Model based estimation of posaconazole tablet and suspension bioavailability in hospitalised children using real–world therapeutic drug monitoring data in patients receiving intravenous and oral dosing

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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 gastro-resistant/delayed-released tablet formulations available. In Europe posaconazole is used off-label in children and there is an urgent need for greater understanding of posaconazole pharmacokinetics in this special population.

A population pharmacokinetic model was developed using posaconazole therapeutic drug monitoring data following intravenous and oral dosing in hospitalised children, thus enabling estimation of paediatric 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 1-compartment model with first order absorption and non-linear 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 dose, 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 hospitalised children following intravenous, tablet and suspension dosing simultaneously. Key to the credible joint estimation of tablet and suspension bioavailability has been incorporation of saturable posaconazole clearance into the model. To aid rational posaconazole dosing in children the model has been used alongside published pharmacodynamic targets to predict the probability of target attainment using typical paediatric dosing regimen.

KEYWORDS: Posaconazole; paediatric dosing; bioavailability; population pharmacokinetics.

INTRODUCTION

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 for use in Europe for adults in 2005, with Merck Sharp and Dohme (MSD) initially launching the oral suspension, followed by a gastro-resistant/delayed release tablet and then an intravenous (IV) formulation. Recently, in the US, a new posaconazole suspension has been approved for use in children above 2 years of age. (1). However, in Europe, paediatric posaconazole use is still off-label, with children often receiving the suspension product, due to inability to swallow tablets. As more formulation options are becoming 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 IV 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 L/hr to 6.9 L/hr (determined by non-compartmental analysis, NCA) and inter-individual variability was 32%. Half-life increased from 19 hrs at 50 mg to 25 hours at 300 mg and the mean volume of distribution of posaconazole was 261 L (226-295 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 faecal excretion with only trace amounts of posaconazole measured in urine (5). Posaconazole is a substrate for P-gp 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, 8, 9, 10, 11, 12).

Previous population PK analysis of paediatric 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 dose, 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 gastro-resistant/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 dosing in conjunction with a high fat meal.

Here, we present the population PK analysis of real world posaconazole TDM data from hospitalised children receiving both IV and oral posaconazole. While previous studies have reported paediatric posaconazole PK data, simultaneous model based analysis of IV, suspension and tablet data to enable estimation of formulation dependant F in children has not previously been reported.

RESULTS

Pharmacokinetic model building for the paediatric population was informed by previously published adult dose escalation data in a first step. These results were then taken forward as initial estimates to inform the scaled paediatric model parameters. Subsequently, the paediatric TDM data was analysed.

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 IV dose escalation (50-300 mg) data published by Kersemaker et. al. (4). Introducing saturable clearance further improved the model (-ΔOFV 34.82 for one df). Saturable clearance is represented by parameters CL_{sat} , the maximum (or saturated) rate of clearance and K_m, the concentration at which clearance is half its maximal value. Figure 1A presents the model predicted concentration-time profiles versus the extracted observed data and Figure 1B the estimated model parameters along with visualisation of the impact of posaconazole concentration on adult adjusted clearance. CL_{sat} is estimated to be 12.11 L/hr/70kg, total volume of distribution (Vss = V1 + V2) is 260.2 L/70kg and Km is 0.49 mg/L (490 ng/mL, 0.7 µM). No inter–individual variability (IIV) was estimated for these data as only the average concentration–time profiles were available.

The clearance and volume of distribution parameter estimates were carried forward 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 Ka_{tab} fixed to the previously estimated value of 0.588 /hr (15) tablet F was estimated to be 0.59 (5.9% RSE) and visually C_{max} and AUC_{24} were well described.

Observed Pardiatric TDM and Covariate Data The final paediatric dataset is described 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, 1.8 to 35.5 mg/kg for the IV, tablet and suspension formulations respectively. Across all formulations, 69% percent of the plasma levels were collected during periods of concomitant proton–pump inhibitor (PPI) administration and 49% of levels during a period of diarrhoea. Non-surgical prophylaxis accounts for the majority (43.7%) of in-patient poaconazole dosing.

