mg/L [2]. Our simulations show that the recommended posaconazole oral suspension therapeutic dose of 400 mg bid or 200 mg qid is adequate to reach this target at steady state under fed conditions, but not under fasted conditions for which > 90% or > 70% of the individuals do not achieve this target, respectively (Fig. 4). This is an urgent alert for hematological patients after receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes or hematopoietic stem cell transplant recipients who are commonly not capable of taking food and often have gastrointestinal mucositis, which could lead to an even lower exposure in comparison to the healthy population [36, 46]. The DR tablet and IV formulations are only approved for prophylactic purposes by the Food and Drug Administration, while the European Medicines Agency has approved both formulations as first-line therapy for treating (refractory) invasive aspergillosis, as well as refractory fusariosis, chromoblastomycosis, and coccidioidomycosis [47]. Based on our simulation results in healthy volunteers in Fig. 4, the recommended dosage of the DR tablet under the fed condition and IV formulation yielded an AUC_{24h} ≥22.3 mg*h/L for more than 95% of individuals at steady state. Yet, only about 66% of the simulated healthy individuals could achieve this treatment target when the DR tablet is administered under the fasted condition. For this reason, the DR tablet should be used with caution for treating the *Aspergillus* pathogen with an attenuated minimum inhibitory concentration in patients who are intolerant to food, owing to the risk of suboptimal exposure.

5 Conclusions

This study characterized the pharmacokinetics for all three available formulations of posaconazole in a healthy population. The dose-dependent nonlinear *F* and difference in this function between fed and fasted conditions were quantified for the oral suspension. The pharmacokinetic superiority of the DR tablet was demonstrated under both fed and fasted conditions compared with the oral suspension. The impact of food on the *F* of the DR tablet is larger than anticipated, which suggests that administering the DR tablet with food should be considered to enhance absorption. Future investigations quantifying the pharmacokinetic differences between healthy individuals and patients for the three formulations are warranted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-022-01819-8.

Acknowledgments Data were shared under a contract between Merck & Co and Radboud University Medical Center. We thank Merck & Co., Inc., Kenilworth, NJ, USA for sharing their data on healthy volunteers. We thank all the healthy volunteers involved in these trials.

Declarations

Funding The work of Lu Chen was supported by the China Scholarship Council.

Conflicts of Interest/Competing Interests No disclosures are applicable for this work. Disclosures outside of this work: RJB has served as a consultant to Astellas Pharma, Inc., F2G, Amplyx, Gilead Sciences, Merck Sharp & Dohme Corp., Mundipharma, and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp., and Pfizer, Inc. All contracts were through Radboud University Medical Center, and all payments were invoiced by Radboud University Medical Center. None of the other authors has a conflict of interest to declare.

Ethics Approval Each clinical study involved in this paper received ethics approval.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Part of the data that support the findings of this study is available from Radboud University Medical Center but restrictions apply to the availability of these data. Data from Merck & Co were obtained under confidentiality and were used under license for the current study, thus are not publicly available.

Code Availability The NONMEM code for the final model can be found in the ESM.

Authors' Contributions Conception and design of the research: LC, EHJK, CAJK, and RJB; data collection: RJB; data analysis: LC and ARH; interpretation of findings: LC, EHJK, ARH, CAJK, and RJB; drafting the manuscript: LC; critical revision of manuscript: EHJK, ARH, CAJK, and RJB; and approval of the final manuscript: LC, EHJK, ARH, CAJK, and RJB.

References

1. EMA. Summary of posaconazole characteristics. 2022 January 6, 2022. https://www.ema.europa.eu/en/documents/product-information/noxafil-epar-product-information_en.pdf. Accessed 1 Feb 2022.
2. European Committee on Antimicrobial Susceptibility Testing. Posaconazole: rationale for the EUCAST clinical breakpoints, version 3.0. 4 February, 2020. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/

