AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Model Based Estimation of Posaconazole Tablet and Suspension Bioavailability in Hospitalized Children Using Real-World Therapeutic Drug Monitoring Data in Patients Receiving Intravenous and Oral Dosing

Zoe Kane,[a] Iek Cheng,[a,b] Orlagh McGarrity,[b] Robert Chiesa,[c] Nigel Klein,[a] Mario Cortina-Borja,[a] Joseph F. Standing,[a,b] Silke Gastine[a]

[a]Great Ormond Street Institute of Child Health, University College London, London, United Kingdom
[b]Department of Pharmacy, Great Ormond Street Hospital, London, United Kingdom
[c]Department of Bone Marrow Transplantation, Great Ormond Street Hospital, London, United Kingdom

ABSTRACT Invasive fungal infections are a major cause of morbidity and mortality for immunocompromised patients. Posaconazole is approved for treatment and prophylaxis of invasive fungal infection in adult patients, with intravenous, oral suspension, and gastroresistant/delayed-released tablet formulations available. In Europe, until very recently, posaconazole was used off-label in children, although a new delayed-release suspension approved for pediatric use is expected to become available soon. A population pharmacokinetic model was developed which uses posaconazole therapeutic drug monitoring data following intravenous and oral dosing in hospitalized children, thus enabling estimation of pediatric suspension and tablet oral bioavailability. In total, 297 therapeutic drug monitoring plasma levels from 104 children were included in this analysis. The final model was a one-compartment model with first-order absorption and nonlinear elimination. Allometric scaling on clearance and volume of distribution was included *a priori*. Tablet bioavailability was estimated to be 66%. Suspension bioavailability was estimated to decrease with increasing doses, ranging from 3.8% to 32.2% in this study population. Additionally, concomitant use of proton pump-inhibitors was detected as a significant covariate, reducing suspension bioavailability by 41.0%. This is the first population pharmacokinetic study to model posaconazole data from hospitalized children following intravenous, tablet, and suspension dosing simultaneously. The incorporation of saturable posaconazole clearance into the model has been key to the credible joint estimation of tablet and suspension bioavailability. To aid rational posaconazole dosing in children, this model was used alongside published pharmacodynamic targets to predict the probability of target attainment using typical pediatric dosing regimen.

KEYWORDS posaconazole, pediatric dosing, bioavailability, population pharmacokinetics, pediatric drug therapy, pediatric infectious disease, pharmacokinetics

Invasive fungal infections (IFIs) present a serious risk for morbidity and mortality in immunocompromised patients undergoing both solid organ and stem cell transplantation. Posaconazole was first approved in Europe for use for adults in 2005, with Merck Sharp and Dohme (MSD) initially launching an oral suspension, followed by a gastroresistant/delayed release tablet and then an intravenous (i.v.) formulation. Recently, in the US, a new posaconazole suspension has been approved for use in children over 2 years of age (1). However, in Europe, pediatric posaconazole use is still off-label, with children often receiving the suspension product due to their inability to swallow tablets. This new suspension is also expected to become available soon in Europe. As more formulation options become

Address correspondence to Silke Gastine, s.gastine@ucl.ac.uk, or Joseph F. Standing, j.standing@ucl.ac.uk.

The authors declare no conflict of interest.

Received 16 January 2023
Returned for modification 14 February 2023
Accepted 18 April 2023
Published 1 June 2023

available for posaconazole dosing in children, there is an urgent need for greater understanding of posaconazole pharmacokinetics (PK) and its formulation-dependent absorption and absolute bioavailability (F) in this special population (2).

Posaconazole is lipophilic (logP = 4.6), dibasic, poorly soluble, and highly plasma protein-bound (97% to 99% bound, predominately to albumin) (3). Posaconazole PK after i.v. dose escalation (50, 100, 150, 200, and 300 mg) in healthy adults (n = 9) follows bi-exponential distribution and elimination, with saturable clearance. Clearance decreased on dose escalation from 10.9 to 6.9 L/hr (determined by non-compartmental analysis, NCA) and inter-individual variability (IIV) was 32%. Half-life increased from 19 h at 50 mg to 25 h at 300 mg, and the mean volume of distribution of posaconazole was 261 L (226 to 295 L) (4).

Posaconazole undergoes metabolism in healthy adults, primarily mediated by uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes (especially UGT1A4). The predominant route of elimination is through fecal excretion, with only trace amounts of posaconazole measured in urine (5). Posaconazole is a substrate for P-glycoprotein efflux, and biliary and intestinal secretions are likely (6). The PK of the original posaconazole suspension has been extensively studied in both adult healthy volunteers and patients at risk of IFIs (7–12).

Previous population PK analysis of pediatric posaconazole therapeutic drug monitoring (TDM) data has confirmed that exposure following suspension posaconazole dosing increases in a sub-proportional manner (13). This is thought to be due to a reduction in the fraction of dose absorbed with escalating dosage due to the poor intestinal solubility of posaconazole. As observed in adults, elevated gastric pH also reduces exposure in children following suspension dosing (13). The gastroresistant/delayed-release tablet formulation that was approved in Europe in 2014 was developed specifically to improve the extent of oral absorption relative to the suspension and to overcome issues such as the requirement for multiple daily doses in conjunction with a high-fat meal.

Here, we present a population PK analysis of real-world posaconazole TDM data from hospitalized children receiving both i.v. and oral posaconazole. While previous studies have reported pediatric posaconazole PK data, simultaneous model-based analysis of i.v., suspension, and tablet data to enable estimation of formulation-dependent F in children has not previously been reported.

RESULTS

Pharmacokinetic model building for the pediatric population was first informed by previously published adult dose-escalation data. These results were then used as initial estimates to inform the scaled pediatric model parameters.

Subsequently, the pediatric TDM data were analyzed.

Pharmacokinetic model building: adult literature data. A two-compartment model was found to be superior (difference in objective function value [–ΔOFV] = 24.95 for two degrees of freedom [df]) to a one-compartment model when using linear clearance to describe the i.v. dose escalation (50 to 300 mg) data published by Kersemaekers et al. (4). Introducing saturable clearance further improved the model (–ΔOFV = 34.82 for one df). Saturable clearance is represented by the parameters CL_{sat}, the maximum (or saturated) rate of clearance, and K_m, the concentration at which clearance is half its maximum value. Figure 1A presents the model-predicted concentration-time profiles versus the extracted observed data and Fig. 1B shows the estimated model parameters along with visualization of the impact of posaconazole concentration on adult adjusted clearance. The CL_{sat} was estimated to be 12.11 L/hr/70 kg, the total volume of distribution (Vss = V1 + V2) is 260.2 L/70 kg, and the K_m is 0.49 mg/L (490 ng/mL, 0.7 μM). No IIV was estimated for these data because only the average concentration-time profiles were available.