The median [inter-quartile range, IQR] alanine aminotransferase (ALT) and plasma protein albumin (ALB) concentrations in blood were 49 [33-83] U/L and 33 [30-36] g/L respectively. Of the 297 plasma levels in the final data set 94.3% have an ALT concentration measured within 24 hours, for ALB this is higher at 98.3%.

The measured plasma concentrations pooled by formulation and compared to the calculated time after last dose (TALD) are presented in Figure 2. Nineteen of the 297 plasma concentrations in this dataset (6.4%) are reported as below the limit of quantification (BLOQ) these include 5 tablet and 14 suspension levels.

The paediatric data set included 47 plasma levels collected after IV dosing in 13 children. Cross over data (plasma levels following oral and IV dosing) was available for 7 of the 13 subjects. The IV data set includes data from children aged 2.8 to 13.8 years, weighing 12.0 to 52.9 kg.

Pharmacokinetic model building - paediatric 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 for suspension and tablets separately. Allometric weight scaling was included *a priori*. Base model parameter estimates are presented in Supplementary Table S1. Tablet bioavailability estimated from this lin-

ear model was 1.39 (41.1% 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).

Non-linear clearance with parameters fixed to adult estimates increased OFV but tablet F decreased below 1. A sensitivity analysis varying Km found a value of 2 mg/L to adequately predict the observed data. Addition of IIV to volume, tablet F and suspension D_{50} was tested in a next step, however, the data set only supported estimation of IIV on CL_{sat} and volume of distribution .

Covariate analysis revealed PPI co-administration on F_{sus} to significantly improve the model (-ΔOFV 50.72 for 1 df). No further covariate effects were found to be significant at a level of p<0.01 on backward elimination. Age was not tested in the model as no relationship was detected with CL_{sat} using visual exploration of the base model, see Figure 3.

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

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

Pharmacokinetic simulations and probability of target attainment predictions The age and weight distributions of the full hypothetical population are presented in supplementary information Figure S2, the median (range) age and weight were 4.5 years (0.51 to 16.0 years) and 19.1 kg (2.88 to 79.67 kg) respectively. The median age and weight in each simulation group are presented in Figure S3.

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

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

DISCUSSION

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 non-linear 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. (16, 17, 18, 19, 15) While an acceptable description of this sparse paediatric TDM dataset could be achieved with a model employing linear clearance, it 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 improving predictions for tablet exposures was only achieved through estimation of a tablet bioavailability > 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). Volume of distribution for the IV formulation is reported at 261 L, whereas V/F for tablet is stated at 394 L and oral suspension at 1774 L. This agrees well with the adult estimated V of 250 L for IV and the derived Tablet V/F of 379L 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 1406 L.

Our estimated adult CL_{sat} of 12 L/h/70kg would equal CL/F of 60 L/h/70kg for oral suspension taking the model estimated median bioavailability of around 20%. At the C_{avg} of 0.7 mg/L, CL is reduced to 10 L/h/70kg, which equivalent to 50 L/h/70kg for CL/F. This agrees well with the range of CL/F of 30 to 113 L/h for oral suspension reported in literature (16, 17, 18). For tablet data a CL/F is reported at 7.3 and 8 L/h (19, 15), which is lower than a converted CL/F of 12.5 L/h at C_{avg} of 0.7 mg/L taking the estimated 80% bioavailability into account.

The reason non-linearity of posaconazole CL has not previously been found in suspension PK modelling is likely due to the fact that 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 tablet F is estimated to be > 1 if clearance is assumed to be linear. Whilst this has not previously been reported in human PK models, it has however been seen preclinically in IV/tablet crossover studies in dog (21).

When we tried to estimate K_m and CL_{sat} using this paediatric dataset, K_m would go to the upper boundary essentially collapsing clearance back to a linear process. F_{tab} would however be estimated well over 1. A value of 2 mg/L for the K_m was identified through parameter sensitivity analysis and rationalised since between 97-99% of posaconazole is bound to plasma proteins (3). Thereby only small increases in plasma protein binding moving from healthy adults to a sick paediatric population could lead to commensurate increases in the free/unbound posaconazole K_m.

