Optimizing antifungal treatment through pharmacometrics: dosing considerations to enhance outcome

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Chapter 4

Meta-PK analysis of posaconazole upon dosing of oral suspension, delayed-release tablet, and intravenous infusion in patients versus healthy volunteers: impact of clinical characteristics and race

This chapter is based upon:

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Abstract

Objectives We previously developed an integrated population pharmacokinetic model for posaconazole oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous (IV) infusion in healthy volunteers (HV). Here we extended that model to patients and investigated the potential impact of clinical characteristics and the Chinese race on posaconazole pharmacokinetics.

Methods 1046 concentrations from 105 prospectively studied Caucasian patients receiving either of the three formulations were pooled with 3898 concentrations from 182 HV. Clinical characteristics were tested for significance. The Chinese racial impact was assessed using 292 opportunistic samples from 80 Chinese patients receiving SUS.

Results Bioavailability of the SUS (F_{sus}) in patients decreases from 38.2% to 24.6% when the dose increases from 100 mg to 600 mg. The bioavailability of DR-tablet (F_{tab}) was 59% regardless of dose. Mucositis, diarrhea, administration through a nasogastric tube, and concomitant use of proton pump inhibitors or metoclopramide, respectively reduced F_{sus} by 61%, 36%, 44%, 48%, and 29%, putting patients with these characteristics at increased risk of inadequate exposure. Clearance decreases from 7.0 to 5.1 L/h once patient's albumin is <30 g/L. Patients showed an 84.4% larger peripheral volume of distribution (V_p) and 67.5% lower intercompartmental clearance (Q) compared to HV. No racial difference could be identified.

Conclusions Posaconazole pharmacokinetics is considerably different in patients *versus* HV, with altered F_{sus} that is also impacted by clinical covariates, a F_{tab} similar to fasted conditions in HV, and altered parameters for clearance, V_p, and Q. No evidence suggests that Chinese patients require a different dose compared to Caucasian patients.

Keywords formulation, oral bioavailability, nonlinearity, hematology patient, Chinese

4.1 Introduction

Posaconazole is widely used for preventing or treating invasive fungal diseases (IFDs). It is currently available as an oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous (IV) infusion [1, 2]. We previously performed an integrated analysis characterizing the pharmacokinetics of all three formulations in healthy volunteers (HV), but these findings cannot be directly extrapolated to patients as their physiology may be altered or impacted by concomitant treatment. Particularly in hematology patients, pathologies and concomitant treatments are anticipated to decrease posaconazole exposure, putting them at risk for breakthrough infections or therapeutic failure [3-5]. Moreover, Chinese population was reported to have a reduced clearance (CL) compared to the global population [6], but this has not yet been confirmed in clinical practice. Although exact targets remain debated, in both prophylactic and therapeutic settings higher treatment success rates were achieved in patients with higher posaconazole exposure [7, 8].

In this study, we expand the integrated population pharmacokinetic model for all three posaconazole formulations in HV to patients, by quantifying the pharmacokinetics and investigating the influence of clinical characteristics and the Chinese race.

4.2 Methods

4.2.1 Data included in the analysis

Pharmacokinetic data were pooled from two published patient studies, hereafter referred to as patient study 1 (SUS) [7] and patient study 2 (DR-tablet and IV) [9], and eight studies in HV [10], both including mainly Caucasian individuals (see Table 1). This included 1046 concentrations from 105 patients (92% were diagnosed with hematological malignancy) receiving either of the three posaconazole formulations under various dosage regimens [7, 9] and 3898 concentrations from 182 HV that were previously analyzed [10].

In addition, a total of 292 opportunistic blood measurements (>90% trough level) from 80 Chinese patients receiving posaconazole SUS were collected from the First Affiliated Hospital of Xi'an Jiaotong University between Jan 2016 to June 2018 (Table 1). For these samples, a validated liquid chromatography-tandem mass spectrometry assay was used to measure posaconazole plasma concentrations within a quantification range from 0.005 to 5.0 mg/L [11]. Information on drug prescriptions, sampling times, and covariates was retrieved from the electronic health record using a standardized template. The actual dosing time of the SUS for these Chinese patients was not reported and thus assumed to be each mealtime at 8:00, 12:00, and 19:00, starting at the first meal after the prescription.

Table 1 Summary of the pharmacokinetic data from healthy volunteers and patients[a] included in this analysis

Characteristics		SUS			DR-tablet		IV	
Population [reference]		HV [12-14]	Patients [7]		HV [13, 15]	Patients [9]	HV [13, 16-18]	Patients [9]
No. of studies		3	1 (study 1)	1	3	1 (study 2)	4	1 (study 2)
No. of subjects		75	82	80	67	19	74	21
Race		Caucasian	Caucasian [7]	Chinese	Caucasian	Caucasian	Caucasian	Caucasian
Dosage (mg)	Single dose	100	NA	NA	100, 300, 400	NA	50, 100, 200, 250, 300	NA
	Multiple dose	Day 1: 200 qd; Day 2: 200 bid; Day 3-10: 400 bid	median dose (range): prophylaxis: 200 tid (40 bid - 300 tid); treatment: 400 bid (200 tid - 400 tid)	median dose: 400 mg bid (range 100 mg bid to 300 mg tid)	300 mg bid on day 1 followed by 300 qd	Day 1: 300 bid; Day 2-12: 300 qd; Day 13: 200 qd	NA	Day 1: 300 bid; Day 2-12: 300 qd; Day 13: 200 qd
Duration of sampling after the last dose (h)	Single dose	168	NA	NA	168	NA	48 - 168	NA
	Multiple dose	12	21S	94	48	26	NA	28
No. of concentrations		1028	465	292	1924	263	946	318
No. of BQL concentrations		141 (13.7%)	35 (7.5%)	0 (0%)	110 (5.7%)	1 (0.38)	48 (5.1%)	0 (0%)
No. of concentrations per subject, median (range)		13 (11-16)	3 (1-42)	2.5 (1-18)	13 (2-65)	17 (1-28)	12 (10-20)	16 (1-26)
Available covariates		Food status	Mucositis, administration through a nasogastric tube, diarrhea, PPIs, metoclopramide, ranitidine, sex, age, weight, BMI	Diarrhea, PPIs, sex, age, weight	Food status, comedications (antacid, ranitidine, esomeprazole, metoclopramide)	Mucositis, plasma citrulline, albumin, hematocrit, sex, age, weight, BMI	NA	Sex, age, weight, BMI

SUS oral suspension, *DR-tablet* delayed-release tablet, *IV* intravenous infusion, *HV* healthy volunteer, *NA* not applicable, *BQL* below the quantification limit, *bid* twice daily, *tid* three times daily, *qd* once daily, *PPIs* proton pump inhibitors, *BMI* body mass index

[a]89% of all patients are hematology patients. The proportion of hematology patients in Caucasian patients who received posaconazole SUS [7], in Chinese patients who received posaconazole SUS, and in Caucasian patients who received crossover DR-tablet and IV [9], is 91%, 85%, and 100%, respectively.

4.2.2 Population pharmacokinetic model

The population pharmacokinetic model was developed using the nonlinear mixed-effects modeling software NONMEM 7.5.0 supported by Pirana 3.0.0, PsN 5.2.6, and Xpose 4.7.2 [19]. In patients, 3.44% of concentrations below the quantification limit were excluded.

