

# **Optimizing antifungal treatment through pharmacometrics: dosing considerations to enhance outcome**

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## **Chapter 3**

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

This chapter is based upon:

Chen L, Krekels EHJ, Heijnen AR, Knibbe CAJ, Bruggemann RJ. An Integrated Population Pharmacokinetic Analysis for Posaconazole Oral Suspension, Delayed-Release Tablet, and Intravenous Infusion in Healthy Volunteers. Drugs. 2023 Jan;83(1):75-86.

#### Abstract

Background Posaconazole is widely used for prophylaxis and treatment of invasive fungal diseases. Due to the limited and variable absorption of the initially available oral suspension, a delayed-released tablet (DR-tablet) and IV formulation were developed.

Objective This study characterizes the pharmacokinetics, including the absolute oral bioavailability (F), of all posaconazole formulations in healthy volunteers. Methods Data from 182 healthy volunteers with 3898 densely sampled posaconazole concentrations were pooled from 8 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 versus fasted), nonlinearity, and for the DR-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 DR-tablet. For the suspension, both a food effect and a dose-dependent nonlinear F were quantified, resulting in lower F when fasted or at a higher dose. The typical F 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 F of the DR-tablet was 58.8% (95% confidence interval [CI] 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% (CI 45.2-59.2%). The impact of comedication on the absorption of the DRtablet 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 DR-tablet under fasted conditions fail to achieve this target, while for the suspension this percentage varies between 55% and 85%, depending on the dose. Conclusion For both oral posaconazole formulations, we quantified F and absorption rate, including food effects, in healthy volunteers. 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 was larger than anticipated, suggesting that administering the DR-tablet with food enhances absorption.

Keywords posaconazole, oral bioavailability, healthy volunteers

#### 3.1 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 tablet (DR-tablet) and intravenous infusion (IV) [1, 3]. Erratic absorption, both in terms of rate of absorption and extent of absorption (i.e. bioavailability) 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 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  $(C_{trough}) \ge 0.7 \text{ mg/L}$  is included in the label as a target for preventing IFDs [11-13]. A treatment target of  $C_{trough} \ge 1.0 \text{ mg/L}$  or  $\ge 1.25 \text{ mg/L}$  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 DR-tablet to 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 bioavailability (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.

#### 3.2 Methods

#### 3.2.1 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 8 clinical studies, with different formulations, dosages

(ranging from 50 - 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], P06356 [18], and two studies in the Radboudumc, Nijmegen, the Netherlands [19, 20]. In a crossover study P04975, sixteen 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 the 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, 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 literature. We searched PubMed for clinical trials which 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 case that multiple studies met the criteria, studies with longer sampling duration and 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 model evaluation [6, 7, 15, 16, 19].

#### 3.2.2 Population pharmacokinetic model

The population pharmacokinetic model was developed using the nonlinear mixedeffects 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, USA) [22]. Data processing and visualization were performed with R 4.1.1 and RStudio 1.4.1717. Due to the long run times, the M1 method for which observations below the quantification limit (BQL) 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 BQL 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 (SAEM) method were adopted for models using the M1 and M3 methods, respectively.

Characteristics		Suspension [15, 16, 19]	DR-tablet [10, 16]	IV [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 bidª	300 qd⁵	NA
Duration of sampling	Single dose	168	168	48, 144, 168
after the last dose (h)	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

Table 1 Summary of the pharmacokinetic data included in this analysis

*DR-tablet* delayed-release tablet, *IV* intravenous infusion, *NA* not available, *BQL* below the quantification limit, *bid* twice daily, *qd* once daily <sup>®</sup>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 <sup>b</sup>300 mg bid on the first day followed by 300 mg qd

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 (GOF) 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 ( $F_{susmax}$ ) and for

the oral suspension dose that could achieve half of the  $F_{sus,max}$  ( $D_{50,sus}$ ) under fed and fasted conditions (see Equation 1).