Tablet bioavailability estimated by this analysis is 66% (22.1% RSE). The fasted state tablet F reported to the EMEA as part of clinical development was 54% (31.9 %CV) (22). In addition an absolute bioavailability study in healthy adult Chinese subjects has been published recently and after 300 mg IV/tablet crossover (n=18 Chinese subjects) in the fasted state the geometric mean F of the tablet is 42.2%, Tmax 4.0 hours (range; 2-

6 hours). 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 patients fed or fasted status was unavailable.

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

Concomitant PPI dosing is known to be an important covariate influencing suspension exposure (F_{sus}). Our analysis was able to re-confirm this finding with concomitant PPI dosing on F_{sus} reducing suspension bioavailability by 41% (27.5% RSE). This is in agreement with the effect estimated by Boonsathorn et. al.; 42% 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 administered alongside a PPI.

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

The construction of a population pharmacokinetic model further enabled us to simulate different dosing regimen for the three formulations to allow a side-by-side exposure comparison and evaluation against PKPD indices. This was expressed through probability of target attainment calculations in Figure 6.

Pharmacodynamic target definition varies across literature. Jang et. al. published in 2010 on the posaconazole exposure-response relationship, which suggest C_{avg} of > 700 ng/mL to yield adequate antifungal coverage (24). Posaconazole efficacy in pre–clinical models by Gastine et. al. found an AUC_{24} of ≥ 30 mg.h/L or C_{min} > 1 mg/L to be relevant (25). While Groll et. al. report intravenous/PO crossover PK data using the 'new' posaconazole suspension in children and target an exposure window of C_{avg} 500 ng/mL to 2500 ng/mL (26). Probability of Target attainment were therefore performed for multiple indices: AUC_{24} of ≥ 30 mg.h/L; C_{avg} of > 500 ng/mL (which is equivalent to an AUC_{24} of ≥ 12 mg.h/L) and a C_{min} of >1 mg/L, which was also suggested by Gastine et. al. due to better monitoring feasibility during clinical practice.

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

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

Finally, following IV dosing the PTA results 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 4-6 year, 10 mg/kg once daily intravenous dosing is predicted to ensure 92.2% of children achieve an AUC_{24} ≥ 30 mg.h/L and 74.4% would have a steady state trough > 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 exposures. For example the 95th percentile of trough concentrations (after 7 days prior dosing of 10 mg/kg QD IV to 4-6 year old's) is predicted to be 51.6 mg/L, see Figure S6. With a recommended C_{avg} below 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 a C_{avg} > 500 ng/mL) all age groups are predicted to exceed 84.2% PTA after q24hr IV doses of 5 mg/kg or above. This is in good agreement with the paediatric IV PK study results reported by Groll et. al. where the authors found that after 7 days of dosing 4.5 and 6.0 mg/kg once daily, 90% of participants achieved a C_{avg} > 500 ng/mL (26).

There are limitations to our analysis that stem from the retrospective assessment of sparse real world TDM data combined with the relatively small number of patients contributing IV and tablet PK levels to the dataset. Because of this the dataset did not support estimation of Km and this parameter was fixed based on findings from modelling of adult IV data ,and parameter sensitivity analysis performed using the paediatric 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 paediatric formulation.

CONCLUSION

From real–world TDM data, more understanding of posaconazole PK in children can be generated.

The model that has been presented successfully describes the bioavailability differences seen following tablet and suspension dosing in children. Key to this has been 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 are then further reduced by concomitant PPIs.

The model has been used to evaluate typical paediatric IV, tablet and suspension dosing regimens using published PD targets. These simulations highlight, that both IV and tablet formulations are capable of achieving adequate posaconazole exposures across the pediatric population. However for the original/old suspension formulation,

that is still widely used across Europe, escalation of dose beyond 10 mg/kg is essentially pointless and even with TID dosing many children are likely to be left with sub-therapeutic posaconazole exposures.

MATERIALS AND METHODS

A retrospective analysis of posaconazole TDM data captured by a single specialist paediatric hospital electronic health records (EHRs) between Jan 2017 and July 2021 was performed. The study was approved by the London and South East Research Ethics Committee under ref. no. 21/LO/0646.

Preparation of the PK modelling data file was performed 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. The assay's lower limit of quantification (LLOQ) ranged from 0.02-0.2 mg/L (20 to 200 mg/L) and the respective value was accounted for each sample.

Time-varying covariate data incorporated into the modelling data file included age, BW, PPI co–administration, occurrence of diarrhoea, hepatic impairment surrogate ALT and ALB. Last observation carried forward method was applied to handle missing covariates. Information regarding episodes of diarrhoea were manually collated by a hospital pharmacist from patient records. For IV dosing a nominal infusion time of 90 minutes as per the local guidance was used to calculate infusion rate (mg/hr).

Population PK modelling 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 LLOQ during one dose cycle was retained in the data set (M6 method, (28)).

Since published intravenous posaconazole pharmacokinetic data in healthy adults demonstrated, that over a dose range of 50 to 300 mg (0.7 to 4.3 mg/kg assuming a 70 kg body weight) clearance is saturable (4) the decision was made to evaluate the paediatric TDM data using both linear and non-linear clearance models. To help inform paediatric model parameterisation, published rich PK data following tablet (14) and IV dosing (4) in adult populations was extracted and modelled. 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. Inter–individual variability (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 only employed if one component was estimated to be negligible. For nested models, the likelihood ratio test was employed to detect significant model improvement. Assuming the difference in log likelihood between two nested modes was asymptotically Chi–squared distributed, a drop in the log likelihood ratio of >6.64 per degree of freedom was needed to be significant at a level of $\alpha < 0.01$ and >3.84 at a level of $\alpha < 0.05$. For univariate forward selection covariates were included if p<0.05 but removed from the combined covariate model if p>0.01 on backward elimination.

Non-linear 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} , the maximum (or saturated) rate of clearance and K_m, the concentration at which clearance is half its maximal value.

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

Due to wide–ranging body weight in the observed study population, allometric scaling was included *a priori* using a fixed exponent of 0.75 on CLsat and linear scaling on volume of distribution see Equation 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 diarrhoea and PPI dosing as 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). Due to metabolism being an important route of elimination for posaconazole and in light of previous findings by Petitcollin et. al. (15) regarding 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 were modelled using a power function centred on the median value see Equation 4 and categorical covariates evaluated by estimation of their fractional change of any given fixed effect see Equation 5.

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

$$COV_{categorical} = (1 + \theta) \tag{5}$$

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).

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

Due to the sparse nature of TDM data, absorption rate constants (Ka) for suspension (Ka_{sus}) and tablets (Ka_{tab}) were fixed based on prior adult estimates (33, 15). The effect of BW on Ka was also tested using the approach previously employed by Boonsathorn et. al. using a fixed exponent of -0.25, see 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, goodness of fit (GOF) plots and visual predictive checks (VPC) using n=1000 simulations and visualised using Xpose4 (34, 35).

Pharmacokinetic Simulations and Target Attainment Using the observed baseline demographic information for the children included in the final modelling dataset 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; 0.5-2, 2-4, 4-6, 6-9, 9-12, 12-16 years. Using body weight, the Boyd method (31) was used to calculate body surface area. Simulations with or without PPI were performed for suspension. Tablet simulations were performed at 100, 200, 300, 400 and 500 mg once daily (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 three times daily (TID). While tablet dosing in children less than 6 years of age maybe impractical, all age groups were simulated for all formulations as this provides clinicians the most flexibility when selecting the appropriate formulation for a respective individual patient.

A full PK time course was simulated for 8 days (T_{last} = 192 hours) and AUC_{24} and C_{min} from the last 24 hour period were used in calculation of the probability of target attainment (PTA) using previously published PD targets of 30 mg.hr/L (AUC_{24} at steady state) and 1 mg/L (C_{min} at steady state) (25). This proposed AUC_{24} of 30 mg.hr/L, corresponds to a C_{avg} of 1250 ng/mL, which is higher than a previously suggested posaconazole C_{avg} target of 700 ng/mL(36, 37, 24). More recently a steady state C_{avg} of between 500 ng/mL (0.5 mg/L) and 2500 ng/mL (2.5 mg/L) has been used as an alternative PD target (26) and as such a $C_{avg} \geq$ 0.5 mg/L (which is equivalent to an AUC_{24} at steady state of $\geq$ 12 mg.h/L) was also included in the PTA assessments.