Posaconazole_RD_v3.0_final_final_18_02.pdf. Accessed 1 Feb 2022.
3. FDA. Noxafil instruction. March 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205053s1lbl.pdf. Accessed 1 Feb 2022.
4. Chen L, Krekels EHJ, Verweij PE, Buil JB, Knibbe CAJ, Brüggemann RJM. Pharmacokinetics and pharmacodynamics of posaconazole. Drugs. 2020;80(7):671–95.
5. Ullmann AJ, Cornely OA, Burchardt A, Hachem R, Kontoyiannis DP, Topelt K, et al. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. Antimicrob Agents Chemother. 2006;50(2):658–66.
6. Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. Br J Clin Pharmacol. 2004;57(2):218–22.
7. Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother. 2009;53(3):958–66.
8. Cornely OA, Duarte RF, Haider S, Chandrasekar P, Helfgott D, Jimenez JL, et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. J Antimicrob Chemother. 2016;71(3):718–26.
9. Duarte RF, Lopez-Jimenez J, Cornely OA, Laverdiere M, Helfgott D, Haider S, et al. Phase 1b study of new posaconazole tablet for prevention of invasive fungal infections in high-risk patients with neutropenia. Antimicrob Agents Chemother. 2014;58(10):5758–65.
10. Kraft WK, Chang PS, van Iersel ML, Waskin H, Krishna G, Kersemaekers WM. Posaconazole tablet pharmacokinetics: lack of effect of concomitant medications altering gastric pH and gastric motility in healthy subjects. Antimicrob Agents Chemother. 2014;58(7):4020–5.
11. Jang SH, Colangelo PM, Gobburu JV. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. Clin Pharmacol Ther. 2010;88(1):115–9.
12. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348–59.
13. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med. 2007;356(4):335–47.
14. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24(Suppl. 1):e1-38.
15. Krishna G, Ma L, Martinho M, O'Mara E. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrobi Agents Chemother. 2012;56(8):4196–201.
16. EMA. Posaconazole tablet assessment report: EPAR-scientific discussion-extension. 20 February, 2014. EMEA/H/C/000610/X/0028. https://www.ema.europa.eu/en/documents/variation-report/noxafil-h-c-610-x-0028-epar-scientific-discussion-extension_en.pdf. Accessed 1 Feb 2022.
17. EMA. Posaconazole injection assessment report: EPAR assessment report: variation. 24 Jul 2014. EMEA/H/C/000610/X/0033. https://www.ema.europa.eu/en/documents/variation-report/noxafil-h-c-610-x-0033-epar-assessment-report-variation_en.pdf. Accessed 1 Feb 2022.
18. Kersemaekers WM, van Iersel T, Nassander U, O'Mara E, Waskin H, Caceres M, et al. Pharmacokinetics and safety study of posaconazole intravenous solution administered peripherally to healthy subjects. Antimicrob Agents Chemother. 2015;59(2):1246–51.
19. Bruggemann RJ, van Luin M, Colbers EP, van den Dungen MW, Pharo C, Schouwenberg BJ, et al. Effect of posaconazole on the pharmacokinetics of fosamprenavir and vice versa in healthy volunteers. J Antimicrob Chemother. 2010;65(10):2188–94.
20. Wasmann RE, Smit C, van Donselaar MH, van Dongen EPA, Wiezer RMJ, Verweij PE, et al. Implications for IV posaconazole dosing in the era of obesity. J Antimicrob Chemother. 2020;75(4):1006–13.
21. Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother. 2003;47(9):2788–95.
22. Keizer RJ, Karlsson MO, Hooker A. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol. 2013;2(6): e50.
23. Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2008;35(4):401–21.
24. Rousseau A, Léger F, Le Meur Y, Saint-Marcoux F, Paintaud G, Buchler M, et al. Population pharmacokinetic modeling of oral cyclosporin using NONMEM: comparison of absorption pharmacokinetic models and design of a Bayesian estimator. Ther Drug Monit. 2004;26(1):23–30.
25. Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007;34(5):711–26.
26. Ruiz-Garcia A, Tan W, Li J, Haughey M, Masters J, Hibma J, et al. Pharmacokinetic models to characterize the absorption phase and the influence of a proton pump inhibitor on the overall exposure of dacomitinib. Pharmaceutics. 2020;12(4):330.
27. Zhou H. Pharmacokinetic strategies in deciphering atypical drug absorption profiles. J Clin Pharmacol. 2003;43(3):211–27.
28. Hare RK, Gertsen JB, Astvad KMT, Degn KB, Løkke A, Stegger M, et al. In vivo selection of a unique tandem repeat mediated azole resistance mechanism (TR_{120}) in Aspergillus fumigatus CYP51A. Denmark Emerg Infect Dis. 2019;25(3):577–80.
29. Hens B, Pathak SM. In silico modeling approach for the evaluation of gastrointestinal dissolution, supersaturation, and precipitation of posaconazole. Mol Pharm. 2017;14(12):4321–33.
30. Krishna G, Ma L, Vickery D, Yu X, Wu I, Power E, et al. Effect of varying amounts of a liquid nutritional supplement on the pharmacokinetics of posaconazole in healthy volunteers. Antimicrob Agents Chemother. 2009;53(11):4749–52.
31. Dieringer TD, Schaenman JM, Davis MR. Enteral feeding tube administration with therapeutic drug monitoring of crushed posaconazole tablets and opened isavuconazonium sulfate capsules. J Antimicrob Chemother. 2022;77(5):1417–23.
32. EMA. Noxafil EPAR assessment report. 16 September, 2021. https://www.ema.europa.eu/en/documents/variation-report/noxafil-h-c-610-ii-0062-epar-assessment-report-variation_en.pdf. Accessed 25 May 2022.
33. Kohl V, Muller C, Cornely OA, Abduljalil K, Fuhr U, Vehreschild JJ, et al. Factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic stem cell transplantation. Antimicrob Agents Chemother. 2010;54(1):207–12.
34. Petitcollin A, Boglione-Kerrien C, Tron C, Picard S, Lalanne S, Nimubona S, et al. Population pharmacokinetics and monte-carlo simulations of posaconazole administered as tablets in a real-life cohort of patients with hematological malignancies: towards dose reduction? Fundam Clin Pharmacol. 2017;31:19.