The model structure was adapted from the HV model [10], which included a two-compartment model with respectively four and eight absorption transit compartments for SUS and DR-tablet. In patients, adjustments in the number of absorption transit compartments were tested for the DR-tablet (study 2) [9], but not for the SUS because of the sparse nature of the data (study 1) [7]. Inter-individual variability (IIV) was included on bioavailability (F), the first-order rate constant between absorption transit compartments (k_{tr}), CL, and volume of distribution of the central compartment (V_c). Different error models were assessed for each patient study to describe residual unexplained variability. Structural and stochastic model selection was based on the reduction objective function value (OFV) 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 population.

Concentration-nonlinearity was tested on CL using the Michaelis-Menten equation. Like HV [10], dose-nonlinearity on F was incorporated *a priori* for the SUS in patients using a sigmoidal function but with parameters reestimated to values independent of food-status, as information on food-status was missing in patient's data. Tested covariates and their distribution were respectively summarized in Table S1 and Table S2. Correlation among the continuous covariates was summarized in Fig. S1. Binary covariates including concurrent diarrhea, mucositis, administration through nasogastric tubes, and comedication of proton pump inhibitors (PPIs), metoclopramide, or ranitidine, were investigated on both k_{tr} and F of the SUS (F_{sus}). Mucositis as binary covariate and continuous citrulline levels were tested as covariates on both k_{tr} and F of the DR-tablet (F_{tab}). Albumin and hematocrit levels were available from study 2 [9] and were investigated as continuous covariates on CL, V_c, the peripheral volume of distribution (V_p), and intercompartmental clearance (Q). Hypoalbuminemia was also tested as a binary covariate with three different cut-offs at <35, <30, and <25 g/L. Demographic covariates, including sex, age, and weight, were tested on the disposition parameters. Being a patient was tested as a binary covariate on each pharmacokinetic parameter as well as an additional IIV at the end of the covariate analysis, to prevent early identification of this covariate as a surrogate for a more mechanistic covariate. If a covariate was unique to a specific study, it was exclusively evaluated within that study. The covariate analysis followed a forward inclusion and backward deletion step, using an OFV decrease of >3.84 (P <0.05) and >10.83 (P <0.001) for statistical significance, respectively. Shark plots in

Xpose 4 were used to ascertain that the statistical significance of covariate effects was driven by a sufficient number of individuals [20].

Potential pharmacokinetic differences in Chinese patients were assessed. First, the final model developed for Caucasian patients was directly extrapolated to Chinese patients to inspect the fit from (stratified) GOF-plots and normalized prediction distribution error (NPDE). Second, the distribution of individual parameter values between the Chinese patients and Caucasian patients was visually inspected for potential bias. Subsequently, the Chinese race was tested as binary covariate on all parameters. Finally, the model fit was assessed upon inclusion of a 25% CL reduction in Chinese patients, according to a previous finding in Chinese subjects [6].

The predictive performance of the final model in Caucasian patients was assessed by an NPDE analysis based on 1,000 simulations and stratified by formulation. Validation results for the HV were presented previously [10].

4.2.3 Illustration of model findings

To illustrate differences among the posaconazole formulations and the obtained covariate effects, we simulated typical concentration-time profiles of recommended dosage regimens for each formulation in hypothetical patients with different covariates. For the SUS this included 200 mg three times daily (tid) for prophylaxis of IFDs, 400 mg two times daily (bid), and 200 mg four times daily (qid) for treatment purposes. For the DR-tablet and IV, a loading dose of 300 mg bid on the first day followed by a maintenance dose of 300 mg once daily (qd) was simulated [1, 2]. Stochastic simulations incorporating the IIV were performed in 1000 virtual patients to illustrate the distribution of trough concentrations (C_{trough}) and 24-h area under the curve (AUC_{24h}) on day 1, 5, and 14.

4.3 Results

4.3.1 Population pharmacokinetic model

The same number of transit compartments from the healthy volunteers remained the best option for describing the absorption of the DR-tablet in patients (study 2) [9]. Fig. S2 shows the model structure [10] that was used to describe the pharmacokinetic data in patients and HV. A proportional and a combined residual error model were respectively applied for patient study 1 [7] and patient study 2 [9]. Parameter estimates of the final model are presented in Table 2 and the corresponding NONMEM code is provided in the supplement.

Table 2 Posaconazole pharmacokinetic parameter estimates in the final model

Population parameter value [unit]	Parameter estimate (RSE%) [%shrinkage]
$F_{sus} = F_{sus,max} \times \left(1 - \frac{Dose}{Dose + D_{50}}\right) \times (1 + \theta_{F_{sus},MUC}) \times (1 + \theta_{F_{sus},PPIs}) \times (1 + \theta_{F_{sus},NG}) \times (1 + \theta_{F_{sus},DIAR}) \times (1 + \theta_{F_{sus},METO})$	
$F_{sus,max}$ [%]	0.429 (10.5)
D_{50} [mg]	806 (fixed)
$\theta_{F_{sus},MUC}$ [-]	-0.608 (6.80)
$\theta_{F_{sus},PPIs}$ [-]	-0.484 (9.0)
$\theta_{F_{sus},NG}$ [-]	-0.440 (13.0)
$\theta_{F_{sus},DIAR}$ [-]	-0.362 (19.2)
$\theta_{F_{sus},METO}$ [-]	-0.292 (32.4)
F_{tab} [%]	0.588 (fixed)
$k_{tr,sus} = k_{tr,sus,noCOV} \times (1 + \theta_{k_{tr},sus,PPIs})$	
$k_{tr,sus,noCOV}$ [h^{-1}]	2.21 (3.30)
$\theta_{k_{tr},sus,PPIs}$ [-]	-0.857 (2.70)
$k_{tr,tab}$ [h^{-1}]	2.52 (2.40)
$CL = CL_{noCOV} \times (1 + \theta_{CL,hypoalbuminemia})$	
CL_{noCOV} [L/h]	7.03 (3.30)
$\theta_{CL,hypoalbuminemia}$ [-]	-0.276 (20.3)
V_c [L]	144 (4.70)
$V_{p,PAT} = V_{p,HV} \times (1 + \theta_{V_p,PAT})$	
$V_{p,HV}$ [L]	119 (3.10)
$\theta_{V_p,PAT}$ [-]	0.844 (29.7)
$Q_{PAT} = Q_{HV} \times (1 + \theta_{Q,PAT})$	
Q_{HV} [L/h]	50.6 (4.90)
$\theta_{Q,PAT}$ [-]	-0.675 (10.3)
Inter-individual variability in %CV	
F_{sus} [a,b]	0.285 (22.7) [43.4]
F_{tab} [a,b]	0.553 (58.4) [55.7]
$k_{tr,sus}$	20.5 (10.1) [58.3]
$k_{tr,tab}$	27.3 (11.2) [53.0]
CL	32.1 (6.10) [14.5]
V_c	38.3 (11.5) [29.6]
Residual error in %CV	
$\sigma_{prop,study1}$	47.6 (5.50) [6.90]
$\sigma_{prop,study2}$	16.2 (10.8) [4.80]
$\sigma_{addi,study2}$ (mg/L)	0.0712 (31.6) [4.80]