SUPPLEMENTAL MATERIAL

SupplementalMaterials.docx includes the model code of the final paediatric posaconazole model, Figure S1 showing combined goodness-of-fit plots, Figure S2 and Figure S3 showing detailed graphical exploration of the virtual population used for simulations and Figures S4 -S6 with plasma concentration time curves constructed from the simulations. Table S1 presents the base model parameter estimates.

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Informed consent: 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, reference 21/LO/0646.

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TABLES

TABLE 1 Study population demographic, formulation and bioanalytical information.

Population Variable	Formulation	Median (Range) or Number
Age at baseline observation (years)	IV	9.7 (2.8 - 13.8)
	Tablet	13.8 (8.9 - 16.8)
	Suspension	4.7 (0.4 - 16.5)
Weight at baseline observation (kg)	IV	35.0 (12.0 - 52.9)
	Tablet	44.0 (26.8 - 86.1)
	Suspension	16.2 (4.3 - 61.3)
Number of patients providing plasma levels	IV	13[1]
	Tablet	18[2]
	Suspension	83[2]
Dose (mg/kg)	IV	4.5 (2.0 - 11.5)
	Tablet	5.6 (1.6 - 10.6)
	Suspension	9.3 (1.8 - 35.5)
Plasma concentrations μ g/mL	IV	1.8 (0.1 - 5.4)
	Tablet	2.0 (0.01 - 11.4)
	Suspension	0.5 (0.01 - 9.3)
Number of plasma concentrations	IV	47
	Tablet	39
	Suspension	211

[1]Of which seven patients also provide oral plasma levels

[2]Of which three patients provide tablet and suspension plasma levels

TABLE 2 Final population pharmacokinetic model parameter estimates. All disposition terms are centred 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 $\eta_i/\eta_i) * 100$

Parameter	Estimate (%RSE)	IIV %CV (%RSE)	Bootstrap 90% CI
CL_{sat} (L/hr/70kg)	13.47 (11.8)	57 (20.5)	11.2 - 15.7
K_m (mg/L)	2 (fixed)	-	-
V (L/70kg)	186.01 (37.6)	120 (33.1)	114 - 258
Ka_{tab} (/hr)	0.59 (fixed)	-	-
Ka_{sus} (/hr)	0.2 (fixed)	-	-
Tablet F	0.66 (21)	-	0.45 - 0.87
Suspension D_{50} (mg/BSA)	43.25 (14.2)	-	31.4 - 55.1
θ_{ppi} on F_{sus}	-0.41 (27.5)	-	-0.54 - -0.28
Proportional Error (%)	63 (22.1)	-	0.5 - 0.74

FIGURES

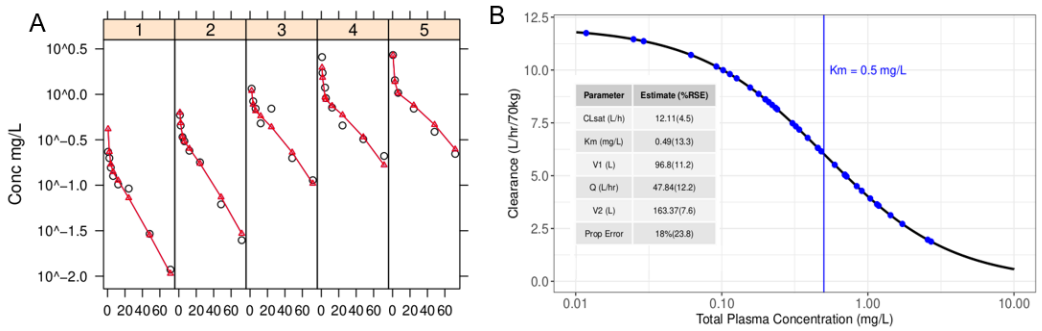

FIG 1 **Adult IV dose escalation modelling. (A) Observed model predicted concentration time profiles. Red line, model prediction; open black circles, observed concentrations. (B) Visualisation of the effect of posaconazole concentration on adult adjusted clearance. Blue circles; observed posaconazole concentrations.**