The clearance and volume of distribution parameter estimates were used to model adult tablet PK data taken from the control arm of the 5-way crossover study published by Kraft et al. (400-mg tablet, n = 20 healthy adults) (14). With $K_{a_{tab}}$ (K_a, absorption rate

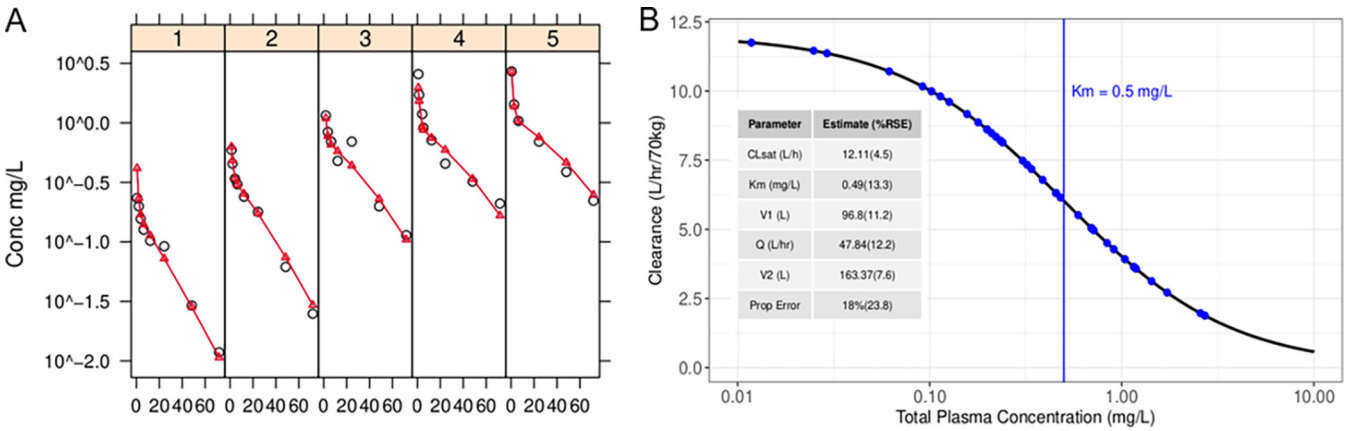

FIG 1 Adult intravenous (i.v.) dose escalation modeling. (A) Observed model predicted concentration time profiles. Red line, model prediction; open black circles, observed concentrations. (B) Visualization of the effect of posaconazole concentration on adult adjusted clearance. Blue circles; observed posaconazole concentrations.

constant) fixed to the previously estimated value of 0.588/hr (15), tablet F was estimated to be 0.59 (5.9% relative standard error, RSE) and C_{max} and AUC_{24} were well-described visually.

Observed pediatric TDM and covariate data. The final pediatric data set is shown in Table 1. Age and body weight (BW) of patients in the study population ranged from 0.4 to 16.8 years (median 6.2 years) and 4.3 to 86.1 kg (median 19.5 kg), respectively.

Dose frequency varied between the formulations and doses ranged from 2.0 to 11.5, 1.6 to 10.6, and 1.8 to 35.5 mg/kg for the i.v., tablet, and suspension formulations, respectively. Across all formulations, 69% of the plasma levels were collected during periods of concomitant proton pump-inhibitor (PPI) administration and 49% were collected during a period of diarrhea. Non-surgical prophylaxis accounted for the majority (43.7%) of inpatient posaconazole dosing.

The median (interquartile range, IQR) alanine aminotransferase (ALT) and plasma protein albumin (ALB) concentrations in blood were 49 (IQR = 33 to 83) U/L and 33 (30 to 36) g/L, respectively. Of the 297 plasma levels in the final data set, 94.3% had an ALT concentration measured within 24 h; for ALB, this was higher, at 98.3%.

The measured plasma concentrations pooled by formulation and compared to the calculated time after last dose (TALD) are presented in Fig. 2. Nineteen of the 297

TABLE 1 Study population demographic, formulation, and bioanalytical information[a]

Population variable	Formulation	Median (range) or *n*
Age at baseline observation (yrs)	i.v.	9.7 (2.8–13.8)
	Tablet	13.8 (8.9–16.8)
	Suspension	4.7 (0.4–16.5)
Body wt at baseline observation (kg)	i.v.	35.0 (12.0–52.9)
	Tablet	44.0 (26.8–86.1)
	Suspension	16.2 (4.3–61.3)
No. of patients providing plasma levels	i.v.	13[b]
	Tablet	18[c]
	Suspension	83[c]
Dose (mg/kg)	i.v.	4.5 (2.0–11.5)
	Tablet	5.6 (1.6–10.6)
	Suspension	9.3 (1.8–35.5)
Plasma concentrations (μg/mL)	i.v.	1.8 (0.1–5.4)
	Tablet	2.0 (0.01–11.4)
	Suspension	0.5 (0.01–9.3)
No. of plasma concentrations	i.v.	47
	Tablet	39
	Suspension	211

[a]i.v., intravenous.
[b]Seven of these patients also provided oral plasma levels.
[c]Three of these patients provided tablet and suspension plasma levels.

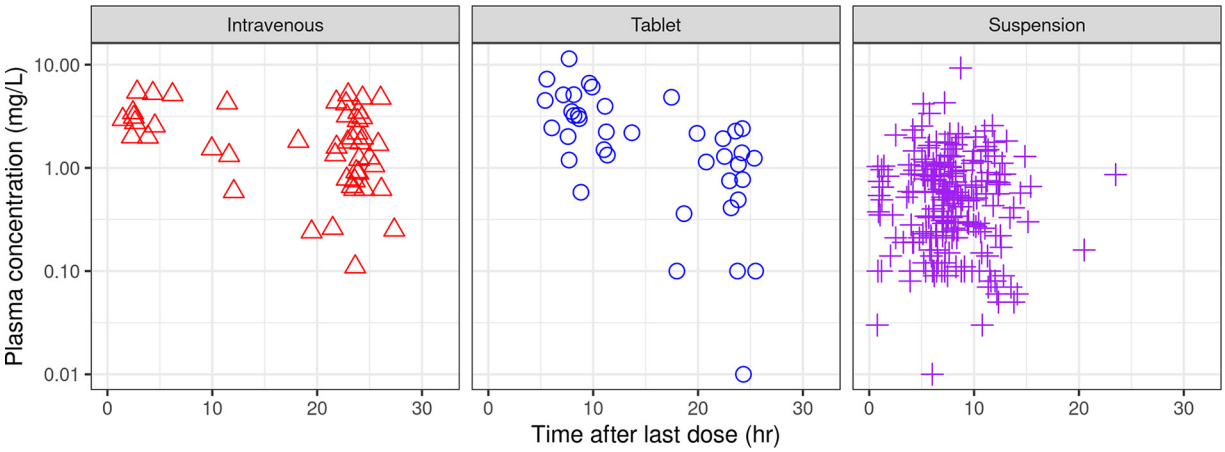

FIG 2 Pooled plasma concentrations (therapeutic drug monitoring [TDM] levels) versus calculated time after last dose included in the final modeling data set. Left to right: i.v., tablet, and suspension data.

plasma concentrations in this data set (6.4%) were reported as below the limit of quantification (BLOQ); these included 5 tablet and 14 suspension levels.

The pediatric data set included 47 plasma levels collected after i.v. dosing in 13 children. Crossover data (plasma levels following oral and i.v. dosing) were available for 7 of the 13 subjects. The i.v. data set includes data from children aged 2.8 to 13.8 years and weighing 12.0 to 52.9 kg.

Pharmacokinetic model building: pediatric real-world data. The base structural model was a one-compartment model with linear clearance. IIV was introduced only on clearance. A combined error model was used to describe residual unexplained variability. Bioavailability was estimated separately for suspension and tablets. Allometric weight scaling was included *a priori*. Base model parameter estimates are presented in Table S1 in the supplemental material. Tablet bioavailability estimated from this linear model was 1.39 (41.1% relative standard error, RSE). No improvement was seen with a two-compartment model. Adding dose-dependent bioavailability for the suspension improved the overall fit (–ΔOFV = 21.26), but tablet F remained above 1 (F_{tab} = 1.36 with 33.4% RSE).

Nonlinear clearance with parameters fixed to adult estimates increased the OFV, but tablet F decreased below 1. A sensitivity analysis with varying K_m found a value of 2 mg/L to adequately predict the observed paediatric data. Next, addition of IIV to volume, tablet F, and suspension D_{50} (dose at which F is 50%) was tested; however, the data set only supported estimation of IIV on CL_{sat} and volume of distribution.

Covariates found to be significant at ($P < 0.01$ upon backward elimination) included dose and PPI co-administration on suspension exposure; ΔOFV = 71.5 and 50.7 respectively. Age was not tested in the model because no relationship was detected with CL_{sat} using visual exploration of the base model (see Fig. 3).

The final pediatric population pharmacokinetic model consisted of a one-compartment model with nonlinear elimination. Bioavailability was estimated separately for tablet and suspension data. A dose-dependent decrease in bioavailability was detectable for suspension. Also, an effect of concomitant PPI use was estimated on suspension bioavailability. Additive error was removed in the final model because it was estimated to be zero.

Table 2 presents the final model parameter estimates. The NONMEM code is included in the supplemental material. Goodness-of-fit (GOF) plots and prediction-corrected visual predictive checks (VPCs) split by formulation are presented in Fig. 4. Combined GOF plots can be found in Fig. S1. Covariate effects alongside the effect of plasma concentration on clearance are visualized in Fig. 5. The model-estimated, dose-independent tablet bioavailability is included in Fig. 5 for comparison.

Pharmacokinetic simulations and probability of target attainment predictions. Age and weight distributions of the entire hypothetical population are presented in

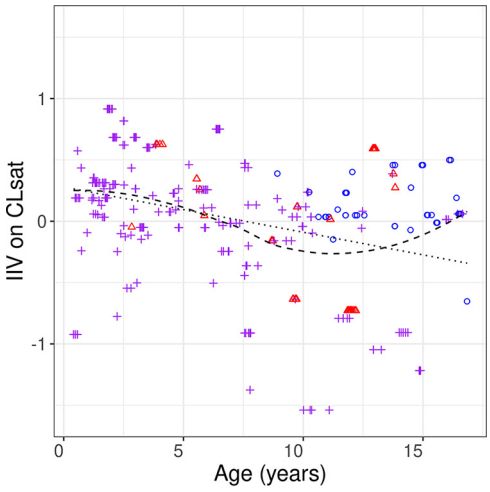

FIG 3 Effect of age on clearance (IIV, inter-individual variability; CL_{sat}, maximum (or saturated) rate of clearance) assessed using the base model. Points: i.v., red triangle; tablet, blue circle; suspension, purple cross. Lines; less smooth, black dashed line; linear regression, black dotted.

Fig. S2; the median (range) age and weight were 4.5 (0.51 to 16.0) years and 19.1 (2.88 to 79.67) kg, respectively. The median age and weight in each simulation group are presented in Fig. S3.

To visually assess the model predicted time to steady state for the different formulations using 'typical' dosing regimens, 5 mg/kg once-daily (QD) tablet and i.v. simulations are compared with 10 mg/kg thrice-daily (TID) suspension simulations (both with and without PPI). Median (50th percentile) concentration-time profiles for all age groups following 8 days of dosing using these 'typical' regimens are presented in Fig. S4. The predicted 2.5th, 50th, and 95th percentiles for each regimen in the 4- to 6-year-old age group on day 8 of dosing are compared in Fig. S5. The youngest child in the observed population to receive a posaconazole tablet was 8.9 years. However, visualization of all formulations was conducted across all chosen age groups to allow a theoretical comparison. That said, it is also acknowledged that swallowing a tablet can be challenging for most 4-year-olds.

Figure 6 presents the probability of target attainment (PTA) for all age groups. To aid comparisons between the tablet and liquid formulations, the red circle shows the PTA for the 4- to 6-year-old group at a dose of 10 mg/kg using either QD i.v. or tablet dosing and TID suspension-dosing.

DISCUSSION

TABLE 2 Final population pharmacokinetic model parameter estimates[a]

Parameter	Estimate (%RSE)	IIV %CV (%RSE)	Bootstrap 90% CI
CL_{sat} (L/hr/70kg)	13.47 (11.8)	57 (20.5)	11.74 to 16.07
K_m (mg/L)	2 (fixed)		
V (L/70kg)	186.01 (37.6)	120 (33.1)	128 to 272
$K_{a_{tab}}$ (/hr)	0.59 (fixed)		
$K_{a_{sus}}$ (/hr)	0.2 (fixed)		
Tablet F	0.66 (21.0)		0.50 to 0.94
Suspension D_{50} (mg/BSA)	43.25 (14.2)		35.4 to 58.2
θ_{ppi} on F_{sus}	−0.41 (27.5)		−0.53 to −0.27
Prop Error (%)	63.0 (22.1)		51.8 to 75.5

[a]All disposition terms are centered on a fully mature 70-kg individual using allometric scaling with exponents of 1 for volume and 0.75 on CL_{sat}. Condition number for the final model is 43.7 and 70% of bootstrap runs were successful. IIV %CV = (standard error η_i / η_i) × 100. IIV, inter-individual variability; RSE, relative standard error; CL_{sat}, maximum (or saturated) rate of clearance; K_m, concentration at which clearance is half its maximum value; V/F, volume of distribution; K_a, absorption rate constant; F, bioavailability; D_{50}, dose at which F is 50%; BSA, body surface area; θ_{ppi}, fractional change in suspension bioavailability during concomitant proton pump-inhibitor (PPI) dosing.

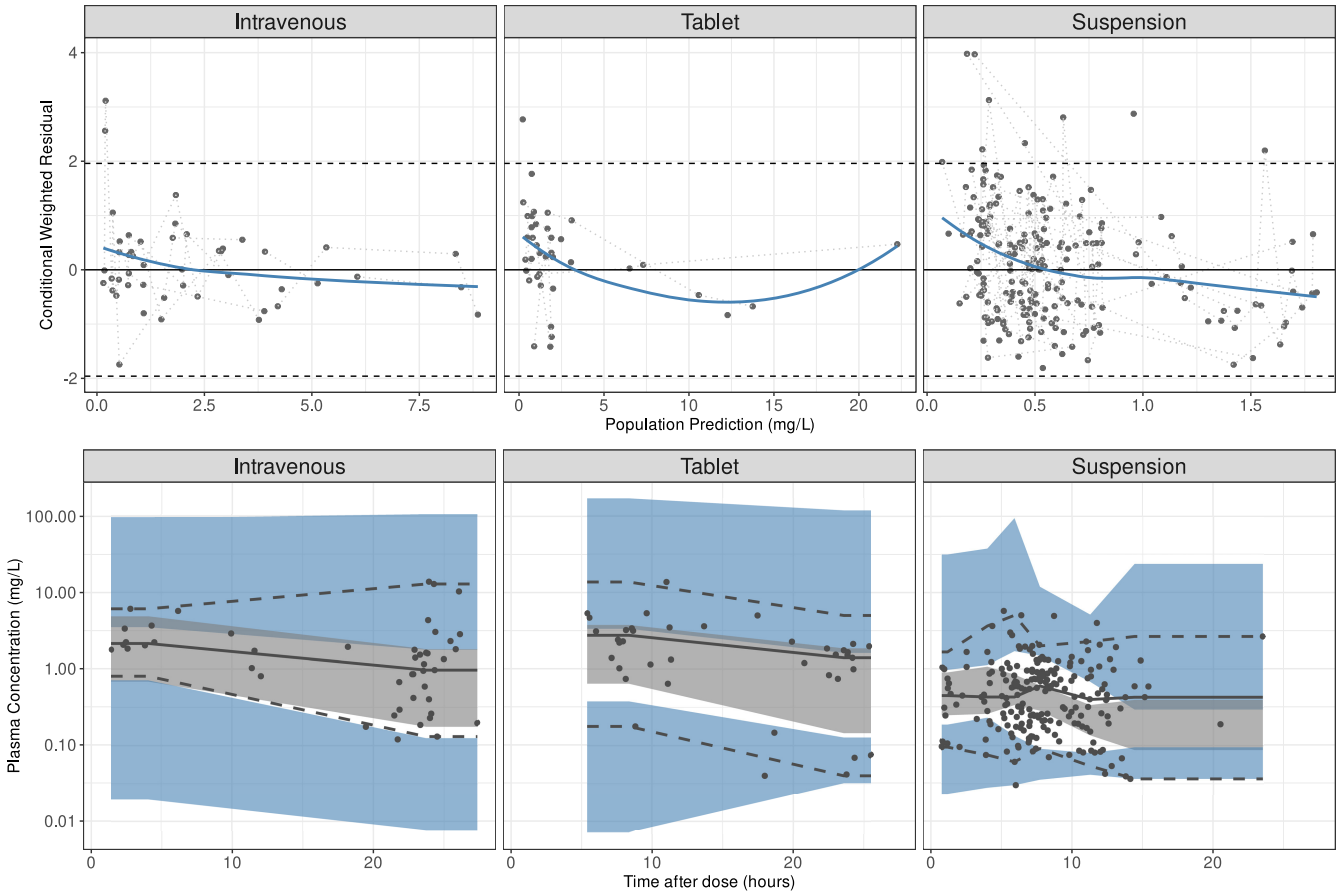

FIG 4 Conditional weighted residuals (CWRES) versus population prediction (top row) and prediction-corrected visual predictive check (VPC) plots stratified by formulation for the final model (bottom row). VPCs show the observed data (black circles), 2.5th, 50th, and 97.5th percentiles of the observed data (black lines) compared with 95% confidence intervals of the corresponding simulations from the final model (shaded areas).

Here, we describe the first intravenous and oral population PK model based on real-world therapeutic drug monitoring data from immunocompromised children. This enabled the first joint estimation of posaconazole tablet and suspension oral bioavailability in children. It is also the first population PK model estimating the nonlinear clearance previously reported by Kersemaekers et al. (4), which was key to a meaningful estimation of tablet bioavailability.

The starting point for our model development was a one-compartment distribution and elimination model with linear clearance. Indeed, this model is used in most published posaconazole models irrespective of the underlying study population (15–19). While an acceptable description of this sparse pediatric TDM data set could be achieved with a model using linear clearance, this did not allow meaningful estimation of both tablet and suspension F. Although this model was able to reconcile the low exposures seen following suspension dosing, significantly improved predictions for tablet exposures were only achieved through estimation of a tablet bioavailability of >1. Thus, our analysis suggests that the poor exposure seen following suspension dosing is not simply due to poor intestinal posaconazole solubility but is also compounded by a saturable clearance mechanism.

A comparison of different formulations and their NCA-based parameters has been published by Dekkers et al. (20). The volume of distribution (V/F) for the i.v. formulation is reported at 261 L, whereas the V/F for tablet is reported at 394 L and the V/F for oral suspension at 1,774 L. This agrees well with the adult estimated V of 250 L for i.v. and the derived tablet V/F of 379 L when considering the estimated F of 66%. With an estimated oral suspension bioavailablility of 18% at a common adult dose of 200 mg, V/F is calculated at 1,406 L.

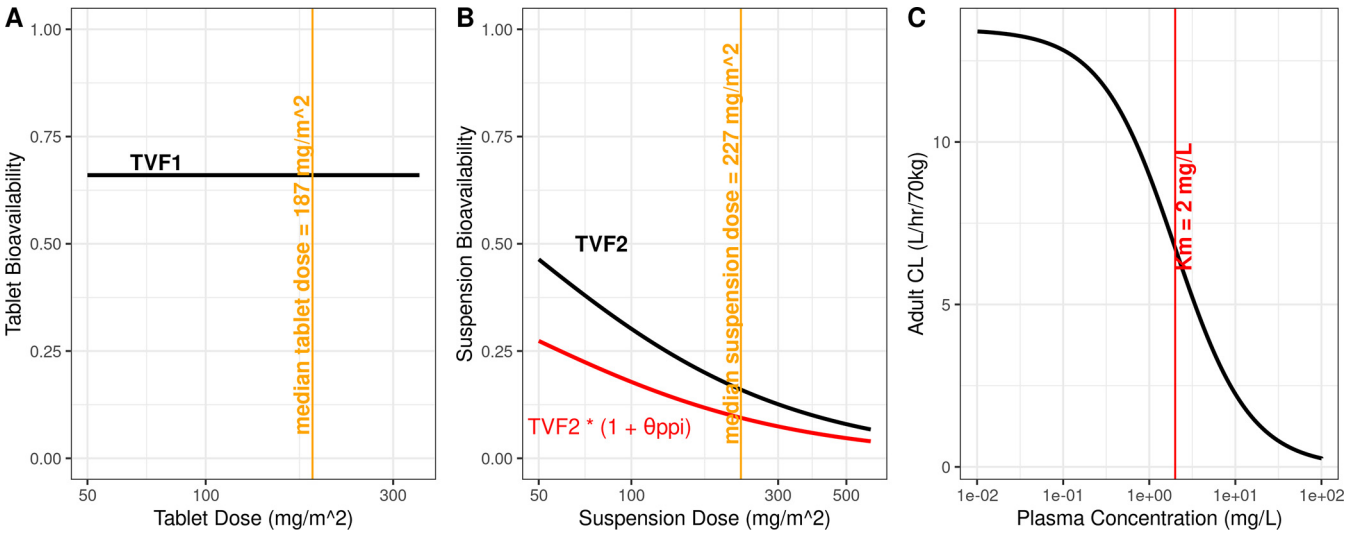

FIG 5 Visualization of the model-estimated (A) tablet bioavailability, (B) covariates affecting suspension bioavailability, and (C) concentration-dependence of clearance in the final model. TVF1, typical value of tablet bioavailability; TVF2, typical value of suspension bioavailability; θ_{ppi}, fractional change in suspension bioavailability during concomitant proton pump-inhibitor (PPI) dosing.

Our estimated adult CL_{sat} of 12 L/h/70 kg would equal the CL/F of 60 L/h/70 kg for the oral suspension using the model-estimated median bioavailability of around 20%. At a C_{avg} (average steady-state concentration) of 0.7 mg/L, CL is reduced to 10 L/h/70 kg, which equivalent to 50 L/h/70 kg for CL/F. This agrees well with the CL/F range of 30 to 113 L/h for oral suspension reported in literature (16–18). For tablet data, the CL/F is reported at 7.3 and 8 L/h (15, 19), which is lower than the converted CL/F of 12.5 L/h at C_{avg} of 0.7 mg/L considering the estimated 80% bioavailability.

The reason that non-linearity of posaconazole CL has not previously been found in suspension PK modeling is likely because the intestinal absorption is so poor that nonlinear clearance was masked. The enhanced solubility of posaconazole in the tablet combined with real-world dosing in the fed state means that tablet F is estimated to be >1 if clearance is assumed to be linear. Although this has not previously been reported in human PK models, it has been seen preclinically in i.v./tablet crossover studies in dogs (21).

When we tried to estimate K_m and CL_{sat} using this pediatric data set, K_m would move to the upper boundary, essentially collapsing clearance back into a linear process. However, F_{tab} would be estimated well over 1. A K_m value of 2 mg/L was identified through parameter sensitivity analysis and was rationalized because 97% to 99% of posaconazole is bound to plasma proteins (3). Therefore, only small increases in plasma protein binding when moving from a healthy adult to a sick pediatric population could lead to commensurate increases in the free/unbound posaconazole K_m.

The tablet bioavailability estimated by this analysis was 66% (22.1% RSE). The fasted-state tablet F reported to the European Medicines Agency (EMA) as part of clinical development was 54% (31.9% coefficient of variation [CV]) (22). Additionally, in a recently published absolute bioavailability study of healthy adult Chinese subjects, after 300-mg i.v./tablet crossover (n = 18 Chinese subjects) in the fasted state, the geometric mean F of the tablet was 42.2% with a T_{max} (time to maximum concentration of drug in serum) of 4.0 h (range: 2 to 6 h). The authors also found that tablet exposure increased 2-fold in the fed state (fed state F_{tab} = 87.1%) (23). Unfortunately for our real-world data, information on the fed or fasted status of these patients was unavailable.

The suspension D_{50} was estimated previously by Boonsathorn et al. to be 99 mg/m^2 (13). Due to the lack of i.v. data availability at the time, this was estimated relative to the tablet CL/F and thus estimated relative to tablet exposure. Figure 5 shows how the estimated suspension bioavailability evolved across the dose range evaluated in this study population. With i.v. data available for this analysis, we estimate the suspension D_{50} relative to i.v. exposure to be 43.25 mg/m^2 (14.2% RSE).

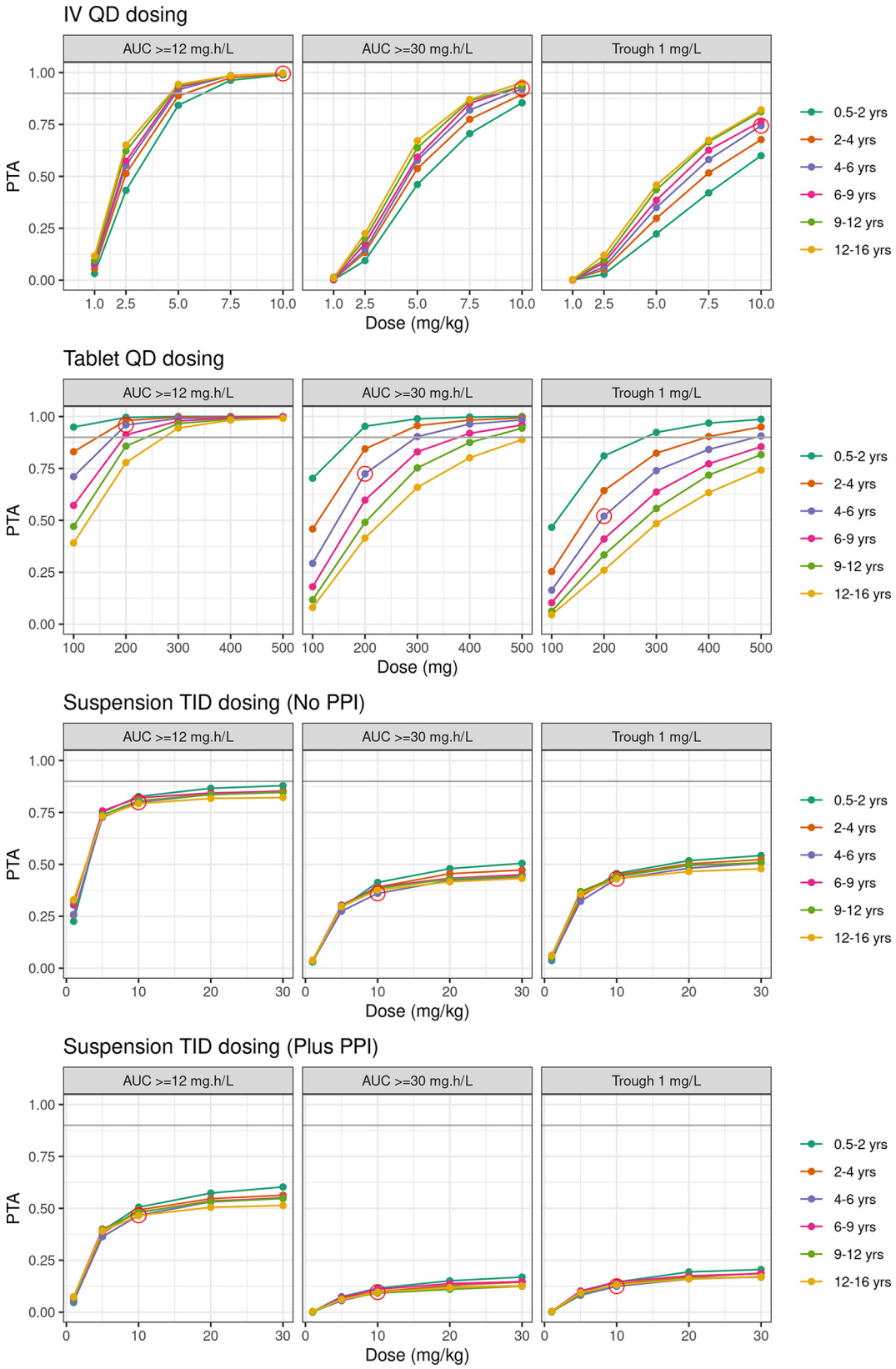

FIG 6 Probability of target attainment (PTA) for all simulation age groups after 8 days of once-daily dosing for i.v. and tablet and thrice-daily dosing for suspension. Solid gray horizontal reference line indicates where 90% of the population was predicted to exceed the respective pharmacodynamic target. Red circles compare the PTA predictions following a 10-mg/kg dose using the different formulations/administration routes for a typical 4- to 6-year-old.

Concomitant PPI dosing is known to be an important covariate influencing F_{sus}. Our analysis reconfirmed this finding with concomitant PPI dosing on F_{sus} reducing suspension bioavailability by 41% (27.5% RSE). This is in agreement with the 42% effect estimated by Boonsathorn et al. and the 45% estimated by Dolton et al. in healthy volunteers (13, 16). Figure 5 shows that at the highest suspension dose evaluated (625 mg/m^2), only 3.8% of the posaconazole given to the patient is estimated to reach the systemic circulation when it is administered alongside a PPI.

While diarrhea has previously been reported to be an important covariate on F_{sus} (13), this covariate effect was not retained when employing a 1% significance level in the backward elimination step. However, curating information regarding the occurrence of diarrhea is complex and also highly subjective, relying on one individual's interpretation of diverse patient history notes. It should also be of noted that the percentage of posaconazole levels in this modeling data set identified as being collected during periods of diarrhea was higher, 49%, than the 20% of samples identified in the Boonsathorn data set.

Constructing a population pharmacokinetic model further enabled us to simulate different dosing regimens for the three formulations to allow a side-by-side exposure comparison and evaluation against PK/PD (PD, pharmacodynamic) indices. This was expressed through the probability of target attainment calculations shown in Fig. 6.

Pharmacodynamic target definition varies across literature. In 2010, Jang et al. published a report on the posaconazole exposure-response relationship, which suggested that a C_{avg} of $>$700 ng/mL would yield adequate antifungal coverage (24). Posaconazole efficacy in preclinical models by Gastine et al. found an AUC_{24} of $\geq$30 mg · h/L or a C_{min} of $>$1 mg/L to be relevant (25). Meanwhile, Groll et al. reported intravenous/peroral (PO) crossover PK data using the 'new' posaconazole suspension in children and targeting an exposure window of C_{avg} 500 to 2,500 ng/mL (26). Therefore, probability of target attainment was performed for multiple indices: AUC_{24} of $\geq$30 mg*h/L; C_{avg} of $>$500 ng/mL (equivalent to an AUC_{24} of $\geq$12 mg*h/L) and C_{min} of $>$1 mg/L, which was also suggested by Gastine et al. due to better feasibility monitoring during clinical practice.

PTA following suspension TID dosing irrespective of concomitant PPI treatment suggests little difference in PTA when using the two targets previously described by Gastine et al. (24, 25). Considering the 4- to 6-year age group, with PPI, the PTAs at steady state following a 10 mg/kg thrice-daily dosing regimen are 9.7% and 12.5% for the AUC and trough target, respectively. For the lower C_{avg} target of $>$500 ng/mL ($AUC_{24} \geq$ 12 mg*h/L), this increases to 46.6%.

The probability of target attainment following once-daily tablet dosing is described for multiples of the unit tablet strength (100 mg) rather than on a mg/kg basis because this was considered to be more useful to clinicians. However, to allow direct comparison to a suspension of 10 mg/kg given thrice daily, and i.v. given at 10 mg/kg once daily, a 200-mg tablet dose to the 4- to 6-year-old group was highlighted (equates to a 10 mg/kg once-daily tablet in a 20-kg child). Here, the probability of achieving a steady-state AUC_{24} of $\geq$30 mg*h/L is 72.4% and 52.0% for exceeding a trough of 1 mg/L. If the AUC_{24} target is reduced to $\geq$ 12 mg*h/L, the 4- to 6-year-old age group is predicted to exceed 90% PTA after a once-daily 200-mg tablet, and all age groups are predicted to exceed 75% PTA. Thus, tablet administration is more likely to reach adequate exposures than the suspension currently available in Europe.

Finally, the PTA results following i.v. dosing show that, in contrast to the oral formulations, it is easier to achieve the AUC_{24} targets than the C_{min} target. Again, focusing on a typical 4- to 6-year-old, 10-mg/kg once-daily i.v. dosing is predicted to ensure that 92.2% of children achieve an AUC_{24} of $\geq$30 mg*h/L and 74.4% would have a steady-state trough of $>$1 mg/L. However, while this regimen is predicted to result in 74.4% of the population exceeding trough concentrations of 1 mg/L, it is also predicted that part of the population is at risk of high exposure. For example, the 95th percentile of trough concentrations (after 7 days prior dosing of 10 mg/kg QD i.v. to 4- to 6-year-olds) is predicted to be 51.6 mg/L (see Fig. S6). With the recommended C_{avg} of $<$2.5 mg/L used by Groll et al., this highlights the estimated high inter-individual

variability in the underlying population PK model. Therefore, therapeutic drug monitoring after posaconazole administration with subsequent dose adaptation is warranted. If the AUC_{24} target is reduced to ≥12 mg*h/L (equivalent to $C_{avg} > 500$ ng/mL), all age groups are predicted to exceed 84.2% PTA after 24-hr i.v. doses of 5 mg/kg or higher. This is in good agreement with the pediatric i.v. PK study results reported by Groll et al., where it was found that after 7 days of once-daily 4.5- and 6.0-mg/kg doses, 90% of participants achieved a C_{avg} of >500 ng/mL (26).

The limitations of our analysis stem from the retrospective assessment of sparse real-world TDM data combined with the relatively small number of patients who contributed i.v. and tablet PK levels to the data set. Because of this, the data set did not support estimation of K_m, and this parameter was fixed based on findings from modeling of adult i.v. data and parameter sensitivity analysis was performed using the pediatric data.

The FDA granted regulatory approval of a new suspension posaconazole product to MSD in May 2021 (1), and hopefully this will also be available to children in Europe in the near future. This new oral suspension combines the improved absorption characteristics of the tablet with the added dosing flexibility of a typical liquid pediatric formulation.

Conclusion. A greater understanding of posaconazole PK in children has been generated from real-world TDM data.

This presented model successfully describes the bioavailability differences observed following tablet and suspension dosing in children, key to this has been the incorporation of saturable posaconazole clearance into the model. Due to the sparse nature of posaconazole TDM data, extrapolation of PK in adult populations informed the base model. Covariate analysis confirmed previously reported dose-dependent decreases in suspension bioavailability, which were then further reduced by concomitant PPIs.

This model was used to evaluate typical pediatric i.v., tablet, and suspension dosing regimens using published PD targets. These simulations highlight that both i.v. and tablet formulations can achieve adequate posaconazole exposure across the pediatric population. However, for the original/old suspension formulation still widely used across Europe, dose escalation beyond 10 mg/kg is essentially pointless, and even with TID dosing many children are likely to be left with sub-therapeutic posaconazole exposure.

MATERIALS AND METHODS

We performed a retrospective analysis of posaconazole TDM data captured by a single specialist pediatric hospital's electronic health records (EHRs) between Jan 2017 and July 2021. This study was restricted to retrospective de-identified data. As such patients or their parents were not required to provide informed consent. The study was approved by the London and South East Research Ethics Committee under reference no. 21/LO/0646.

The PK modeling data file was prepared in R (version 4.1) (27) using posaconazole dosing information (formulation type, dose, route of administration, dose frequency, and dose date/time). Corresponding posaconazole plasma concentration data were collected as part of routine TDM. Posaconazole bioanalysis was performed by external laboratories working under Good Clinical Laboratory Practice standards using a high-performance liquid chromatography-mass spectrometry (HPLC-MS) method. The assay's lower limit of quantification (LLOQ) ranged from 0.02 to 0.2 mg/L (20 to 200 mg/L) and the respective values were recorded for each sample.

Time-varying covariate data incorporated into the modeling data file included age, BW, PPI co-administration, occurrence of diarrhea, and hepatic impairment surrogate ALT and ALB. The last observation carried forward method was used to handle missing covariates. Information regarding episodes of diarrhea were manually collated by a hospital pharmacist from patient records. For i.v. dosing, a nominal infusion time of 90 min, per local guidelines, was used to calculate the infusion rate (mg/hr).

Population PK modeling and simulation was undertaken using first-order conditional estimation method with interaction (FOCEI) in NONMEM version 7.4.3. During data file preparation, posaconazole TDM levels that were reported as less than the LLOQ were replaced with 1/2 the associated LLOQ. Only the first value below the LLOQ during each dose cycle was retained in the data set (M6 method [28]).

Because published intravenous posaconazole pharmacokinetic data in healthy adults have shown that clearance is saturable over a dose range of 50 to 300 mg (0.7 to 4.3 mg/kg assuming a 70-kg body weight) (4), we decided to evaluate the pediatric TDM data using both linear and non-linear clearance models. To help inform pediatric model parameterization, published rich PK data following tablet (14) and i.v. dosing (4) in adult populations were extracted and modeled. Adult PK data extraction was done using a web-based application called WebPlotDigitizer version 4.5 (29).

Pharmacokinetic model development. One- and two-compartment models with first-order absorption and either linear or non-linear clearance from the central compartment were evaluated. IIV was tested on clearance and volume of distribution assuming a log-normal distribution, and on tablet and suspension F

using logistic transformation. A combined error model was tested initially, and separate additive or proportional models were only employed if one component was estimated to be negligible. For nested models, the likelihood ratio test was used to detect significant model improvement. Assuming that the difference in log likelihood between two nested modes was asymptotically chi-square–distributed, a drop in the log-likelihood ratio of >6.64 per degree of freedom was needed for significance at $\alpha < 0.01$ and a ratio of >3.84 was needed at $\alpha < 0.05$. For univariate forward selection, covariates were included if $P < 0.05$ but were removed from the combined covariate model if $P > 0.01$ on backward elimination.

Nonlinear clearance was accounted for using a Michaelis–Menten type function as shown in equation 1. This allows clearance to vary depending on the concentration *C* in plasma based on two parameters, CL_{sat} and K_m.

$$CL = \frac{CL_{sat} \times [C]}{K_m + [C]} \tag{1}$$

Due to the wide-ranging body weight observed in the study population, allometric scaling was included *a priori* using a fixed exponent of 0.75 on CL_{sat} and linear scaling on volume of distribution; see equations 2 and 3. A standard weight of 70 kg was used to allow comparison of parameter estimates with previous studies.

$$CL_{sat,i} = CL_{sat,pop} \times \left(\frac{BW_i}{70}\right)^{0.75} \tag{2}$$

$$V_i = V_{pop} \times \left(\frac{BW_i}{70}\right)^{1} \tag{3}$$

Covariate effects were evaluated for dose, concomitant diarrhea, and PPI dosing because these have previously been reported to be significant determinants of suspension F (13, 30).

Posaconazole is known to undergo phase 2 metabolism (5) and to be highly plasma protein-bound (3). Because metabolism is an important route of elimination for posaconazole and previous findings by Petitcollin et al. (15) described a potential association of ALT with posaconazole clearance, ALT was tested as a continuous covariate on clearance. Finally, because posaconazole is highly plasma protein-bound, ALB was tested on the volume of distribution.

Continuous covariate effects ($COV_{continuous}$) were modeled using a power function centered on the median value (equation 4, the θ defines estimated covariate parameter for continuous covariates) and categorical covariates ($COV_{categorical}$) were evaluated by estimating their fractional change of any given fixed effect (equation 5, the θ defines estimated covariate parameter for categorical covariates).

$$COV_{continuous} = \left(\frac{COV_i}{COV_{median}}\right)^{\theta} \tag{4}$$

$$COV_{catagorical} = (1 - \theta) \tag{5}$$

The function described by Boonsathorn et al. (13) was used to account for the effect of dose on bioavailability; see equation 6, where *D* is the dose in mg/m^2 and D_{50} is the dose at which F is 50%. IIV was tested on D_{50} assuming a log-normal distribution. To calculate dose per body surface area (BSA), we used the Boyd method to estimate BSA based solely on body weight (31, 32).

$$F = 1 - \frac{D}{(D + D_{50})} \tag{6}$$

Due to the sparse nature of TDM data, absorption rate constants (K_a) for suspension ($K_{a_{sus}}$) and tablets ($K_{a_{tab}}$) were fixed based on prior adult estimates (15, 33). The effect of BW on K_a was also tested using the approach previously employed by Boonsathorn et al. using a fixed exponent of −0.25, as in equation 7.

$$Ka_i = Ka_{pop} \times \left(\frac{BW_i}{70}\right)^{-0.25} \tag{7}$$

Decisions during model development were made based on the likelihood-ratio test, GOF plots, and VPC using $n = 1{,}000$ simulations and visualized using Xpose4 (34, 35).

Pharmacokinetic simulations and target attainment. Using the observed baseline demographic information for the children included in the final modeling data set, the variance-covariance matrix was calculated between log-transformed age and weight. From this, $n = 10{,}000$ hypothetical children were simulated and categorized into age-based groups: 0.5 to 2, 2 to 4, 4 to 6, 6 to 9, 9 to 12, and 12 to 16 years. Using body weight, the Boyd method (31) was used to calculate BSA. Simulations with and without PPI were performed for suspension. Tablet simulations were performed at 100-, 200-, 300-, 400-, and 500-mg QD, iv. simulations at 1, 2.5, 5, 7.5 and 10 mg/kg QD, and suspension simulations at 1, 5, 10, 20 and 30 mg/kg TID. Although tablet dosing in children less than 6 years of age may be impractical, all

age groups were simulated for all formulations because this provides clinicians the most flexibility when selecting the appropriate formulation for each individual patient.

A full PK time course was simulated for 8 days (T_{last} = 192 h) and AUC_{24} and C_{min} from the last 24 h period were used to calculate the PTA using previously published PD targets of 30 mg*h/L (AUC_{24} at steady state) and 1 mg/L (C_{min} at steady state) (25). This proposed AUC_{24} of 30 mg*h/L corresponds to a C_{avg} of 1,250 ng/mL, which is higher than the previously suggested posaconazole C_{avg} target of 700 ng/mL (24, 36, 37). More recently, a C_{avg} of 500 ng/mL (0.5 mg/L) to 2,500 ng/mL (2.5 mg/L) has been used as an alternative PD target (26), and thus a C_{avg} of ≥0.5 mg/L (equivalent to a steady-state AUC_{24} of ≥12 mg*h/L) was also included in the PTA assessments.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.6 MB.

ACKNOWLEDGMENTS

We acknowledge the Digital Research team at the Great Ormond Street Hospital for Children for collating and de-identifying the data.

Z.K. received a PhD scholarship from UCL. J.F.S. was supported by a UK MRC fellowship (MR/M008665/1). Support at the institution level came from the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children, an NHS Foundation Trust, and University College London.

S.G., J.F.S., and R.C. conceived the study, which was carried out by Z.K. with help from I.C., O.McG., and M.C.-B. under the supervision of J.F.S. and S.G. All authors contributed to data interpretation and writing/revising the manuscript.

REFERENCES

1. FDA. 2021. Noxafil Powder Mix for delayed-release oral suspension. Available from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214770Orig1s000Approv.pdf. FDA, Silver Spring, MD.
2. Chen L, Krekels EHJ, Verweij PE, Buil JB, Knibbe CAJ, Brüggemann RJM. 2020. Pharmacokinetics and pharmacodynamics of posaconazole. Drugs 80:671–695. https://doi.org/10.1007/s40265-020-01306-y.
3. Hens B, Pathak SM, Mitra A, Patel N, Liu B, Patel S, Jamei M, Brouwers J, Augustijns P, Turner DB. 2017. *In Silico* modeling approach for the evaluation of gastrointestinal dissolution, supersaturation, and precipitation of posaconazole. Mol Pharm 14:4321–4333. https://doi.org/10.1021/acs.molpharmaceut.7b00396.
4. Kersemaekers WM, van Iersel T, Nassander U, O'Mara E, Waskin H, Caceres M, van Iersel MLPS. 2015. Pharmacokinetics and safety study of posaconazole intravenous solution administered peripherally to healthy subjects. Antimicrob Agents Chemother 59:1246–1251. https://doi.org/10.1128/AAC.04223-14.
5. Krieter P, Flannery B, Musick T, Gohdes M, Martinho M, Courtney R. 2004. Disposition of posaconazole following single-dose oral administration in healthy subjects. Antimicrob Agents Chemother 48:3543–3551. https://doi.org/10.1128/AAC.48.9.3543-3551.2004.
6. FDA. 2014. Noxafil injection clinical pharmacology and bioinformatics review. Available from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205596Orig1s000ClinPharmR.pdf. FDA, Silver Spring, MD.
7. Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. 2007. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Pharmacotherapy 27:1627–1636. https://doi.org/10.1592/phco.27.12.1627.
8. Krishna G, Ma L, Vickery D, Yu X, Wu I, Power E, Beresford E, Komjathy S. 2009. Effect of varying amounts of a liquid nutritional supplement on the pharmacokinetics of posaconazole in healthy volunteers. Antimicrob Agents Chemother 53:4749–4752. https://doi.org/10.1128/AAC.00889-09.
9. Krishna G, Moton A, Lei M, Medlock MM, McLeod J. 2009. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother 53:958–966. https://doi.org/10.1128/AAC.01034-08.
10. Krishna G, Ma L, Martinho M, O'Mara E. 2012. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrob Agents Chemother 56:4196–4201. https://doi.org/10.1128/AAC.00222-12.
11. Courtney R, Pai S, Laughlin M, Lim J, Batra V. 2003. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother 47:2788–2795. https://doi.org/10.1128/AAC.47.9.2788-2795.2003.
12. Abutarif MA, Krishna G, Statkevich P. 2010. Population pharmacokinetics of posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Curr Med Res Opin 26:397–405. https://doi.org/10.1185/03007990903485056.
13. Boonsathorn S, Cheng I, Kloprogge F, Alonso C, Lee C, Doncheva B, Booth J, Chiesa R, Irwin A, Standing JF. 2019. Correction to: Clinical pharmacokinetics and dose recommendations for posaconazole in infants and children. Clin Pharmacokinet 58:141. https://doi.org/10.1007/s40262-018-0722-x.
14. Kraft WK, Chang PS, Van Iersel MLPS, Waskin H, Krishna G, Kersemaekers WM. 2014. Posaconazole tablet pharmacokinetics: lack of effect of concomitant medications altering gastric pH and gastric motility in healthy subjects. Antimicrob Agents Chemother 58:4020–4025. https://doi.org/10.1128/AAC.02448-13.
15. Petitcollin A, Boglione-Kerrien C, Tron C, Nimubona S, Lalanne S, Lemaitre F, Bellissant E, Verdiera MC. 2017. Population pharmacokinetics of posaconazole tablets and Monte Carlo simulations to determine whether all patients should receive the same dose. Antimicrob Agents Chemother 61:e01166-17. https://doi.org/10.1128/AAC.01166-17.
16. Dolton MJ, Brüggemann RJ, Burger DM, McLachlan AJ. 2014. Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis. Antimicrob Agents Chemother 58:6879–6885. https://doi.org/10.1128/AAC.03777-14.
17. Kohl V, Müller C, Cornely OA, Abduljalil K, Fuhr U, Vehreschild JJ, Scheid C, Hallek M, Rüping MJ. 2010. Factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic stem cell transplantation. Antimicrob Agents Chemother 54:207–212. https://doi.org/10.1128/AAC.01027-09.
18. Vehreschild JJ, Müller C, Farowski F, Vehreschild MJ, Cornely OA, Fuhr U, Kreuzer KA, Hallek M, Kohl V. 2012. Factors influencing the pharmacokinetics of prophylactic posaconazole oral suspension in patients with acute myeloid leukemia or myelodysplastic syndrome. Eur J Clin Pharmacol 68:987–995. https://doi.org/10.1007/s00228-012-1212-y.
19. Peña-Lorenzo D, Rebollo N, Sánchez-Hernández JG, Zarzuelo-Castañeda A, Vázquez-López L, Otero MJ, Pérez-Blanco JS. 2022. Population pharmacokinetics of a posaconazole tablet formulation in transplant adult allogeneic