RSE relative standard error of the estimate, *F* absolute oral bioavailability, F_{sus} population value of F for the oral suspension $F_{sus,max}$ the maximum F_{sus}, D_{50} oral suspension dose that could achieve half of the $F_{sus,max}$, $\theta_{F_{sus},MUC}$ proportional influence of mucositis on F_{sus}, $\theta_{F_{sus},NG}$ proportional influence of using a nasogastric tube on F_{sus}, $\theta_{F_{sus},PPIs}$ proportional influence of concomitant use of proton pump inhibitors on F_{sus}, $\theta_{F_{sus},DIAR}$ proportional influence of diarrhea on F_{sus}, $\theta_{F_{sus},METO}$ proportional influence of concomitant use of metoclopramide on F_{sus}, *DR-tablet* delayed-release tablet, F_{tab} population value of F for DR-tablet, k_{tr} first-order absorption rate constant, and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, $k_{tr,sus,noCOV}$ $k_{tr,sus}$ without covariate impact, $\theta_{k_{tr},sus,PPIs}$ proportional influence of concomitant use of proton pump inhibitors on $k_{tr,sus}$, $k_{tr,tab}$ k_{tr} of the DR-tablet regardless of food intake, *CL* clearance, CL_{noCOV} CL without covariate impact, $\theta_{CL,hypoalbuminemia}$ proportional influence of hypoalbuminemia on CL, V_c volume of distribution of the central compartment, V_p volume of distribution of the peripheral compartment, $V_{p,PAT}$ V_p in patients, $V_{p,HV}$ V_p in healthy volunteers, $\theta_{V_p,PAT}$ proportional influence of being a patient on V_p, *Q* intercompartment clearance between central and peripheral compartments, Q_{PAT} Q in patients, Q_{HV} Q in healthy volunteers, $\theta_{Q,PAT}$ proportional influence of being a patient on Q, *CV* coefficient of variation, $\sigma_{prop,study1}$ proportional residual error in study 1 [7], $\sigma_{prop,study2}$ proportional residual error in study 2 [9], σ_{addi} additive residual error in study 2 [9].

[a]The variability of F was added within the logit domain and is presented as the variance[b]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 interval for 200 mg and 400 mg of oral suspension were 15.5-59.9% and 12.4-53.4% respectively. The 95% distribution interval for the DR-tablet is 24.9-86.0% regardless of dose

Compared with the HV, patients showed an 84.4% larger V_p and 67.5% lower Q. Yet, no significant difference in V_c and CL could be identified between patients *versus* HV. A different nonlinear F_{sus} with a lower maximum F_{sus} was identified in patients vs. HV. Using a nonlinear equation (see Table 2) it was derived that in patients the typical F_{sus} decreases from 38.2% to 24.6% with a dose increase from 100 mg to 600 mg, regardless of food-status. Additionally, mucositis, diarrhea, administration through a nasogastric tube, and concomitant use of PPIs or metoclopramide, reduced the F_{sus} proportionally by 60.8%, 36.2%, 44.0%, 48.4%, and 29.2%, respectively. PPIs were also found to reduce the k_{tr} of the SUS by 85.7%, causing a delay in peak concentrations. For the DR-tablet, F in patients was 58.8%, which is comparable to the value for HV. The typical F of the two posaconazole oral formulations under various scenarios is illustrated in Fig. 1. Incorporating nonlinear CL in patients did not improve the model significantly (P>0.05). Opposed to incorporating albumin as a continuous covariate on CL, having hypoalbuminemia as a binary covariate with an optimized cut-off at 30 g/L statistically significantly improves the fit. The estimates indicate that patients presented with hypoalbuminemia have an altered CL of 5.1 L/h compared with the CL of 7.0 L/h in those without. No significant differences in the IIV between HV and patients could be identified.

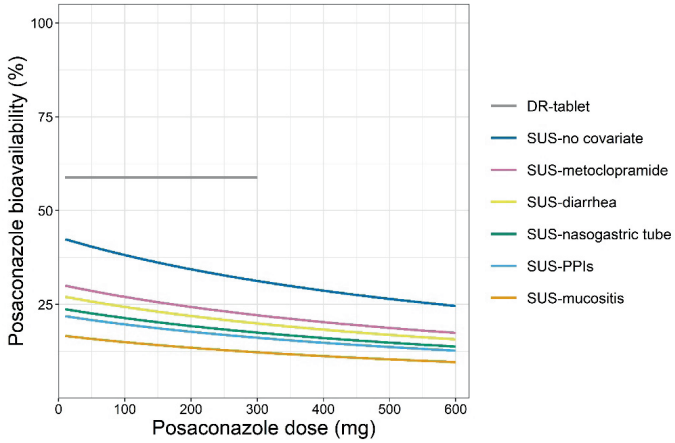

Fig. 1 Posaconazole bioavailability *versus* dose in the studied dose ranges for the delayed-released tablet (DR-tablet, no covariates were identified) and the oral suspension (SUS) in patients with and without the presence of a single covariate effect.

PPIs proton pump inhibitors

Stratified GOF-plots of the final model in supplementary Fig. S3 and Fig. S4 suggest that the model describes both healthy volunteers and Caucasian patients' data well for each formulation. The stratified NPDE results in supplementary Fig. S5 and Fig. S6 indicate an accurate predictive performance of the final model regarding both the structural and stochastic model for both population under each formulation. The GOF-plots in Fig. 2 and the NPDE results in Fig. S7 demonstrate that the pharmacokinetics in Chinese patients are not distinct from the Caucasian patients

after employing a direct extrapolation from the final model. The increased variability in Chinese patients observed in the NPDE likely results from assumptions for dose time. Moreover, the distribution of individual parameter deviations of Chinese patients *versus* Caucasian patients (Fig. S8), approximates a normal distribution with a mean of 0, as expected for a population that does not deviate from the population that was used to develop a model. Estimated deviations in parameter values for Chinese patients compared to Caucasian patients were negligible and lacked statistical significance. Incorporating 25% lower CL in our Chinese patients did not improve the model fit coupled with an increased OFV (P <0.001). Combined, all these results suggest the pharmacokinetics of posaconazole in Chinese patients to not be different from Caucasian patients.

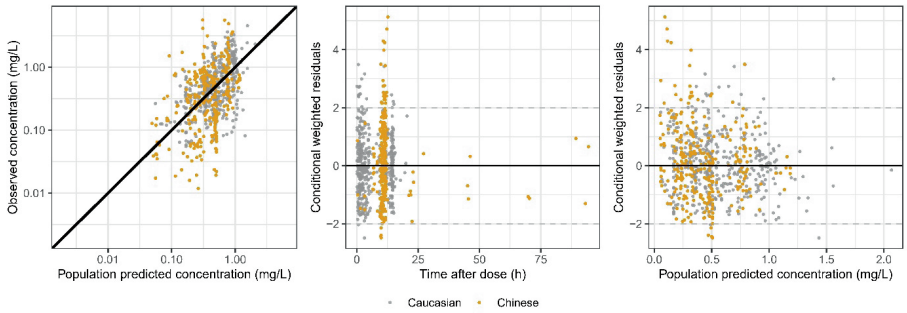

Fig. 2 Goodness-of-fit plots of the final model in the Caucasian (grey) and Chinese patients (orange) receiving the oral suspension.