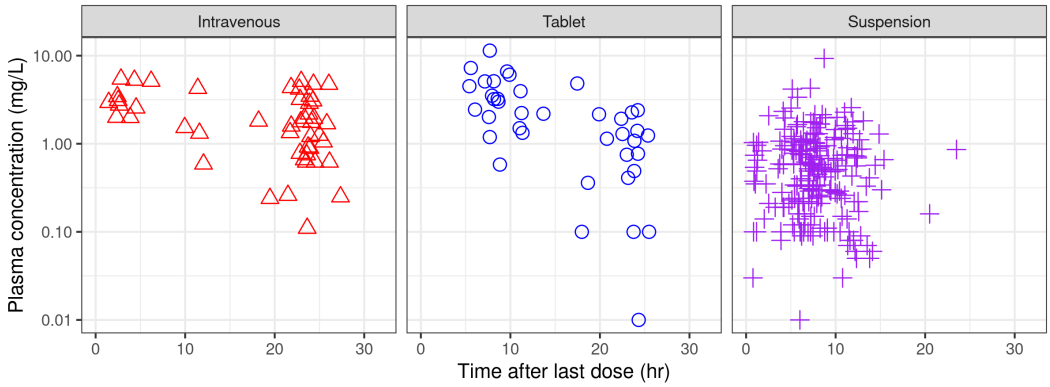

FIG 2 **Pooled plasma concentrations (TDM levels) versus calculated time after last dose (TALD) included in the final modelling dataset. Panels from left to right: IV, tablet and suspension data.**

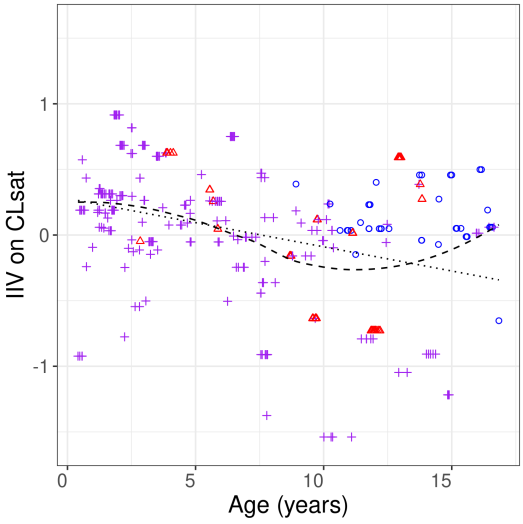

FIG 3 **Effect of age on clearance assessed using the base model. Points; IV - red triangle, tablet - blue circle, suspension - purple cross. Lines; loess smooth - black dashed line, linear regression - black dotted.**