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

In which  $F_{sus,fed}$  represents the population value of F for the suspension under fed condition,  $F_{sus,max,fed}$  represents the maximum F of the suspension under fed condition, Dose represents the suspension dose that was given,  $D_{50,sus,fed}$  represents oral suspension dose that could achieve half of the  $F_{sus,max,fed}$  under fed condition. Assuming the literature value of 4.91 for the ratio of F between fed and fasted condition 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 oral suspension dose that could achieve half of the maximum F under fasted condition ( $D_{50,sus,fasted}$ ) and  $D_{50,sus,fed}$  (see Equation 2).

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

Among three studies administering the oral suspension under 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. 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 (NPDE) 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.

#### 3.2.3 Illustration of model findings

To illustrate the exposure differences for the three posaconazole formulations, concentration-time profiles after a single dose of 300 mg posaconazole oral suspension (fed and fasted), DR-tablet (fed and fasted), and IV, 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 once daily (bid) on the first day followed by a maintenance dose of 300 mg once daily (qd) for both 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 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 (AUC<sub>24b</sub>).

#### 3.3 Results

#### 3.3.1 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). IIV was included on F, the first-order rate constant between absorption transit compartments ( $k_{r}$ ), CL, and volume of distribution of the central compartment.

Including nonlinear CL decreased OFV significantly compared with the linear CL, but the GOF 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 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 condition, and 33.2-80.4% for the DR-tablet under fasted condition. The IOVs were slightly higher than the IIVs in F (0.401 vs. 0.290) and k<sub>tr</sub> (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 supplementary material. GOF plots of the final model are included in supplemental Fig. S2 and suggest that the model described the data well for each formulation. The NPDE results shown in Supplementary Fig. S3A and S3B indicate an accurate predictive performance of the final model regarding both the structural and stochastic model for each formulation. Fig. S3C 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 literature with doses ranging from 100 mg to 400 mg (Table S2). 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). Bootstrap results in Table 2 indicate that the final model was robust and all model parameters were estimated with good precision.

Parameters	Parameter estimates (RSE%) [%shrinkage] Bootstrap <sup>a</sup> median (95% CI		
Population parameter values [units]		^	
$F_{sus,fed} = F_{sus,max,fed} \times \left(1 - \frac{Dose}{Dose + D_{50,f}}\right)$	$\left(\frac{1}{ed}\right)$		
$F_{sus,fasted} = \frac{F_{sus,max,fed}}{2.85} \times \left(1 - \frac{1}{Dose + \frac{32}{5597.4}}\right)$	$ \left. \begin{array}{c} bose \\ 249 \times D_{50,fed} \\ + 5.871 \times D_{50,fed} \end{array} \right) $		
F <sub>sus,max,fed</sub> [%]	63.3 (8.10)	63.8 (34.9-71.6)	
D <sub>50,fed</sub> [mg]	1390 (60.5)	1017 (205-2217)	
F <sub>tab,fed</sub> [%]	99.5 (fixed)	99.5 fixed	
F <sub>tab,fasted</sub> [%]	58.8 (3.80)	58.6 (53.9-64.2)	
$k_{tr,sus,fed} = k_{tr,sus,fasted} * (1-\theta_{sus,fed,ktr})$			
k <sub>tr,sus,fasted</sub> [h <sup>-1</sup> ]	2.20 (6.70)	2.2 (1.99-2.4)	
$ heta_{ m sus, fed,  ktr}$ [-]	0.522 (6.90)	0.525 (0.465-0.567)	
k <sub>tr,tab</sub> [h <sup>-1</sup> ]	2.70 (5.60)	2.59 (2.44-2.72)	
CL [L/h]	6.65 (2.70)	6.97 (6.65-7.18)	
V <sub>c</sub> [L]	152 (4.80)	153 (135-166)	
V <sub>P</sub> [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 <sub>sus</sub> <sup>b,c</sup>	0.206 (25.1) [50.9]	0.210 (0.100-2.94)	
F <sub>tab</sub> <sup>b,c</sup>	0.290 (26.9) [52.1]	0.320 (0.180-0.570)	
k <sub>tr,sus</sub>	20.7 (12.3) [47.5]	20.3 (15.7-25.9)	
k <sub>tr,tab</sub>	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 <sub>c</sub>	31.3 (10.0) [19.6]	32.7 (26.8-36.8)	
Inter-occasion variability <sup>d</sup> in %CV			
F <sub>tab</sub> b,c	0.401 (19.7) [67.0-76.3] <sup>e</sup>	0.433 (0.290-0.612)	
k <sub>tr,tab</sub>	31.5 (6.20) [65.0-74.2]°	31.8 (26.0-38.1)	
Residual error			
σ <sub>prop</sub>	18.8% (0.600)	18.7% (17.4%-20.3%)	
$\sigma_{\rm addi}({ m mg/L})$	0.0025 (4.50)	0.0023 (0.0008-0.0039)	

#### Table 2 Pharmacokinetic parameter estimates for the final posaconazole model

RSE relative standard error of the estimate, Cl confidence interval, F absolute oral bioavailability, Fsus, fed population value of F for the oral suspension under fed condition,  $D_{solver}$  oral suspension dose that could achieve half of the  $F_{unamated}$  under fed condition, DR-tablet delayed-release tablet,  $F_{unated}$  population value of F for DR-tablet under face condition,  $k_{transfer}$  for DR-tablet under face condition,  $k_{transfer}$  (so the oral suspension under fed condition,  $k_{transfer}$  (so the oral suspension under fasted condition,  $k_{transfer}$  (so the oral suspension),  $k_{transfer}$  (so the oral suspensi

compartment, Q intercompartment clearance between central and peripheral compartments,  $CV^{\mu}$  coefficient of variation,  $\sigma_{\mu\sigma\rho}$  proportional residual error <sup>B</sup>Bootstrap success rate was 63% for the final model using the M3 method (n = 63 out of 100) <sup>b</sup>The variability of F was added within the logit domain and was presented as the variance. <sup>CA</sup> 95% distribution interval with the 2.5th and 97.5th percentiles calculated by  $\begin{pmatrix} e^{i(\frac{1}{LP}-198\kappa\sqrt{ap^2})} \\ 1e^{i(\frac{1}{LP}-198\kappa\sqrt{ap^2})} \end{pmatrix}$ , was used to describe the inter-individual variability of F. The 95% distribution interval for 200 mg of oral suspension under fed and fasted conditions were 33.7-75.1% and 6.2-28.0%,  $\begin{pmatrix} e^{i(\frac{1}{LP}-198\kappa\sqrt{ap^2})} \\ 1e^{i(\frac{1}{LP}-198\kappa\sqrt{ap^2})} \end{pmatrix}$ ,  $\frac{e^{i(\frac{1}{LP}+198\kappa\sqrt{ap^2})}}{1e^{i(\frac{1}{LP}+198\kappa\sqrt{ap^2})}}$ ) fed and fasted conditions were 98.6-99.8% and 3.2-80.4%, respectively. The 95% distribution interval for the DR-tablet under fed and fasted conditions were 98.6-99.8% and 3.2-80.4%, respectively of each occasion are different and therefore were summarized as a range

#### 3.3.2 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 to 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 with that of the DR-tablet under fasted condition.



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

Fig. 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 condition. The AUC of the oral suspension under fasted condition yields approximately one-quarter of the exposure value of the oral suspension under fed condition or DR-tablet under fasted condition, and one-sixth of the exposure of the DR-tablet under fed condition or IV.

Fig. 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  $C_{trough} \ge 1.25 \text{ mg/L}$  at steady state. However, under fasted conditions, the DR-tablet regimen yields a prophylactic steady-state  $C_{trough} \ge 0.7 \text{ mg/L}$ .

but fails to achieve treatment values of  $\geq 1$  mg/L, while all three suspension regimens even fail to achieve the prophylactic target when fasted.



**Fig. 2** Posaconazole concentration-time profiles in a typical healthy individual receiving a 300 mg single dose given as 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)



**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

tid three times daily, bid two times daily, qd once daily

The simulations in Fig. 4 were performed to present the distribution of posaconazole concentration and  $AUC_{_{24h}}$  versus time over one week in 1000 healthy individuals.

With food intake, both recommended prophylactic posaconazole oral regimens of 200 mg tid of the oral suspension and 300 mç
bid on the first day followed by 300 mg qd thereafter of the DR-tablet, yield a C $_{ m trainerb}$ $\ge$ 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 <sub>terreb</sub> ≥1.0 mg/L on day 7. The recommended IV regimen of 300 mg bid on the firs
day followed by 300 mg qd yields a steady-state C <sup>rouch</sup> ≥1.0 mg/L in over 70% of the population.



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 25<sup>th</sup>, 50<sup>th</sup> (median), and 75<sup>th</sup> percentiles, and whiskers represent the 5<sup>th</sup> (b) in 1000 simulated healthy volunteers receiving commonly prescribed posaconazole regimens for the oral suspension, Fig. 4 Distribution of posaconazole concentration-time profiles (a) and distribution of the area under the curve per day (AUC $_{24h}$ ) and 95<sup>th</sup> percentiles (i.e., 90% distribution interval)

*tid* three times daily, *bid* two times daily, *qd* once daily

(A) (A) (A)

#### 3.4 Discussion

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

It should be kept in mind however, 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 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 hours 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 estimation 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).

For the DR-tablet, an absolute F of 54% was reported previously in 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 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 IV [32]. As a result of the positive food effect, the recommended dosage regimen of DR-tablet in healthy volunteers yields a typical  $C_{trough} \ge 1.25$  mg/L under fed conditions, but fails to achieve  $C_{trough} \ge 1$  mg/L under fasted conditions (Fig. 3) [2]. Similar to the oral suspension, the U.S. Food and Drug Administration (FDA) suggests administering the posaconazole DR-tablet with food to increase the exposure, while the European Medicines Agency (EMA) 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 results in this formulation being favored in the clinic and sometimes even being used in crushed form for administration through enteral tubes [31]. Results of our analysis do however have no bearing on the exposure profile of DR-table 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 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 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 have 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, are 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<sub>24b</sub>/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 MIC breakpoints of A. 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 gid is adequate to reach this target at steady state under fed conditions, but not under fasted condition for which >90% or >70% of the individuals fail to 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 suffer from gastrointestinal mucositis, which could lead to 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 FDA, while the EMA 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 DR-tablet under fed condition and IV yielded an AUC<sub>24h</sub> ≥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 fasted condition. For this reason, the DR-tablet should be used with caution for treating Aspergillus pathogen with an attenuated MIC in patients who are intolerant to food, due to the risk of suboptimal exposure.

#### 3.5 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 bioavailability 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.

#### 3.6 Supplementary materials



### **Fig. S1** Schematic representation of the integrated pharmacokinetic model for three formulations of posaconazole

*DR-tablet* delayed-release tablet, *IV* intravenous infusion, *F* absolute bioavailability,  $F_{uv}$ , F of the oral suspension,  $F_{uv}$ , F of the DR-tablet,  $k_c$ , first-order absorption rate constant and the rate constant between absorption transit compartments,  $k_c$ , of the oral suspension,  $k_w^{reg}$  of the delayed-release tablet, *CL* clearance, *V* the volume of distribution of the central compartment,  $V_p^{reg}$  the volume of distribution of the central compartment,  $V_p^{reg}$  the volume of distribution of the central compartment, *Q* interdepartmenta clearance



**Fig S2.** Goodness-of-fit plots of the final model for oral suspension, delayedrelease tablet (DR-tablet) and intravenous infusion (IV), with (a) observed *versus* population predicted posaconazole concentrations, (b) observed *versus* individual predicted posaconazole concentrations, (c) conditional weighted residuals *versus* time after dose and (d) *versus* population predicted posaconazole concentrations. The solid lines in plots (a) and (b) represent the line of identity (y=x)

#### Integrated posaconazole PK in healthy volunteers



**Fig. S3** Normalized prediction distribution error (NPDE) *versus* time after dose (**a**), NPDE *versus* predicted concentrations (**b**), and the probability of posaconazole concentration being below the limit of quantification (Pr[Y<LOQ]) *versus* time after dose (**c**) of the final model for oral suspension, delayed-release tablets (DR-tablet) and intravenous infusion (IV). In plot **a** and **b**, each prediction interval (95%) of simulated concentrations (**n** = 1000) is plotted as a colored area (blue for the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles and pink for the median). The corresponding 2.5<sup>th</sup>, 50<sup>th</sup>, and 97.5<sup>th</sup> percentiles of the observed and predicted data are plotted as solid and dotted lines, respectively. Concentrations detected below the limit of quantification are indicated in steel blue color in the scatter plots. In **c**, lines represent the observed (solid) and median predicted (dotted) proportion below the LOQ, where the blue shaded areas represent the 95% confidence intervals based on simulated concentrations (**n** = 1000)

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Study	Merck-49	75 [1]	Radboudumc [2]	Merck-7691 [3]		Merck-7764 [4]	Merck-778	3 [3]		Merck-4985 [5]	Merck-6356 [6]	Radboudumc [7]
Formulation	Suspensi	ис	Suspension	Suspension	DR-tablet	DR-tablet	DR-tablet		2	N	N	2
Food intake	fasted <sup>a</sup>	fed <sup>a</sup>	fed	fed	fasted	fasted	fasted	fed	AN	NA	NA	NA
Single (SD) or multiple (MD) dose	SD	SD	QW	SD	SD	SD	SD	ДМ	ß	SD	SD	SD
No. of subjects	16	15	20	24	22	21	12	12	12	6	45	œ
Dosage (mg)	100	100	400 bid	100	100	400	300	300 qd	300	200	50, 100, 200, 250, 300	300
Duration of sampling after the last dose (h)	168	168	12	168	168	168	168	168	168	144	168	48
No. of total concentrations	256	240	220	312	286	1304	156	178	156	179	531	80
No. of concentrations per subject, median	16	16	11	13	13	65	13	16	13	20	12	10
No. of BLOQ concentrations	62	48	0	31	45	52	13	0	4	1	43	0
Occasion(s)	1	-	1	1	1	1 - 5	-	+	1	1	1	1
Covariates	food		food	food		food, comedications <sup><math>b</math></sup>	food		NA	NA	NA	NA
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DR-tab delayed-release tablet, /V intravenous infusion, MA not available, *bid* twice daily, *qd* once daily Fed and fasted groups cannot be actinguished based on the accessible data and were considered as different individuals in the analysis \*Consort design with each subject receiving posaconazole DR-tablet four comedications at different treatment periods, including Mylanta, ranitidine, esomeprazole, and metoclopramide \*Participants took breakfast 1h after drug intake

Chapter 3

Table S2 Comparison of AUC values reported in the literature based on noncompartmental analyses and AUC values predicted for the same conditions by our final model for oral suspension.

Reference	Dosing sce	enarios		Reported mean mL]	AUC [ng*h/	Predicted typical AUC [ng*h/mL] (percentage error <sup>a</sup> )
Author Year [2, 8, 3, 1, 9]	Regimen	Dose	Food	AUC type	values	values
Krishna at al. 2012 [1]		100 <sup>b</sup>	Fasted	AUC <sub>0-168h</sub>	2970	2520 (15%)
Krishna et al. 2012 [1]		100 <sup>b</sup>	Fed	AUC <sub>0-168h</sub>	8470	8733 (%)
Merck-EMA-P07691 2014 [3]	Single dose	100 <sup>b</sup>	Fed	AUC <sub>0-168h</sub>	8018	8733 (†9%)
Courtmon at al. 2004 [9]		200	Fasted	AUC	3553	3443 (3%)
Courtriey et al. 2004 [o]		200	Fed	AUC	13885	13660 (2%)
		400	Fasted	AUC <sub>0-168h</sub>	4280	5927 (†38%)
		400	fed	AUC <sub>0-168h</sub>	21000	29078 (†38%)
Krishna et al. 2009 [9]		200 qid	Fasted	AUC <sub>0-168h</sub>	132000	29613 (↓78%)
	Multiple dose	400 bid	Fasted	AUC <sub>0-168h</sub>	52300	23062 (↓56%)
Bruggemann et al. 2010 [2]		400 bid <sup>b,c</sup>	Fed	AUC <sub>0-12h</sub>	30400	29320 (↓4%)

The green color indicates a prediction accuracy with a percentage error of <50%. The red color indicates a poor prediction accuracy with a The green color indicates a prediction accuracy with a percentage error of <50%. The red color indicates percentage error ≥50% 
<sup>a</sup>Percentage error ≥50% 
<sup>b</sup>Cenarios for which data were included in our analysis 
<sup>c</sup>Posaconazole oral suspension 200 mg dd on day 1, 200 bid on day 2, 400 mg bid from day 3 to day 10 *AUC* the area under the concentration-time curve, *tid* three times daily, *bid* two times daily, *qd* once daily

Table S3 Comparison of the ratio in bioavailability between fed and fasted conditions reported in the literature and derived from simulations with our final model. As in our model, differences in AUC are fully driven by differences in bioavailability, AUC ratios are used as a proxy for ratios on bioavailability

Author Year	Single Dose	Reported food effect on AUC <sup>a</sup>	Predicted food effect on AUC <sup>a</sup> (percentage error <sup>b</sup> )
Krishna <i>et al.</i> 2012 [1]	100	2.85	3.46 (↑21%)
Courtney et al. 2004 [8]	200	3.91	3.98 (↑2%)
Krishna <i>et al.</i> 2009 [9]	400	4.91	4.87 (↓1%)

The green color indicates a percentage error of <50% <sup>a</sup>The reported ratio of F was considered as same as the ratio of AUC <sup>b</sup>Percentage error = ((predicted-reported)/observed)\*100%

#### NONMEM Control Stream for the Final Model

\$PROBLEM posaconazole PK of 3 formulations in healthy volunteers \$INPUT ID TIME TAD DV MDV AMT ADDL II CMT RATE EVID DOSE LLOQ BLOQ HALFLOQ FORM NEWSTU STU MD OCC DENSE FOOD DDI MYL RANT ESOM METO FOS SEX WT AGE HT BMI BSA IBW FFM \$DATA LC\_Posaconazole\_3formulations\_20210922\_M3.csv IGNORE=@ \$SUB ADVAN13 TOL=9 \$MODEL COMP=(DEPOT1) ;1 COMP=(DEPOT2) ;2 COMP=/DEPOT2/ :2 COMP=/DEPOT2/ :2 COMP=/(CENT) :3 COMP=/(TRANS1) :5 1st transit compartment sus COMP=/(TRANS2) :6 2nd transit compartment sus COMP=/(TRANS3) :7 3rd transit compartment DR-tab COMP=/(TRANS3) :9 2nd transit compartment DR-tab COMP=/(TRANS7) :10 3rd transit compartment DR-tab COMP=/(TRANS8) :12 5th transit compartment DR-tab COMP=/(TRANS9) :12 5th transit compartment DR-tab COMP=/(TRANS1) :13 6th transit compartment DR-tab COMP=/(TRANS1) :14 7th transit compartment DR-tab COMP=/(TRANS1) :14 7th transit compartment DR-tab COMP=/(TRANS1) :14 7th transit compartment DR-tab \$ABBR REPLACE ETA(OCC\_KTR) = ETA (.9 to 13 by 1) \$ABBR REPLACE ETA(OCC\_FTAB) = ETA (.14 to 18 by 1) ¢PK FFD=0  $\begin{array}{l} \mathsf{FED=0} \\ \mathsf{IF} \ (\mathsf{FOOD.NE.0}) \ \mathsf{FED=1}; \ \mathsf{FOOD=1=fed}, \ \mathsf{FOOD=0=fasted} \\ ; \ \mathsf{FORM=1=sus}, \ \mathsf{FORM=2=DR-tab}, \ \mathsf{FORM=3=iv} \\ \mathsf{IF} \ (\mathsf{FORM.EQ,1}) \ \mathsf{KTR} = \mathsf{THETA} \ (1) \ (\mathsf{THETA} \ (9))) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (1)); \ \mathsf{KTR-sus} \\ \mathsf{IF} \ (\mathsf{FORM.EQ,2} \ \mathsf{AND.NEWSTU.NE.4}) \ \mathsf{KTR} = \mathsf{THETA} \ (2) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (2)); \ \mathsf{KTR-tab} \\ \mathsf{IF} \ (\mathsf{FORM.EQ,2} \ \mathsf{AND.NEWSTU.NE.4}) \ \mathsf{KTR} = \mathsf{THETA} \ (2) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (2)); \ \mathsf{KTR-tab} \\ \mathsf{IF} \ (\mathsf{FORM.EQ,2} \ \mathsf{AND.NEWSTU.EQ.4}) \ \mathsf{KTR} = \mathsf{THETA} \ (2) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (2)); \ \mathsf{KTR-tab} \\ \mathsf{IF} \ (\mathsf{FORM.EQ,2} \ \mathsf{AND.NEWSTU.EQ.4}) \ \mathsf{KTR} = \mathsf{THETA} \ (2) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (2)); \ \mathsf{KTR-tab} \\ \mathsf{IF} \ (\mathsf{FORM.EQ,2} \ \mathsf{AND.NEWSTU.EQ.4}) \ \mathsf{KTR-tab} \ \mathsf{with} \ \mathsf{IOV} \\ \mathsf{CL} = \mathsf{THETA} \ (3) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (3)); \ \mathsf{CL} \ \mathsf{in all populations} \\ \mathsf{V3} = \mathsf{THETA} \ (4) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (4)) \\ \mathsf{V4} = \mathsf{THETA} \ (5) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (5)) \\ \mathsf{Q} = \mathsf{THETA} \ (6) \ \mathsf{^*EXP} \ (\mathsf{ETA} \ (6)) \end{array}$ F1=0 H1=0 FMAXFED = THETA(7) FMAXFAST = FMAXFED/2.85 D50FED = THETA(10) D50FAST = (3249\*D50FED)/(5597.4+(5.871\*D50FED))) IF (FORM=1.AND.FED==0) TVF1 = FMAXFAST\*(1-(DOSE/(D50FAST+DOSE)))) IF (FORM=1.AND.FED==1) TVF1 = FMAXFED\*(1-(DOSE/(D50FED+DOSE)))) IF (CPRM=1.AND.FED==1) TVF1 = FMAXFED\*(1-(DOSE/(D50FED+DOSE)))) LGTBIOS=LOG(TVF1/(1-TVF1)) LGBIOS=LGTBIOS+ETA(7) F1=EXP(LGBIOS)/(1+EXP(LGBIOS)) F2=0 F2=0 IF (FORM.EQ.2.AND.FED.EQ.0) TVF2 = THETA(8) IF (FORM.EQ.2.AND.FED.EQ.1) TVF2 = 0.995 LGTBIOT=LOG(TVF2)(1-TVF2)) IF (FORM.EQ.2.AND.NEWSTU.NE.4) LGBIOT=LGTBIOT+ETA (8) IF (FORM.EQ.2.AND.NEWSTU.EQ.4) LGBIOT=LGTBIOT+ETA (8) +ETA(OCC\_FTAB) F2=EXP(LGBIOT)/(1+EXP(LGBIOT)) F3=1 K34 = Q/V3 K43 = Q/V4 K30 = CL/V3 S3 = V3 \$DES DADT (1) = -KTR\*A (1); SUS DADT (2) = -KTR\*A (2); TAB DADT (3) = KTR\*A (7) + KTR\*A (14) - K30\*A (3) - K34\*A (3) + K43\*A(4) DADT (4) = K34\*A (3) - K43\*A (4) DADT (5) = KTR\*A (3) - K43\*A (4) DADT (6) = KTR\*A (6) - KTR\*A (6) DADT (7) = KTR\*A (6) - KTR\*A (7) DADT (8) = KTR\*A (6) - KTR\*A (7) DADT (9) = KTR\*A (8) - KTR\*A (7) DADT (10) = KTR\*A (9) - KTR\*A (7) DADT (11) = KTR\*A (10) - KTR\*A (10) DADT (11) = KTR\*A (10) - KTR\*A (11) DADT (12) = KTR\*A (12) - KTR\*A (13) DADT (13) = KTR\*A (13) - KTR\*A (14) DADT (15) = A (3) /V3; AUC \$DES \$FRROR AUC=A (15) M3-Method TYPE=1 IF (DV.LT.LLOQ) TYPE=2 IF (MDV==1) TYPE=0 IF (TYPE.EQ.2) DV\_LOQ=LLOQ PROP = THETA(12)\*F ; proportional part ADD = THETA(13) ; additive part SD=SQRT(PROP\*\*2+ADD\*\*2)

IPRED=F IF(COMACT==1) PREDV=IPRED DUM=(LLOQ-IPRED)/SD CUMD=PHI(DUM) IF (TYPE.NE.2.OR. NPDE\_MODE==1) THEN F\_ELAG=0 Y=IPRED+SD\*ERR (1) ENDIE IF (TYPE.EQ.2.AND.NPDE\_MODE==0) THEN F FLAG=1 YECUMD MDVRES=1 ENDIF IF (TYPE.EQ.2) DV\_LOQ=LLOQ IRES = DV-IPRED IWRES = IRES/SD \$THETA (0, 22,5); 1 KTR-sus (0, 27,5); 2 KTR-tab (0, 6,65); 3 CL (0, 152); 4 V3 central compartment (0, 109); 5 V4 peripheral compartment (0, 46,4); 6 Q (0, 0,683,1); 7 F-sus-max-fed (0, 0,588,1); 8 F-tab (-1, -0.522,1); 9 FOOD proportional impact on KTR-sus (100, 1390); 10 D50-FED (0.188); 11 Proportional error (0.0025); 12 Additive error \$THETA \$OMEGA 0.042;1 KTR-sus 0.0854;2 KTR-tab 0.0934:3 CL 0.0934;3 CL 0.0937;4 V3 0 FIX ;5 V4 0 FIX ;6 Q 0.206;7 F-sus 0.29;8 F-tab 0.29;8 F-tab \$OMEGA BLOCK (1) 0.0945; KTR-IOV \$OMEGA BLOCK (1) SAME \$OMEGA BLOCK \$OMEGA BLOCK SAME (1) SAME \$OMEGA BLOCK \$OMEGA BLOCK SAME 0.401; IOV-FTAB SAME Ì1 \$OMEGA BLOCK \$OMEGA BLOCK (1) SAME \$OMEGA BLOCK (1) SAME \$OMEGA BLOCK (1) SAME \$OMEGA BLOCK (1) SAME

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