4.3.2 Illustration of model findings

Since all clinical covariates retained in the final model are binary, the exposure for each clinical scenario was independently simulated and compared with the scenario where the covariate was absent. Fig. 3 presents the simulated typical concentration-time profiles in patients receiving recommended dosages of three posaconazole formulations. All covariate effects except for hypoalbuminemia, lead to a decreased exposure of the SUS, owing to a decreased F_{sus}. We report here that the standard DR-tablet regimen does not have an equivalent exposure to the IV formulation. Despite a lower daily dose compared with the SUS regimens, the DR-tablet attains a similar or higher exposure in the presence of a single covariate. Among the three SUS regimens, 200 mg qid showed the highest exposure.

Fig. 4 presents the distribution of simulated posaconazole C_{trough} and AUC_{24h} in patients on day 1, 5, and 14 in 1000 simulated patients. Without a covariate effect, the probability of target attainment (PTA) of a C_{trough} of ≥0.7 mg/L on day 14 is respectively 66%, 55%, and 90%, using the recommended prophylactic regimen

of SUS 200 mg tid, DR-tablet and IV 300 mg qd. Patients who have mucositis, diarrhea, administration through a nasogastric tube, or concomitant use of PPIs or metoclopramide receiving the prophylactic SUS regimen, achieve a PTA of C_{trough} ≥0.7 mg/L on day 14 ranging from 10%-44%. Without covariate effect, the PTA of C_{trough} ≥1.0 mg/L is respectively 65%, 31%, 28%, and 71%, using the recommended therapeutic regimen of SUS 200 mg qid and 400 mg bid, DR-tablet and IV 300 mg qd, which decreased to respectively 48%, 18%, 15%, and 51%, for the target of C_{trough} ≥1.25 mg/L.

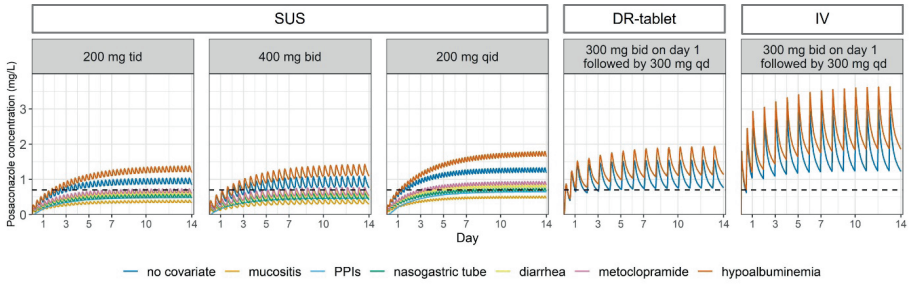

Fig. 3 Typical concentration-time profiles in patients receiving recommended posaconazole doses for oral suspension (SUS), delayed-release tablet (DR-tablet), and intravenous infusion (IV) for two weeks. Profiles were simulated under scenarios with or without single covariates with only relevant covariates included for each formulation. The horizontal dashed line (0.7 mg/L) represents the trough concentration target for prophylaxis in patients.

PPIs proton pump inhibitors, *tid* three times daily, *bid* two times daily, *qd* once daily

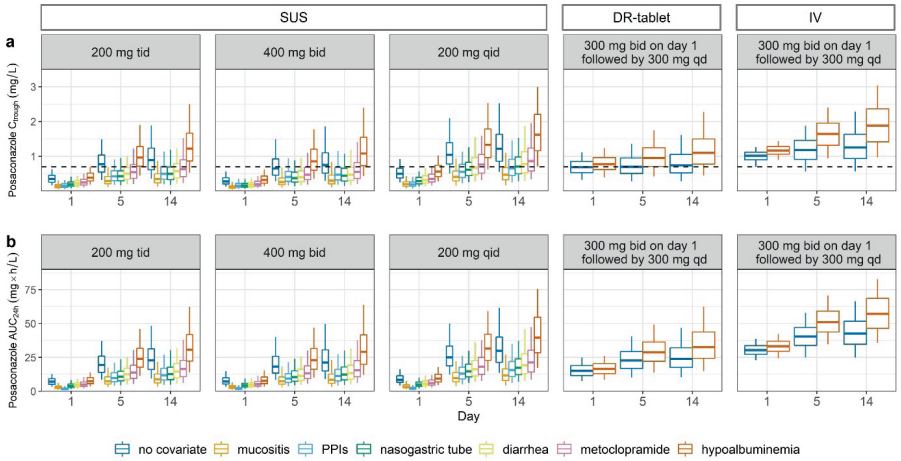

Fig. 4 Distribution of trough concentrations (**a**) and area under the curve per day (AUC_{24h}) (**b**) in 1000 simulated patients receiving recommended posaconazole regimens for the oral suspension (SUS), delayed-release tablet (DR-tablet) and intravenous infusion (IV). Profiles were simulated under scenarios with or without single covariates with only relevant covariates included for each formulation. The boxes represent the 25th, 50th (median), and 75th percentiles, and whiskers represent the 5th and 95th percentiles (i.e., 90% distribution interval). In **a**, the horizontal dashed line represents the concentration target for prophylaxis (0.7 mg/L).

tid three times daily, *bid* two times daily, *qid* four times daily dosing, *qd* once daily

4.4 Discussion

This study is the first to characterize the pharmacokinetics of all currently available formulations of posaconazole in predominantly Caucasian hematology patients in comparison to healthy volunteers. Posaconazole pharmacokinetics in patients is considerably different compared to HV, with altered F_{sus} that is also impacted by clinical covariates, a F_{tab} similar to fasted conditions in HV, and altered parameters for CL, V_p, and Q. F_{tab} is overall higher than the dose-dependent nonlinear F_{sus} and is unaffected by the tested covariates, reasserting the pharmacokinetic superiority of the DR-tablet in patients. No evidence of a racial difference could be found for Chinese patients.

Covariate analysis indicates that patients have an altered typical value of V_p and Q *versus* HV, and those with hypoalbuminemia also have an altered CL. A larger V_p was also reported in patients *versus* HV [6], possibly owing to the capillary leakage, leading to a decreased C_{trough} for all formulations along with the lower Q found in our study. Hypoalbuminemia likely acts as a surrogate for kidney disease and/or severe illness [21], which explains the lower posaconazole CL. In this case, albumin level at 30 g/L, separating normal and mild hypoalbuminemia from moderate and severe hypoalbuminemia [22], was statistically the best cut-off. Mucositis and citrulline level were included on neither F_{tab} nor the k_{tr} of the DR-tablet because it did not reach statistical significance (P<0.05) or the significance was merely driven by one patient. In the Chinese data, the high proportion of trough concentrations could barely inform the absorption, especially considering the missing accurate dosing time and food status, an external validation approach was applied to assess the influence of Chinese race. Yet with the limited data, no evidence points to a different pharmacokinetics of posaconazole between Chinese and Caucasian patients.