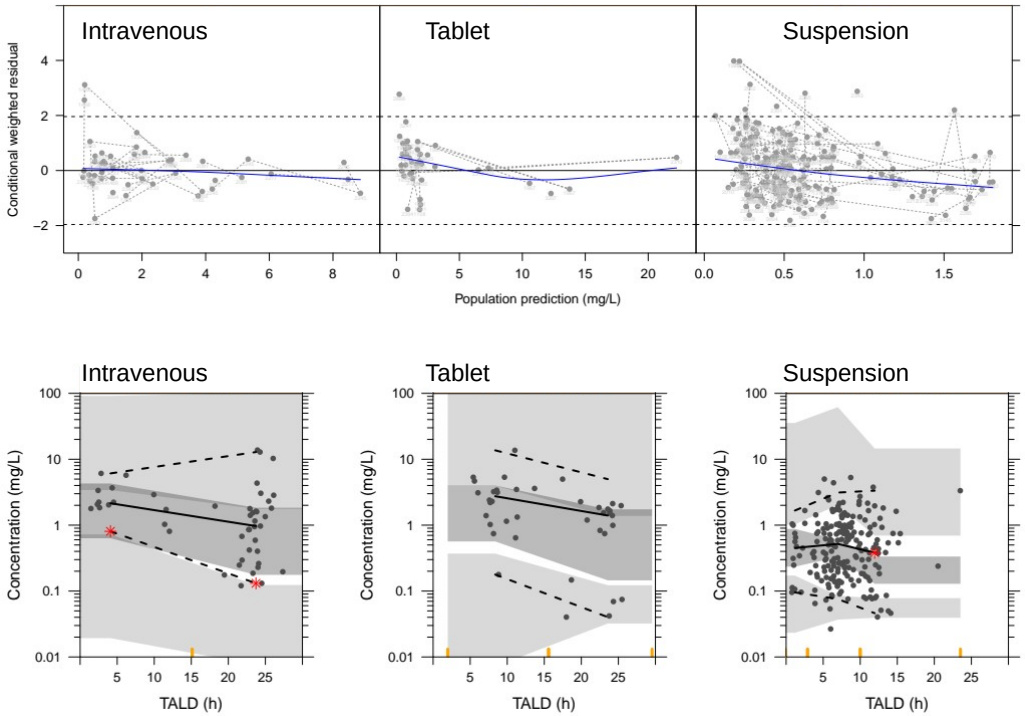

FIG 4 **Conditional weighted Residuals (CWRES) versus population prediction (top row) and prediction-corrected visual predictive check (VPC) plots stratified by formulation for the final model (bottom row). VPCs show the observed data (black circles), 2.5th, 50th and 97.5th percentiles of the observed data (black lines) compared with 95 percent confidence intervals of the corresponding simulations from the final model (shaded areas). TALD, time after last dose administered. In the VPCs a red asterisk highlights that the observed percentile is outside of the model prediction interval.**

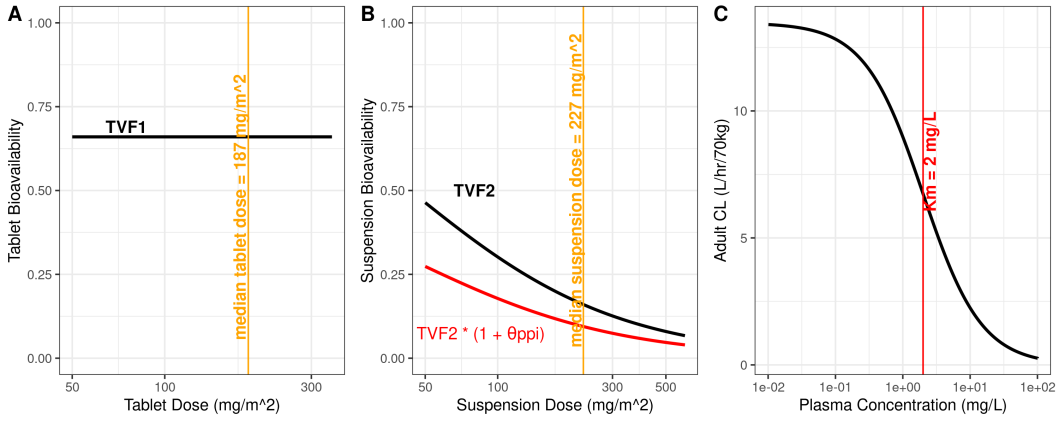

FIG 5 **Visualisation of the model estimated (A) Tablet bioavailability. (B) The covariates effecting suspension bioavailability. (C) The concentration dependence of clearance in the final model. TVF1: Typical value of tablet bioavailability. TVF2: Typical value of suspension bioavailability. θ_{ppi}: Fractional change in suspension bioavailability during concomitant PPI dosing.**

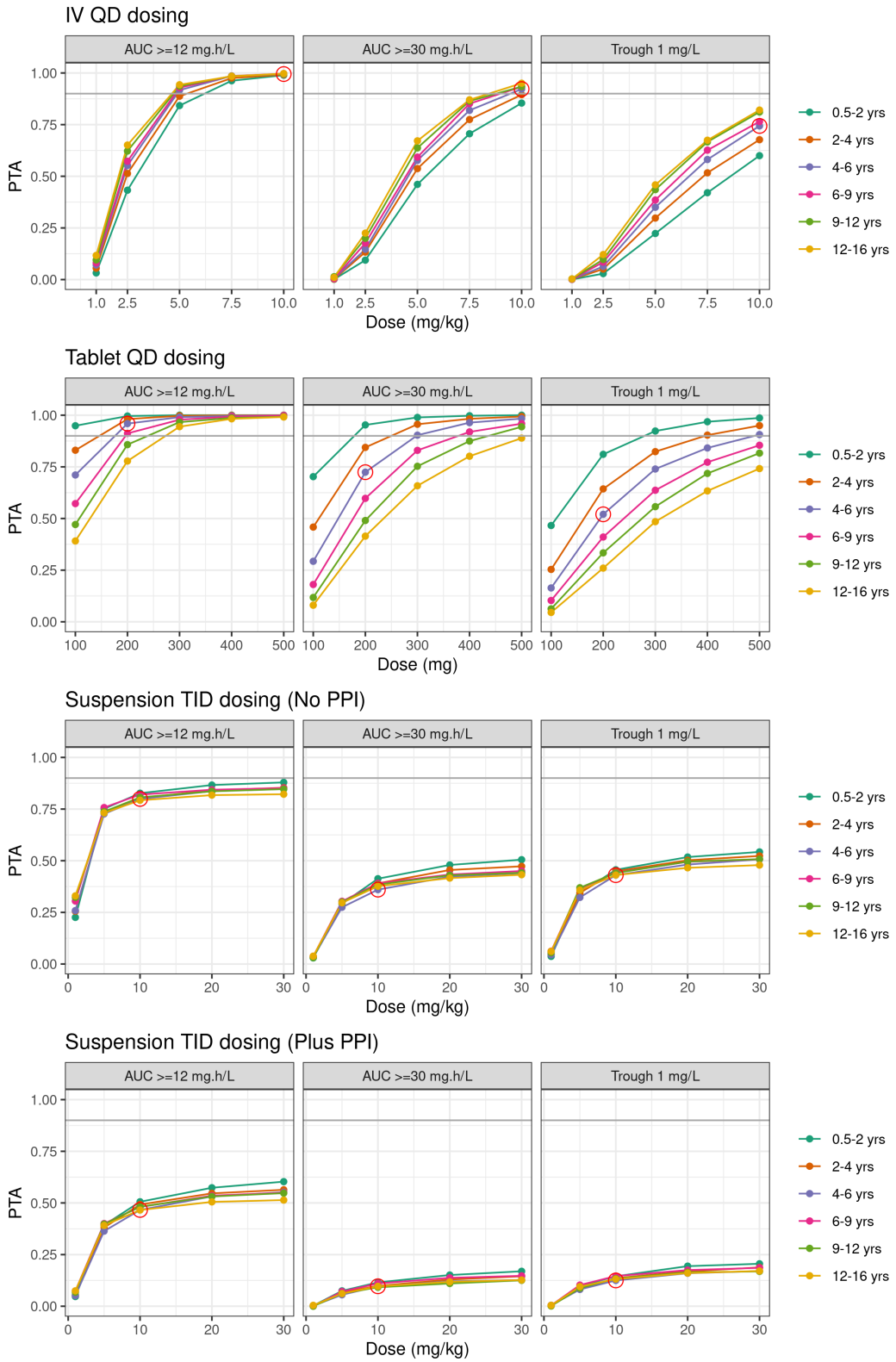

FIG 6 **Probability of target attainment for all simulation age groups after eight days of once daily dosing for IV and tablet, and three times daily dosing for suspension. Solid grey horizontal reference line highlights where 90% of the population are predicted to exceed the respective PD target. The red circles compare the PTA predictions following a 10 mg/kg dose using the different formulations/administration routes for a typical 4-6 year old.**