stem cell recipients. Eur J Pharm Sci 168:106049. https://doi.org/10.1016/j.ejps.2021.106049.
20. Dekkers BGJ, Bakker M, van der Elst KCM, Sturkenboom MGG, Veringa A, Span LFR, Alffenaar JC. 2016. Therapeutic drug monitoring of posaconazole: an update. Curr Fungal Infect Rep 10:51–61. https://doi.org/10.1007/s12281-016-0255-4.
21. Kendall J, Papich MG. 2015. Posaconazole pharmacokinetics after administration of an intravenous solution, oral suspension, and delayed-release tablet to dogs. Am J Vet Res 76:454–459. https://doi.org/10.2460/ajvr.76.5.454.
22. Committee for Medicinal Products for Human Use (CHMP). 2014. EMA assessment report EMA/159150/2014: Noxafil. Available from https://www.ema.europa.eu/en/documents/variation-report/noxafil-h-c-610-x-0028-epar-scientific-discussion-extension_en.pdf. European Medicines Agency, Amsterdam, The Netherlands.
23. Li H, Wei Y, Zhang S, Xu L, Jiang J, Qiu Y, Mangin E, Zhao XM, Xie S. 2019. Pharmacokinetics and safety of posaconazole administered by intravenous solution and oral tablet in healthy Chinese Subjects and effect of food on tablet bioavailability. Clin Drug Invest 39:1109–1116. https://doi.org/10.1007/s40261-019-00833-1.
24. Jang SH, Colangelo PM, Gobburu JV. 2010. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. Clin Pharmacol Ther 88:115–119. https://doi.org/10.1038/clpt.2010.64.
25. Gastine S, Hope W, Hempel G, Petraitiene R, Petraitis V, Mick-Iene D, Bacher J, Walsh TJ, Groll AH. 2021. Pharmacodynamics of posaconazole in experimental invasive pulmonary aspergillosis: utility of serum galactomannan as a dynamic endpoint of antifungal efficacy. Antimicrob Agents Chemother 65:e01574-20. https://doi.org/10.1128/AAC.01574-20.
26. Groll AH, Abdel-Azim H, Lehrnbecher T, Steinbach WJ, Paschke A, Mangin E, Winchell GA, Waskin H, Bruno CJ. 2020. Pharmacokinetics and safety of posaconazole intravenous solution and powder for oral suspension in children with neutropenia: an open-label, sequential dose-escalation trial. Int J Antimicrob Agents 56:106084. https://doi.org/10.1016/j.ijantimicag.2020.106084.
27. R Core Team. 2013. R: a language and environment for statistical computing. Available from http://www.R-project.org. R Foundation for Statistical Computing, Vienna, Austria.
28. Bergstrand M, Karlsson MO. 2009. Handling data below the limit of quantification in mixed effect models. AAPS J 11:371–380. https://doi.org/10.1208/s12248-009-9112-5.
29. Rohatgi A. WebPlotDigitizer version 4.5. Available from https://github.com/ankitrohatgi/WebPlotDigitizer.
30. Bentley S, Davies JC, Gastine S, Donovan J, Standing JF. 2021. Clinical pharmacokinetics and dose recommendations for posaconazole gastro-resistant tablets in children with cystic fibrosis. J Antimicrob Chemother 72:3247–3254. https://doi.org/10.1093/jac/dkab312.
31. Sharkey I, Boddy AV, Wallace H, Mycroft J, Hollis R, Picton S, Chemotherapy Standardisation group of the United Kingdom Children's Cancer Study Group. 2001. Body surface area estimation in children using weight alone: application in paediatric oncology. Br J Cancer 85:23–28. https://doi.org/10.1054/bjoc.2001.1859.
32. Boyd E. 1935. The growth of the surface area of the human body. University of Minnesota Press, Minneapolis, MN.
33. Ezzet F, Wexler D, Courtney R, Krishna G, Lim J, Laughlin M. 2005. Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations. Clin Pharmacokinet 44:211–220. https://doi.org/10.2165/00003088-200544020-00006.
34. Jonsson EN, Karlsson MO. 1999. Xpose: an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed 58:51–64. https://doi.org/10.1016/s0169-2607(98)00067-4.
35. Lindbom L, Pihlgren P, Jonsson EN, Jonsson N. 2005. PsN-Toolkit: a collection of computer intensive statistical methods for non- linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed 79:241–257. https://doi.org/10.1016/j.cmpb.2005.04.005.
36. Cornely OA, Robertson MN, Haider S, Grigg A, Geddes M, Aoun M, Heinz WJ, Raad I, Schanz U, Meyer RG, Hammond SP, Mullane KM, Ostermann H, Ullmann AJ, Zimmerli S, Van Iersel MLPS, Hepler DA, Waskin H, Kartsonis NA, Maertens J. 2017. Pharmacokinetics and safety results from the Phase 3 randomized, open-label, study of intravenous posaconazole in patients at risk of invasive fungal disease. J Antimicrob Chemother 72:3501. https://doi.org/10.1093/jac/dkx382.
37. Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, Lass-Flörl C, Calandra T, Viscoli C, Herbrecht R. 2017. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 102:433–444. https://doi.org/10.3324/haematol.2016.152900.