Compared to the data from healthy volunteers, the patient data is notably sparser during the absorption phase. Despite an average of two to six samples collected within the first six hours after dosing for each patient, this data did not provide sufficient information to support a separate IIV for the two absorption parameters (i.e., F and KTR) in patients as opposed to healthy volunteers. Consequently, all populations, including healthy individuals and patients with varying degrees of illness, shared the same variability, potentially contributing to the significant shrinkage observed in the IIV estimates for F and KTR. However, posaconazole is known for its erratic absorption, and considerable variability has been previously reported and observed in the current data. Despite the high shrinkage values, the inclusion of IIV substantially improved the model fit and was retained in the final model. To achieve the reported, yet not broadly recognized, posaconazole AUC_{24}/MIC target of 167-178 for treating aspergillosis [23-25], a deduced minimum AUC_{24} of 22.3 mg*h/L is required [26]. For this target, the recommended posaconazole SUS therapeutic doses of 400 mg bid or 200 mg qid, respectively yield a PTA of >46% or >71% at steady state in patients

without any of the clinical covariates (Fig. 4) [10]. A lower PTA is achieved when posaconazole SUS is administered to patients with one or more of the identified covariates. The standard IV dose yields an AUC_{24} ≥22.3 mg*h/L in more than 95% of all patients at steady state, while the recommended dosage of DR-tablet only yields a PTA of 81% in patients with hypoalbuminemia and 57% in those without. For this reason, both SUS and DR-tablet should be used with caution for treating Aspergillus with MIC ≥ 0.25 mg/L. Starting with a higher dose and applying therapeutic drug monitoring during the treatment can be helpful regarding the considerable variability in exposure and pathogen susceptibility.

Although lower F for both SUS and DR-tablet was demonstrated in HV under fasted *versus* fed conditions, it should be noted that both F in this study represent intermediate values between fasted and fed conditions as details on food-status were missing for patients. Yet, since 91% of the patients receiving posaconazole SUS and all patients receiving posaconazole DR-tablet suffered from hematological malignancies and they are commonly not capable of taking food, the estimated F is considered to resemble the F under fasted conditions. The higher dose and dosing frequency of the SUS regimens, can to some degree compensate for the low F_{sus}, even resulting in higher C_{trough} compared with the DR-tablet in the absence of covariates (Fig. 3). However in clinical practice, patients who receive posaconazole SUS but are without any of the clinical covariates are hardly ever encountered, which increases the risk of under-exposure.

4.5 Conclusion

Patients have altered posaconazole pharmacokinetics compared to HV which are also impacted by clinical covariates. Model performance was equal for Caucasian and Chinese patients, indicating that a different dose is not needed. For patients, the DR-tablet is superior to SUS with a higher and more stable F, but is not equivalent to IV, as commonly assumed. A considerable proportion of patients is at risk of inadequate exposure when receiving oral posaconazole at standard dose, irrespective of prophylaxis or treatment. In patients with insufficient exposure, switching to IV or increasing DR-tablet dose coupled with therapeutic drug monitoring should be considered to ensure adequate drug exposure.

4.6 Supplementary materials

Table S1 Covariates analyzed during the population pharmacokinetic analysis.

Parameters	F_{sus}	$k_{tr,sus}$	F_{tab}	$k_{tr,tab}$	CL	Q	V_c	V_p
Clinical characteristics	Covariates that could indicate gastrointestinal permeability, or could alter absorption transit time, motility, and gastrointestinal pH: mucositis, administration via nasogastric tube, diarrhea, proton pump inhibitors, metoclopramide, ranitidine		Covariates that could indicate gastrointestinal permeability: mucositis, citrulline		Covariates that could influence posaconazole distribution and clearance of posaconazole in the blood: albumin, hypoalbuminemia, hematocrit			
Population	patient vs. healthy volunteers							
Demographics	sex, age, weight, BMI							

BMI body mass index F_{sus} population value of bioavailability for the oral suspension, F_{tab} population value of bioavailability for DR-tablet, k_{tr} first-order absorption rate constant, and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, *CL* clearance, V_c volume of distribution of the central compartment, V_p volume of distribution of the peripheral compartment, *Q* intercompartmental clearance between central and peripheral compartments

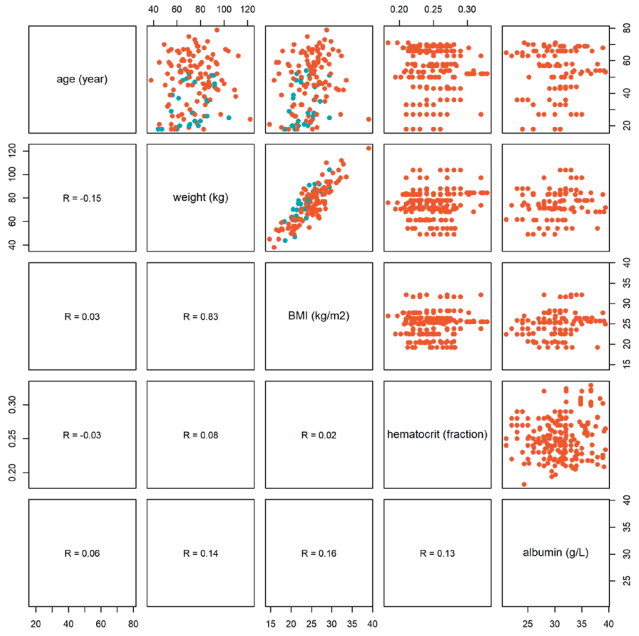

Fig. S1 Correlation between analyzed continuous covariates colored by population (blue = healthy volunteers, orange = patients).

BMI body mass index, *R* Pearson correlation coefficient

Table S2 Summary of the analyzed covariates in the pharmacokinetic analysis.

Characteristics		SUS			DR-tablet		IV	
Population [reference]		HV [12-14]	Patients [7]		HV [13, 15]	Patients [9]	HV [13, 16-18]	Patients [9]
No. of studies		3	1 (study 1)	1	3	1 (study 2)	4	1 (study 2)
No. of subjects		75	82	80	67	19	74	21
Race		Caucasian	Caucasian [7]	Chinese	Caucasian	Caucasian	Caucasian	Caucasian
Continuous covariates	age (year)	37.5 [18, 54]	50 [18, 79]	39 [12, 82]	NA	57 [27, 71]	22 [20, 37]	54 [18, 70]
	weight (kg)	74 [44, 104]	71 [38, 122]	58.5 [32.1, 90]	NA	76.1 [49.1, 104]	72.2 [61.4, 85.4]	77.3 [49.1, 97.2]
	BMI (kg/m2)	23.1 [18.3, 29.4]	24.9 [14.7, 39]	NA	NA	25.5 [19.2, 31.7]	22.5 [20.2, 25.4]	25.3 [19.2, 32.1]
	hematocrit (fraction)	NA	NA	NA	NA	0.26 [0.197, 0.303]	NA	0.247 [0.21, 0.303]
	albumin (g/L)	NA	NA	31.4 [18.9, 45]	NA	30 [24, 39.4]	NA	30 [22, 39.4]
	citrulline (µmol/L)	NA	NA	NA	NA	8.8 [5.6, 26.4]	NA	8.7 [5, 14.2]
Categorical covariates[a]	female (%)	45	43	45	NA	58	50	52
	nasogastric tube (%)	0	10	0	0	NA	0	NA
	mucositis (%)	0	39	18	0	79	0	90
	diarrhea (%)	0	40	9	0	NA	0	NA
	PPIs (%)	0	51	68	0	NA	0	NA
	ranitidine (%)	0	37	0	0	NA	0	NA
	metoclopramide (%)	0	33	0	0	NA	0	NA
	hypoalbuminemia (%)	0	NA	NA	0	63	0	67

SUS oral suspension, *DR-tablet* delayed-release tablet, *IV* intravenous infusion, *HV* healthy volunteer, *NA* not available, *BMI* body mass index, *PPIs* proton pump inhibitors

[a]All categorical covariates, with the exception of the female percentage, were time-varying covariates, and their percentage rates reflect the proportion of patients who exhibited the respective covariate scenario at least once.

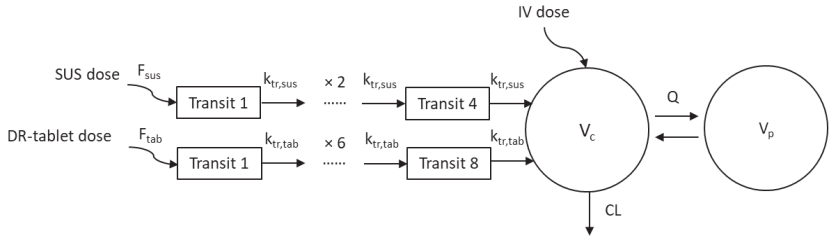

Fig. S2 Schematic representation of the integrated pharmacokinetic model for three formulations of posaconazole.

SUS oral suspension, *DR-tablet* delayed-release tablet, *IV* intravenous infusion, *F* absolute bioavailability, F_{sus} F of the oral suspension, F_{tab} F of the DR-tablet, k_{tr} first-order absorption rate constant and the rate constant between absorption transit compartments, $k_{tr,sus}$ k_{tr} of the oral suspension, $k_{tr,tab}$ k_{tr} of the delayed-release tablet, *CL* clearance, V_c the volume of distribution of the central compartment, V_p the volume of distribution of the peripheral compartment, *Q* intercompartment clearance

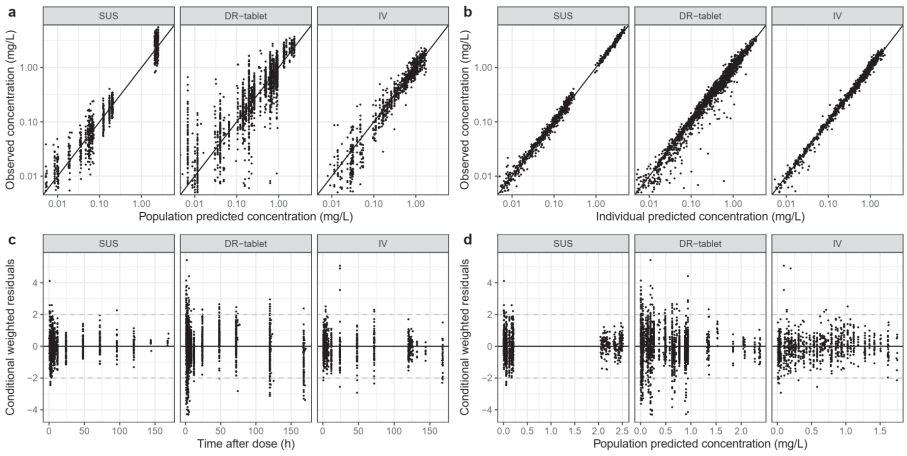

Fig. S3. Goodness-of-fit plots of the final model for oral suspension (SUS, left), delayed-release tablet (DR-tablet, middle) and intravenous infusion (IV, right) in healthy volunteers, with (a) observed *versus* population predicted posaconazole concentrations, (b) observed *versus* individual predicted posaconazole concentrations, (c) conditional weighted residuals *versus* time after dose and (d) *versus* population predicted posaconazole concentrations. The solid lines in each panel represent the line of identity (in panels (a) and (b)), and y=0 (in panels (c) and (d)). The gray dashed lines (in panels (c) and (d)) outlined the predicted 95% reference range assuming a standard normal distribution.

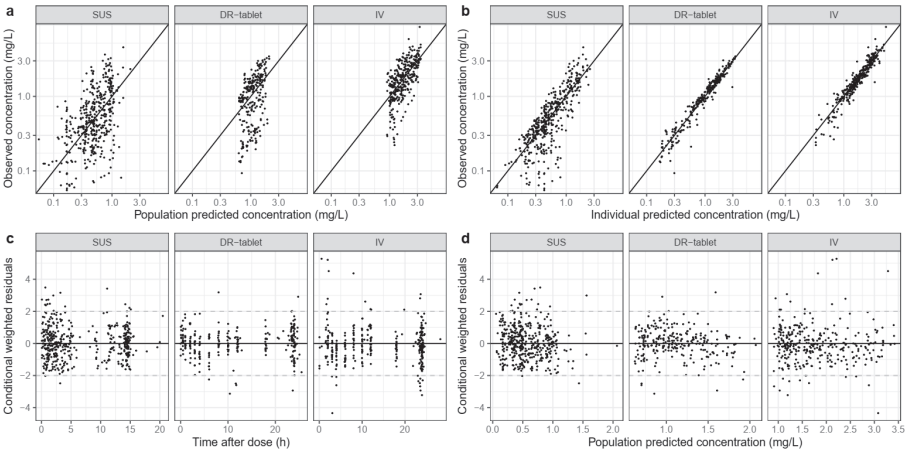

Fig. S4. Goodness-of-fit plots of the final model for oral suspension (SUS, left), delayed-release tablet (DR-tablet, middle) and intravenous infusion (IV, right) in Caucasian patients, with (a) observed *versus* population predicted posaconazole concentrations, (b) observed *versus* individual predicted posaconazole concentrations, (c) conditional weighted residuals *versus* time after dose and (d) *versus* population predicted posaconazole concentrations. The solid lines in each panel represent the line of identity (in panels (a) and (b)), and y=0 (in panels (c) and (d)). The gray dashed lines (in panels (c) and (d)) outlined the predicted 95% reference range assuming a standard normal distribution.

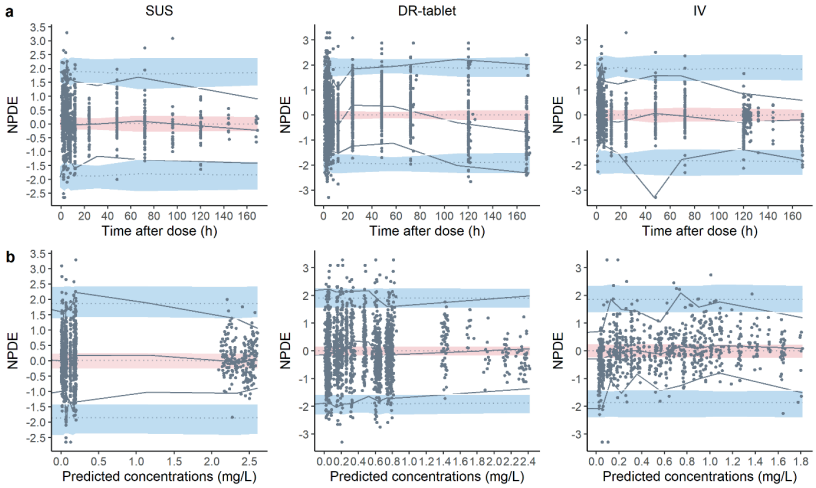

Fig. S5 Normalized prediction distribution error (NPDE) results in healthy volunteers based on the final model for oral suspension (SUS, left), delayed-release tablet (DR-tablet, middle), and intravenous infusion (IV, right), with (a) NPDE *versus* time after dose, (b) NPDE *versus* predicted concentration. In plot **a** and **b**, each 95% prediction interval of simulated concentrations (n = 1000) is plotted as a colored area (blue for the 2.5th and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed and predicted data are plotted as solid and dotted lines, respectively.

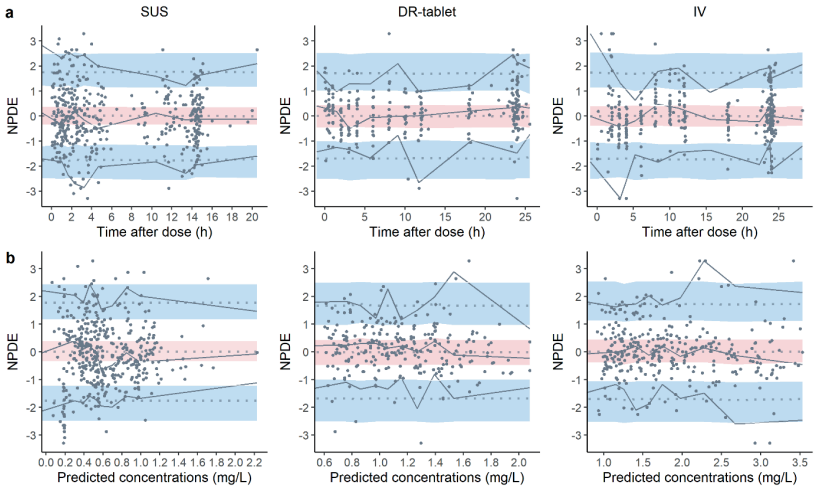

Fig. S6 Normalized prediction distribution error (NPDE) results in Caucasian patients based on the final model for oral suspension (SUS, left), delayed-release tablet (DR-tablet, middle), and intravenous infusion (IV, right), with (a) NPDE *versus* time after dose, (b) NPDE *versus* predicted concentration. In plot **a** and **b**, each 95% prediction interval of simulated concentrations (n = 1000) is plotted as a colored area (blue for the 2.5th and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed and predicted data are plotted as solid and dotted lines, respectively.

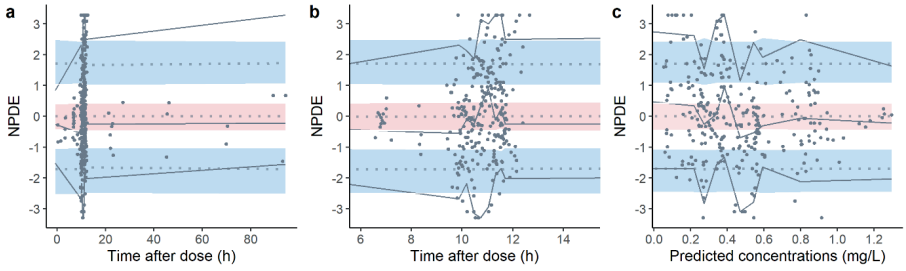

Fig. S7 Normalized prediction distribution error (NPDE) results in Chinese patients receiving the oral suspension based on the final model with (a) NPDE *versus* time after dose for all observations, (b) NPDE *versus* time after dose with the subset of observations within the most densely (>90%) sampled time interval ranging from 6 h to 15 h, (c) NPDE *versus* predicted concentration. In all plots, each 95% prediction interval of simulated concentrations (n = 1000) is plotted as a colored area (blue for the 2.5th and 97.5th percentiles and pink for the median). The corresponding 2.5th, 50th, and 97.5th percentiles of the observed and predicted data are plotted as solid and dotted lines, respectively.

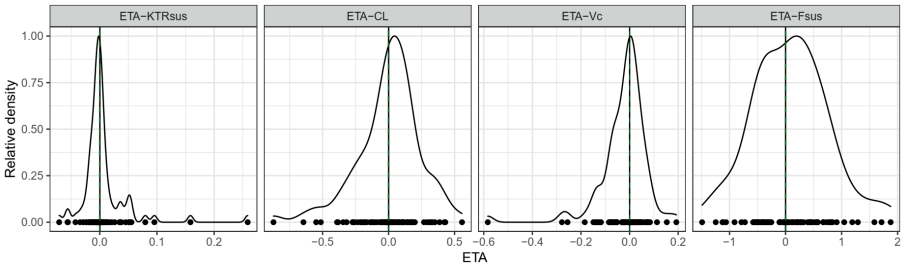

Fig. S8. Distribution of the individual parameter deviations (ETAs) of four pharmacokinetic parameters for Chinese patients receiving the oral suspension from the final estimates in Caucasian patients. MAXEVAL=0 was used in the estimation step to obtain the ETAs of the Chinese patients conditional on the Caucasian patients to achieve the best fit for the Chinese data. The solid vertical lines in plots represent the median of the ETAs (black solid) which overlap with the line x = 0 (green dashed), suggesting that the pharmacokinetic parameters in Chinese patients do not differ from those in Caucasian patients.

NONMEM Control Stream for the Final Model

```
$PROBLEM posaconazole PK of 3 formulations in healthy volunteers and patients
$INPUT ID TIME TAD DV MDV AMT ADDL II CMT RATE EVID DOSE LLOQ BLOQ FORM PAT STU MD OCC DENSE FOOD PPI MYL
RANT ESOM METO FOS NG MUC DIAR SEX AGE WT HT BMI CENTER HP ALB HPOA CITR HEMA
$DATA 367POS_HV_Patients_combineData_20220220.csv
IGNORE=@ IGNORE=(FOS==1) IGNORE=(BLOQ==1) IGNORE=(STU==11)
$SUB ADVAN13 TOL=9

$MODEL
COMP=(DEPOT1) ;1
COMP=(DEPOT2) ;2
COMP=(CENT) ;3
COMP=(PERI) ;4
COMP=(TRANS1) ;5 1st transit compartment SUS
COMP=(TRANS2) ;6 2nd transit compartment SUS
COMP=(TRANS3) ;7 3rd transit compartment SUS
COMP=(TRANS5) ;8 1st transit compartment DR-tab
COMP=(TRANS6) ;9 2nd transit compartment DR-tab
COMP=(TRANS7) ;10 3rd transit compartment DR-tab
COMP=(TRANS8) ;11 4th transit compartment DR-tab
COMP=(TRANS9) ;12 5th transit compartment DR-tab
COMP=(TRANS10) ;13 6th transit compartment DR-tab
COMP=(TRANS11) ;14 7th transit compartment DR-tab
COMP=(AUC) ;15 AUC compartment

; Define IOV for 1 healthy HV (STU==4)
OCC1 = 0
OCC2 = 0
OCC3 = 0
OCC4 = 0
OCC5 = 0

IF(STU==4.AND.OCC==1)OCC1=1
IF(STU==4.AND.OCC==2)OCC2=1
IF(STU==4.AND.OCC==3)OCC3=1
IF(STU==4.AND.OCC==4)OCC4=1
IF(STU==4.AND.OCC==5)OCC5=1

; Define IOV in STU=4 (HV)
IOV_KTRTAB =ETA(9)*OCC1+ETA(10)*OCC2+ETA(11)*OCC3 +ETA(12)*OCC4+ETA(13)*OCC5
IOV_FTAB =ETA(14)*OCC1+ETA(15)*OCC2+ETA(16)*OCC3 +ETA(17)*OCC4+ETA(18)*OCC5
```

```
$PK
FED=0
IF (FOOD/=0) FED=1; FOOD=1=fed, FOOD=0=fasted

; FORM=1=SUS, FORM=2=DR-tab, FORM=3=iv
IF(FORM==1.AND.PAT==0) KTR = THETA(1)*(1+(FED*THETA(9)))*EXP(ETA(1)) ;KTR-sus-all, KTR-PAT-unknown=KTR-HV-fast
IF(FORM==1.AND.PAT==1) KTR = THETA(1)*(1+(PPI*THETA(20)))*EXP(ETA(1)) ;KTR-sus-all, KTR-PAT-unknown=KTR-HV-fast
IF(FORM.EQ.2.AND.STU.NE.4) KTR = THETA(2)*EXP(ETA(2)) ; KTR-tab
IF(FORM.EQ.2.AND.STU.EQ.4) KTR = THETA(2)*EXP(ETA(2)+IOV_KTRTAB) ; KTR-tab

CL = THETA(3)*EXP(ETA(3))
IF(STU==9) CL = THETA(3)*(1+THETA(19)*HPOA)*EXP(ETA(3))
V3 = THETA(4)*EXP(ETA(4))
V4 = THETA(5)*(1+PAT*THETA(18))*EXP(ETA(5))
Q = THETA(6)*(1+PAT*THETA(17))*EXP(ETA(6))

F1=0
FMAXHVFED = THETA(7)
FMAXHVFAST = FMAXHVFED/2.85
D50HVFED = THETA(10)
D50HVFAST = (3249*D50HVFED)/(5597.4+(5.871*D50HVFED))
IF (FORM==1.AND.PAT==0.AND.FED==0) TVF1 = FMAXHVFAST*(1-(DOSE/(D50HVFAST+DOSE))) ;Nonlinear-F-sus-HV-fast
IF (FORM==1.AND.PAT==0.AND.FED==1) TVF1 = FMAXHVFED*(1-(DOSE/(D50HVFED+DOSE))) ;Nonlinear-F-sus-HV-fed
FMAXPAT = THETA(11)*(1+MUC*THETA(12))*(1+NG*THETA(13))*(1+PPI*THETA(14))*(1+DIAR*THETA(15))*(1+METO*THETA(16))
D50PAT = D50HVFAST
IF (FORM==1.AND.PAT==1) TVF1 = FMAXPAT*(1-(DOSE/(D50PAT+DOSE)));nonlinear-F-sus-PAT
LGTBIOS=LOG(TVF1/(1-TVF1))
LGBIOS=LGTBIOS+ETA(7); F-sus-all
F1=EXP(LGBIOS)/(1+EXP(LGBIOS))

F2=0
IF (FORM==2.AND.PAT==0.AND.FED==0) TVF2 = THETA(8) ;F-tab-HV-fasted
IF (FORM==2.AND.PAT==0.AND.FED==1) TVF2 = 0.995 ; F-tab-HV-fed
IF (FORM==2.AND.PAT==1) TVF2 = THETA(8) ;F-tab-PAT=F-tab-HV-fasted
LGTBIOT=LOG(TVF2/(1-TVF2))
IF (FORM.EQ.2.AND.STU.NE.4) LGBIOT=LGTBIOT+ETA(8)
IF (FORM.EQ.2.AND.STU.EQ.4) LGBIOT=LGTBIOT+ETA(8)+IOV_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 (1)-KTR*A (5); SUS
DADT (6) = KTR*A (5)-KTR*A (6)
DADT (7) = KTR*A (6)-KTR*A (7)
DADT (8) = KTR*A (2)-KTR*A (8); TAB
DADT (9) = KTR*A (8)-KTR*A (9)
DADT (10) = KTR*A (9)-KTR*A (10)
DADT (11) = KTR*A (10)-KTR*A (11)
DADT (12) = KTR*A (11)-KTR*A (12)
DADT (13) = KTR*A (12)-KTR*A (13)
DADT (14) = KTR*A (13)-KTR*A (14)
DADT (15) = A (3) /V3; AUC

$ERROR
IPRED = 0.00001
IF(F.GT.0) IPRED = F
IF(PAT==0) Y = IPRED * (1 + EPS(1))+ EPS(2)
IF(STU==9) Y = IPRED * (1 + EPS(3))+ EPS(4)
IF(STU==10) Y = IPRED * (1 + EPS(5))+ EPS(6)

$THETA
(0, 2.29,5) ;1 KTR-sus
(0, 2.75,5) ;2 KTR-tab
(0, 7.25) ;3 CL
(0, 153) ;4 V3
(0, 119) ;5 V4
```

```
(0, 56.6) ;6 Q
(0.633) FIX ;7 F-sus-max-HV-fed
(0.588) FIX ;8 F-tab-HV-fast
(-0.522) FIX ;9 FOOD effect on KTR-sus
(1390) FIX ;10 D50-HV-fed
(0, 0.441,1) ;11 F-sus-max-PAT
(-1, -0.607) ;12 MUConFMAXPAT
(-1, -0.442) ;13 NGonFMAXPAT
(-1, -0.482) ;14 PPIonFMAXPAT
(-1, -0.362) ;15 DIARonFMAXPAT
(-1, -0.293) ;16 METOonFMAXPAT
(-1, -0.714) ;17 PATonQ
(-1, 0.837) ;18 PATonV4
(-1, -0.281) ;19 HPOAonCL-23RadHM
(-1, -0.861) ;20 PPIonKTRSUSPAT

$OMEGA
0.0344 ; 1 KTR-sus
 0.112 ; 2 KTR-tab
 0.0925 ; 3 CL
 0.133 ; 4 V3
 0 FIX ; 5 V4
 0 FIX ; 6 Q
 0.283 ; 7 F-sus
 0.647 ; 8 F-tab
$OMEGA BLOCK(1) 0.0945 FIX ;9 HV-IOV-KTRTAB
 $OMEGA BLOCK(1) 0.0945 FIX
 $OMEGA BLOCK(1) 0.0945 FIX
 $OMEGA BLOCK(1) 0.0945 FIX
 $OMEGA BLOCK(1) 0.0945 FIX
$OMEGA BLOCK(1) 0.401 FIX ;14 IOV-HV-FTAB
 $OMEGA BLOCK(1) 0.401 FIX
 $OMEGA BLOCK(1) 0.401 FIX
 $OMEGA BLOCK(1) 0.401 FIX
 $OMEGA BLOCK(1) 0.401 FIX

$SIGMA
0.0718 ; proERR-HV
 0.0025 ; addiERR-HV
 0.0261 ; proERR-RadHM
 0.00497 ; addiERR-RadHM
 0.205 ; proERR-AUSP
 0 FIX ; addiERR-AUSP
$EST PRINT=5 MAX=9999 METHOD=1 NSIG=2 SIGL=6 INTERACTION POSTHOC NOABORT MSFO=mfi
$COV PRINT=E

$TABLE ID TIME TAD DV MDV AMT ADDL II CMT RATE EVID DOSE LLOQ BLOQ FORM PAT STU MD OCC DENSE FOOD PPI MYL
RANT ESOM METO FOS NG MUC DIAR SEX AGE WT HT BMI CENTER HP ALB HPOA CITR HEMA PRED IPRED ETAS(1:LAST)
CWRES KTR CL V3 V4 Q F1 F2 NOAPPEND NOPRINT ONEHEADER
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