35. Vehreschild JJ, Muller C, Farowski F, Vehreschild MJ, Cornely OA, Fuhr U, 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(6):987–95.
36. Dolton MJ, Bruggemann RJ, Burger DM, McLachlan AJ. Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis. Antimicrob Agents Chemother. 2014;58(11):6879–85.
37. Pena-Lorenzo D, Rebollo N, Sanchez-Hernandez JG, Zarzuelo-Castaneda A, Vazquez-Lopez L, Otero MJ, et al. Population pharmacokinetics of a posaconazole tablet formulation in transplant adult allogeneic stem cell recipients. Eur J Pharm Sci. 2022;1(168): 106049.
38. van Iersel M, Rossenu S, de Greef R, Waskin H. A population pharmacokinetic model for a solid oral tablet formulation of posaconazole. Antimicrob Agents Chemother. 2018;62(7):e02465-e2517.
39. 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(2):397–405.
40. Storzinger D, Borghorst S, Hofer S, Busch CJ, Lichtenstern C, Hempel G, et al. Plasma concentrations of posaconazole administered via nasogastric tube in patients in a surgical intensive care unit. Antimicrob Agents Chemother. 2012;56(8):4468–70.
41. Jansen AME, Muilwijk EW, Van Der Velden WJFM, Maertens JA, Aerts R, Colbers A, et al. Posaconazole bioavailability of the solid oral tablet is reduced during severe intestinal mucositis. Clin Microbiol Infect. 2022;28(7):1003–9.
42. Gubbins PO, Krishna G, Sansone-Parsons A, Penzak SR, Dong L, Martinho M, et al. Pharmacokinetics and safety of oral posaconazole in neutropenic stem cell transplant recipients. Antimicrob Agents Chemother. 2006;50(6):1993–9.
43. Howard SJ, Lestner JM, Sharp A, Gregson L, Goodwin J, Slater J, et al. Pharmacokinetics and pharmacodynamics of posaconazole for invasive pulmonary aspergillosis: clinical implications for antifungal therapy. J Infect Dis. 2011;203(9):1324–32.
44. Lepak AJ, Marchillo K, Vanhecker J, Andes DR. Posaconazole pharmacodynamic target determination against wild-type and Cyp51 mutant isolates of Aspergillus fumigatus in an in vivo model of invasive pulmonary aspergillosis. Antimicrob Agents Chemother. 2013;57(1):579–85.
45. Mavridou E, Bruggemann RJ, Melchers WJ, Mouton JW, Verweij PE. Efficacy of posaconazole against three clinical Aspergillus fumigatus isolates with mutations in the cyp51A gene. Antimicrob Agents Chemother. 2010;54(2):860–5.
46. Kuiken NSS, Rings EHHM, Blijlevens NMA, Tissing WJE. Biomarkers and non-invasive tests for gastrointestinal mucositis. Support Care Cancer. 2017;25(9):2933–41.
47. EMA. Noxafil: EPAR - product information. 22 February, 2022. EMEA/H/C/000610 - II/0067. https://www.ema.europa.eu/en/documents/product-information/noxafil-epar-product-information_en.pdf. Accessed 19 May 2022.

Authors and Affiliations

Lu Chen[1] · Elke H. J. Krekels[1] · Anne R. Heijnen[1] · Catherijne A. J. Knibbe[1,2] · Roger J. Brüggemann[3,4]

✉ Roger J. Brüggemann
Roger.Bruggemann@radboudumc.nl

[1] Division of Systems Pharmacology and Pharmacy, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands

[2] Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands

[3] Department of Pharmacy, Radboud University Medical Center, Geert Grooteplein 10, 6525 GA Nijmegen, The Netherlands

[4] Radboudumc Center for Infectious Diseases and Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands