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Integrated Population Pharmacokinetic Analysis of Voriconazole in Children, Adolescents, and Adults

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To further optimize the voriconazole dosing in the pediatric population, a population pharmacokinetic analysis was conducted on pooled data from 112 immunocompromised children (2 to <12 years), 26 immunocompromised adolescents (12 to <17 years), and 35 healthy adults. Different maintenance doses (i.e., 3, 4, 6, 7, and 8 mg/kg of body weight intravenously [i.v.] every 12 h [q12h]; 4 mg/kg, 6 mg/kg, and 200 mg orally q12h) were evaluated in these children. The adult dosing regimens (6 mg/kg i.v. q12h on day 1, followed by 4 mg/kg i.v. q12h, and 300 mg orally q12h) were evaluated in the adolescents. A two-compartment model with first-order absorption and mixed linear and nonlinear (Michaelis-Menten) elimination adequately described the voriconazole data. Larger interindividual variability was observed in pediatric subjects than in adults. Deterministic simulations based on individual parameter estimates from the final model revealed the following. The predicted total exposure (area under the concentration-time curve from 0 to 12 h [$AUC_{0\text{-}12}$]) in children following a 9-mg/kg i.v. loading dose was comparable to that in adults following a 6-mg/kg i.v. loading dose. The predicted $AUC_{0\text{-}12}$s in children following 4 and 8 mg/kg i.v. q12h were comparable to those in adults following 3 and 4 mg/kg i.v. q12h, respectively. The predicted $AUC_{0\text{-}12}$ in children following 9 mg/kg (maximum, 350 mg) orally q12h was comparable to that in adults following 200 mg orally q12h. To achieve voriconazole exposures comparable to those of adults, dosing in 12- to 14-year-old adolescents depends on their weight: they should be dosed like children if their weight is <50 kg and dosed like adults if their weight is ≥50 kg. Other adolescents should be dosed like adults.

Voriconazole is a broad-spectrum triazole antifungal agent with activity against a wide range of yeasts and filamentous fungi (3, 6, 7, 11) and is approved for various invasive fungal infections worldwide. Voriconazole is extensively metabolized by and is also an inhibitor of the cytochrome P450 (CYP) isozymes, CYP2C19, CYP2C9, and CYP3A4. In adults, voriconazole exhibits nonlinear pharmacokinetics (PK) due to saturation of its metabolism, with large interindividual variability, and CYP2C19 genotyping status, gender, and age are key factors that help explain this variability (12).

The pharmacokinetic/pharmacodynamic target for voriconazole has not been established in the clinical setting, although the preclinical-infection model has suggested the area under the curve (AUC)/MIC ratio is the best predictor of efficacy (1). The predominant non-albicans *Candida* species and *Aspergillus* species in pediatric and adult patients are different; nonetheless, voriconazole has potent *in vitro* activity against all *Candida* species, and voriconazole has demonstrated better *in vitro* activity than itraconazole or amphotericin B against *Aspergillus* spp. (13). Based on the shared pathophysiology in pediatric patients and adults, it is reasonable to expect similar efficacy in pediatric patients at doses matching the total exposures in adults that demonstrated efficacy and safety.

Several PK studies have been conducted in immunocompromised children (2 to <12 years old) (5, 8, 10, 14, 15). In contrast to adults, the nonlinearity of voriconazole PK in children is less pronounced, and the interindividual variability appears to be larger. A population PK analysis was performed previously based on the pooled data from three pediatric studies with a range of single or multiple intravenous (i.v.) doses (i.e., 3, 4, 6, and 8 mg/kg of body weight every 12 h [q12h]) and multiple oral doses (i.e., 4 and 6 mg/kg q12h) (8). This analysis derived the following proposed doses for children: no i.v. loading dose was warranted, 7 mg/kg i.v. q12h was required to match 4 mg/kg i.v. q12h in adults, and 200 mg orally q12h was required to match 200 mg orally q12h in adults. Recently, another pediatric PK study was conducted to confirm the above proposed dosing regimens (5), and the noncompartmental-analysis results indicated that i.v. doses higher than 7 mg/kg are needed to closely match adult exposures and that a weight-based oral dose appeared to be more appropriate than a fixed dose of 200 mg.

Currently, adolescents are recommended to be dosed like adults based on the limited efficacy and safety and sparse PK data on voriconazole in adolescent patients from clinical trials (12). To confirm the appropriateness of this instruction, a PK study in immunocompromised adolescents (12 to <17 years old) was conducted to provide additional PK and safety data, with a focus on young adolescents during the transition period from childhood to adolescence (4). The noncompartmental-analysis results confirmed that voriconazole exposures in the majority of adolescents were comparable to those in adults receiving the same dosing regimens. However, some young adolescents with low body weight had lower voriconazole exposures than adults. The findings on the young adolescents were not unexpected. It is thought that maturation may play an important role in voriconazole metabolism

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during the age transition period (i.e., 12 to 14 years old). It is likely that subjects in this subgroup may metabolize voriconazole more similarly to children than to adults. Body weight appeared to be more important than age in predicting voriconazole PK in this age group.

To further optimize the pediatric dosing regimens, an integrated population PK analysis was performed on data pooled from children, adolescents, and adults in five PK studies. Among them, only the adult PK study was conducted in healthy subjects. It is known that voriconazole pharmacokinetics in adult patients are similar to those observed in healthy subjects (12).

In addition, monitoring voriconazole trough concentrations (C_{min}) may be beneficial to facilitate dose adjustment in critically ill pediatric patients due to large interindividual variability in exposure. However, the timing of the trough sample collection has not been thoroughly evaluated (i.e., when is the earliest time to collect the trough sample). This is a frequently asked question in clinical practice, which can be addressed with simulations from a population PK model.

The objectives of this analysis were to (i) describe the PK of voriconazole and identify factors leading to interindividual variability in children, adolescents, and adults using nonlinear mixed-effects modeling; (ii) use the developed model to derive voriconazole doses for children to match adult exposures and for young adolescents with appropriate age and weight cutoffs to match adult exposures; and (iii) use the developed model to assess the appropriateness of the trough sample collection timing.

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MATERIALS AND METHODS

Study design and pharmacokinetic data. The study design, study population, and timing of plasma sample collection varied among the 5 PK studies and are summarized in Table 1. Detailed descriptions of these studies were published previously (4, 5, 14, 15). In these studies, i.v. voriconazole was administered at a maximum infusion rate of approximately 3 mg/kg/hour, and oral voriconazole (tablet or powder for oral suspension [POS]) was administered at least 1 h before or after a meal. Flexible dosing durations and serial PK sampling days were allowed in pediatric (children and adolescents) studies to accommodate a subject's medical condition.

Population pharmacokinetic modeling. Concentration-time data were analyzed using a nonlinear mixed-effects population analysis approach with NONMEM and the subroutine ADVAN6 (version 7.1.2; Icon Development Solutions, Ellicott City, MD). The graphic processing of the NONMEM output was performed with R (version 2.10.1) (http://www.r-project.org) and Xpose (version 4.2.1) (http://xpose.sourceforge.net). The first-order conditional estimation (FOCE) method, with or without ETA-EPSILON (η-ε) interaction as appropriate, was employed for all model runs. The final model used the FOCE method on log-transformed concentrations. Interindividual variability in the PK parameters was evaluated using exponential random effects, additive random effects on logit scale, or Box-Cox-transformed random effects, as appropriate. Box-Cox transformation could transform a normal distribution into a left or right skewed distribution (11a). Within-subject variability (residual variability) was modeled as study-dependent additive errors on the log-transformed concentrations.

First, the pooled voriconazole concentration data following i.v. dosing were modeled, and different compartmental models were explored with linear and nonlinear (Michaelis-Menten) elimination. Second, voriconazole concentration data from oral dosing were added, and functions for absorption delay (Alag), absorption rate constant (k_a), and oral bioavailability (F1) were explored while keeping the i.v. parameters fixed. Potential outlying data points were identified as an observation with an absolute conditional weighted residual (|CWRES|) of >6. Two outlier records (CWRES < −6) were excluded from the final data set. Third, all parameters were estimated based on all data. Finally, the models from the three steps were reparameterized so that typical PK parameters refer to a 70-kg adult, and potential model reductions were investigated.

Structural-model description. The final structural model used to describe the voriconazole concentration profile is presented in Fig. 1. Compared with the previous model (8), the main change in the present analysis was the description of elimination, from nonlinear elimination to mixed linear and nonlinear eliminations. In the final model, all clearance terms (maximum elimination rate at 1 h [$V_{max,1}$], linear clearance [CL], and intercompartmental clearance [Q]) were scaled allometrically, using a power of 0.75, and all volume terms (central and peripheral volumes of distributions, V_2 and V_3) were scaled allometrically, using a power of 1.

Covariate model building. Only predefined covariate-parameter relationships were tested, which were based on scientific interest and mechanistic plausibility or prior knowledge. Age, weight (WT), CYP2C19 genotyping status, and formulation type (POS versus tablet) were selected for covariate evaluation. Additionally, potential population and study effects were also investigated as a covariate: $STDY_{1\text{-}3,ped}$ (children) versus $STDY_{4,adol}$ (adolescents) versus $STDY_{5,adult}$ (adults). The covariates were tested one by one, and only those that were found to be statistically significant upon deletion (one by one) were retained in the final model. Inclusion of a covariate was guided by the drop in objective function value (OFV) (at least 10.83 for a one-parameter difference), in addition to improvements in the prediction-corrected visual predictive check (pcVPC) (details below).

Goodness of fit and predictive performance. Model selection was based on standard goodness-of-fit (GOF) criteria, including diagnostic plots, precision of parameter estimates, and the OFV. The basic diagnostic plots included observations-versus-population predictions (PRED) and individual predictions (IPRED), individual weighted residuals (IWRES) versus IPRED, and CWRES versus time and PRED. Shrinkage in random effects was computed to guide the appropriateness of using ETA (η, empirical Bayes prediction of the interindividual random effect) and IPRED values in the assessment of GOF (9). Parameters with shrinkage of ≤25% were considered to be reliable for diagnostics. Estimates of parameter precision were obtained from a nonparametric bootstrap to obtain relative standard errors (RSE) on the estimates of all fixed- and random-effect parameters. The parameter uncertainty was described as a percent relative standard error (%RSE).

pcVPC, stratified by study, dosing occasion, and administration route, was utilized to assess the predictive performance of the model, which was used as the primary tool to graphically guide model development (PsN version 3.2 [http://psn.sourceforge.net/] and Xpose). A pcVPC differs from a traditional VPC in that both the observations and the simulated data are normalized for the typical model prediction in each bin of independent variables (2). The percentiles of the prediction-corrected observed voriconazole concentrations were compared with the same metrics derived from 500 simulations of individuals from the original data set, overlaid with the observed data. An appropriate model would have the observed percentiles within the 95% confidence intervals of the percentiles of the simulated data.

Parametric simulations (400 stochastic simulations using the original data set) were also performed to compare observed and simulated area under the curve over a 12-h dosing interval ($AUC_{0\text{-}12}$) as an additional predictive check for 3 studies ($STDY_{3\text{-}5}$), where sampling times were relatively rich. The noncompartmental $AUC_{0\text{-}12}$ was calculated based on both observed and simulated concentrations (at observed time points) using the trapezoidal rule within R. The adequacy of the model was assessed by the distribution of simulated geometric mean $AUC_{0\text{-}12}$s (by dose group) centered around the observed geometric mean $AUC_{0\text{-}12}$.

TABLE 1 Study designs

Study	Population	Cohort(s) (*n*)	Dates	Dosing regimen		Planned PK sampling		
				Day(s)	Dose/duration	Day(s)	No. of samples/ subject	Sampling plan
1	Immunocompromised children (2 to <12 yr)	1 and 2 (12)	Jul–Dec 2000	1	6 mg/kg i.v. q12h	1	≤13	2 min after end of infusion in a.m. and p.m.
				2–4	3 mg/kg i.v. q12h	2		Predose
				5–8	4 mg/kg i.v. q12h	4 and 8		Predose; 2 min after end of infusion; 2–4 h, 4–8 h, and 8–12 h after start of infusion
2	Immunocompromised children (2 to <12 yr)	1 (24)	Jun 2003–Jun 2004	1	6 mg/kg i.v. q12h	1	≤22	i.v. 2 min before end of infusion
				2–4	4 mg/kg i.v. q12h	4		i.v. predose; 2 min before end of infusion; 2, 4, 6, 8, and 12 h after start of infusion
				5–8	6 mg/kg i.v. q12h	8		i.v. predose; 2 min before end of infusion; 4, 6, 8, and 12 h after start of infusion
				9–12	4 mg/kg POS q12h	12		Oral predose; 0.5, 1, 2, 4, 6, 8 and 12 h postdose
		2a (24)		1–4	6 mg/kg i.v. q12h	1	≤22	i.v. 2 min before end of infusion
				5–8	8 mg/kg i.v. q12h	4		i.v. predose; 2 min before end of infusion; 4, 6, 8, and 12 h after start of infusion
				9–12	6 mg/kg POS q12h	8		i.v. predose; 2 min before end of infusion;, 4, 6, 8, and 12 h after start of infusion
						12		Oral predose; 0.5, 1, 2, 4, 6, 8, and 12 h postdose
3	Immunocompromised children (2 to <12 yr)	NA (40)	Dec 2008–Oct 2009	1–7	7 mg/kg i.v. q12h	1 and 7	≤27	i.v. predose; 60 min, 138 min (2 min before end of infusion), 4, 6, 8, and 12 h after start of infusion
				8–14	200 mg POS q12h	14		Oral predose; 1, 2, 4, 6, 8, and 12 h postdose
						4–6		i.v. predose
						11–13		Oral predose
4	Immunocompromised adolescents (12 to <17 yr)	NA (26)	Jun 2008–Dec 2009	1	6 mg/kg i.v. q12h	1	≤27	i.v. predose; 60 min, 118 min (2 min before end of infusion), 4, 6, 8, and 12 h after start of infusion
				2–7	4 mg/kg i.v. q12h	7		i.v. predose; 40 min, 78 min (2 min before end of infusion), 4, 6, 8, and 12 h after start of infusion
				8–14	300 mg tablet q12h	14		Oral predose; 1, 2, 4, 6, 8, and 12 h postdose
						4–6		i.v. predose
						11–13		Oral predose
5	Healthy adults (22 to 55 yr)	NA (35)	Apr 2009–Jul 2009	1	6 mg/kg i.v. q12h	1	≤23	i.v. predose; 60 min, 118 min (2 min before end of infusion), 4, 6, 8, and 12 h after start of infusion
				2–7	4 mg/kg i.v. q12h	7		i.v. predose; 40 min, 78 min (2 min before end of infusion), 4, 6, 8, and 12 h after start of infusion
				8–14	200 mg tablet q12h	14		Oral predose; 1, 2, 4, 6, 8, and 12 h postdose
						6		i.v. predose
						13		Oral predose

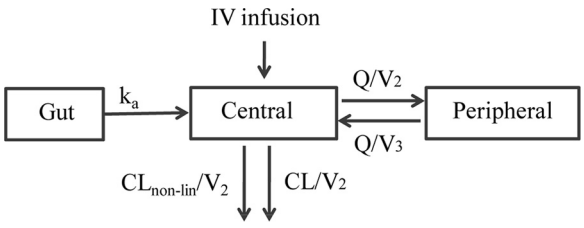

FIG 1 Two-compartment model with first-order absorption and mixed linear (first-order) and nonlinear (Michaelis-Menten and time-dependent V_{max}) elimination used to fit voriconazole i.v. and oral data. CL_{nonlin}, nonlinear clearance [$V_{max}/(C_p + K_m)$, where V_{max} is the time-dependent maximum elimination rate, C_p is the plasma voriconazole concentration, and K_m is the Michaelis-Menten constant].

Model-based simulations under different dosing scenarios. Deterministic simulations were performed using the same individuals from the 5 studies. Specifically, empirical Bayes estimates of individual PK parameters from the final model were created and used to predict individual concentration-time profiles in the same population receiving different voriconazole dosing regimens. This approach was chosen because the interindividual variability of voriconazole was very high. Deterministic simulations take into account correlations between parameters within individuals that are not accounted for in the model, and these individual parameters reflect the observed variability in the study.

Simulated voriconazole total exposures ($AUC_{0\text{-}12}$) in children under different loading and maintenance dosing regimens (e.g., 7, 8, 9, or 10 mg/kg) were compared with the simulated exposures from the adult reference (i.e., 6 mg/kg i.v. q12h on day 1, followed by 4 mg/kg i.v. q12h, and then 200 mg orally q12h).

TABLE 2 Summary of subject demographics

Baseline characteristics	*n* (%)		
	Children[a]	Adolescents[b]	Adults[c]
Total	112	26	35
Gender			
Female	52 (46)	9 (35)	11 (31)
Male	60 (54)	17 (65)	24 (69)
Race			
Caucasian	71 (63)	22 (84)	30 (86)
Black	16 (14)	2 (8)	3 (8)
Asian	5 (5)	1 (4)	
Other	20 (18)	1 (4)	2 (6)
CYP2C19[d]			
UM	2 (2)	2 (8)	
EM	70 (63)	8 (31)	20 (57)
HEM	38 (34)	14 (54)	14 (40)
PM	2 (2)	2 (8)	1(3)
Age (yr)			
Mean	5.75	13.7	35.3
Median (range)	5 (2–11)	13 (12–16)	34 (22–55)
Weight (kg)			
Mean	23.1	56.7	75.1
Median (range)	20.1 (10.8–54.9)	57.1 (30.4–92.2)	76.0 (49.0–97.0)

[a] Studies 1 to 3.
[b] Study 4.
[c] Study 5.
[d] UM, ultra rapid metabolizer; EM, homozygous extensive metabolizer; HEM, heterozygous extensive metabolizer; PM, poor metabolizer. Four children (study 3) and two adolescents (study 4) did not provide CYP2C19 data and were assumed to be EM for modeling purpose. Only studies 3 and 4 had the UM classification (the *17 marker was tested, in addition to the *2, *3, *4, and *5 markers).

For adolescents, 14 different dosing scenarios were created by combining two covariates: age (cutoff, 13, 14, or 15 years old) and weight (cutoff, 40, 45, 50, or 55 kg). Simulated exposures ($AUC_{0\text{-}12}$) in adolescents with different cutoffs receiving either children's or adult's dosing regimens were compared with the simulated exposures in children and adults under their proposed dosing regimens. Simulated exposures from adults were used as the key reference for comparison.

In addition, to assess the appropriateness of trough sample collection timing, voriconazole total exposures ($AUC_{0\text{-}12}$) and C_{min} on days 1 to 7 after i.v. dosing or oral switch in children and adults were simulated. For instance, 9 mg/kg i.v. q12h on day 1 followed by 8 mg/kg i.v. q12h in children, 8 mg/kg i.v. q12h followed by 9 mg/kg (a maximum of 350 mg) orally q12h in children, 6 mg/kg i.v. q12h on day 1 followed by 4 mg/kg i.v. q12h in adults, and 4 mg/kg i.v. q12h followed by 200 mg orally q12h in adults. The voriconazole exposure on day 7 i.v. or orally was used as the reference steady state, and the accumulation was calculated as the ratio of the geometric mean $AUC_{0\text{-}12}$ or C_{min} on a specific day to that on day 7.

Note that since there was a study effect in children, the simulated exposures in children were presented by study: the recent study ($STDY_{3,ped}$) versus other studies ($STDY_{1,ped}$ and $STDY_{2,ped}$) or all children combined from the three studies.

RESULTS

Data for analysis. The voriconazole plasma concentration data were available for a total of 112 immunocompromised children (2,022 observations), 26 immunocompromised adolescents (554 observations), and 35 healthy adults (760 observations). The demographics of these subjects are summarized in Table 2.

Model development. A two-compartment model with first-order absorption and mixed linear (first-order) and nonlinear (Michaelis-Menten; time-dependent V_{max}) elimination adequately described the voriconazole i.v. and oral data for children, adolescents, and adults. The forms of the equation for the final model are presented below.

$$V_{max} = V_{max,1} \cdot \left(1 - V_{max,inh} \cdot \frac{(T - 1)}{(T - 1) + (T_{50} - 1)}\right); \quad \text{time-dependent } V_{max}$$

where V_{max} was allowed to reduce from an initial value with time (T). To increase the model stability, as well as the interpretability of model parameters, the V_{max} function was parameterized so that V_{max} at 1 h ($V_{max,1}$) was the parameter estimated, since there were no PK samples providing information on V_{max} at time zero. The reduction in V_{max} over time was best described by an inhibitory function with a maximum fraction of the inhibition ($V_{max,inh}$). T_{50} described the time in hours after initiation of dosing, where half of the maximum inhibition occurred.

$$K_m = \theta_{Km} \cdot (1 + \theta_{STDY1,ped} \cdot STDY_{1,ped})$$

$$V_{max,1} = \theta_{Vmax,1} \cdot (WT/70)^{0.75} \cdot (1 + \theta_{STDY1,ped} \cdot STDY_{1,ped})$$

$$\text{logit}(V_{max,inh})^{*} = \theta_{Vmax,inh} + \theta_{AGE<12} \cdot (AGE < 12)$$

$$T_{50} = \theta_{T50}$$

$$CL = \theta_{CL} \cdot (WT/70)^{0.75}$$

$$V_2 = \theta_{V2} \cdot WT/70$$

$$V_3 = \theta_{V3} \cdot WT/70$$

$$Q = \theta_Q \cdot (WT/70)^{0.75} \cdot (1 + \theta_{QnotSTDY5,adult} \cdot (1 - STDY_{5,adult}))$$

$$\text{logit}(F1) = \theta_{F1}$$

$$k_a = \theta_{ka} \cdot (1 + \theta_{STDY4,adol} \cdot STDY_{4,adol}) \cdot (1 - STDY_{5,adult}) + \theta_{STDY5,adult} \cdot STDY_{5,adult}$$

$$Alag = \theta_{Alag} \cdot (1 + \theta_{AlagnotSTDY5,adult} \cdot (1 - STDY_{5,adult}))$$

where K_m is the Michaelis-Menten constant, θ is the estimate of fixed effect in NONMEM, ped is children, and adol is adolescents. The asterisk indicates that $V_{max,inh}$ is 100% if an adult is a CYP2C19 heterozygous extensive metabolizer (HEM) or poor metabolizer (PM).

Basic GOF plots showed good predictive performance of the constructed model, and no systematic deviations were observed (data not shown). The ability of the final model to describe the observed data is also reflected in the pcVPC plots (Fig. 2), where voriconazole concentrations were described adequately for the different routes of administration and studies. In addition, the observed geomean $AUC_{0\text{-}12}$s were included within the 95% confidence intervals of the simulated geomeans in all dosing regimens except one (the loading dose in adults; the exposure was slightly underestimated, by approximately 10%) (data not shown). These results further illustrated the reliability of the final population PK model for descriptive and Monte Carlo simulation purposes for $AUC_{0\text{-}12}$ estimation.

Voriconazole parameter estimates from the final model are presented in Table 3. In the final model, four structural PK parameters were population specific (for children, adolescents, or adults): $V_{max,inh}$, Q, k_a, and Alag. In addition, children from the

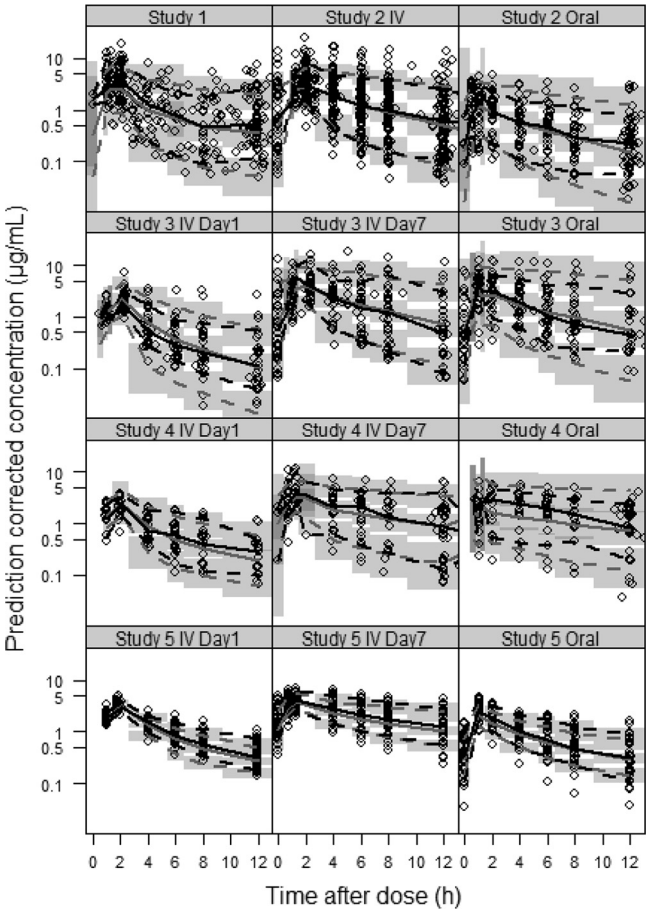

FIG 2 VPC with observed and simulated voriconazole median, 10th and 90th percentile prediction-corrected concentrations, and 80% prediction interval. The open circles represent the prediction-corrected observed concentrations. The black solid and dashed lines and gray solid and dashed lines represent the medians and the 10th and the 90th percentiles of the observed and simulated prediction-corrected voriconazole concentrations, respectively. The shading around these lines represents the 95% confidence interval. The VPC was stratified by study and by protocol day (1st or 7th) for i.v. data and for oral data. No stratification by day for i.v. administration was made for studies 1 and 2.

first study ($STDY_{1,ped}$) had a significantly lower $V_{max,1}$ and K_m than those in the other studies, showing a small study effect. Based on the final parameter estimates, the population PK parameter estimates were computed for a typical child, adolescent, and adult with different body weights (Table 4).

Typical parameter values for K_m, $V_{max,1}$, $V_{max,inh}$, CL, V_2, V_3, Q, F1, k_a, and Alag were estimated with good precision, with a %RSE of <40% (Table 3). The unexplained random interindividual variability (expressed as percent coefficient of variation [CV%]) in these parameters ranged from 14% (for V_2) to 136% (for K_m), with the %RSE of the corresponding variances at ≤78% (Tables 3 and 4). Epsilon shrinkage was 7%, and eta shrinkage was ≤23% for all parameters, except for V_2, where shrinkage was 40%. Correlations were estimated between the parameters describing elimination and distribution (except V_2). K_m and $V_{max,1}$ were 100% correlated in adolescents and adults, and other notable correlations were between K_m and $V_{max,1}$ in children (81%), V_3 and Q (84%), K_m and Q (−60%), and CL and $V_{max,1}$ in children (54%). Residual error was estimated to be 9% and 16% for i.v. and oral data, respectively, in adults, and ranged from 37% to 59% in children and adolescents.

CYP2C19 poor metabolizers. In total, there were five CYP2C19 PMs, including one adult in this data set. It was noted that the exposures in the CYP2C19 PMs from children and adolescents were not among the highest values observed in these studies ($STDY_{2-4}$). Only in adult study 5 did the CYP2C19 PM have the highest voriconazole exposure. Hence, PMs were grouped with HEMs during the covariate analysis. The CYP2C19 genotyping status was evaluated as a potential covariate on K_m, $V_{max,1}$, and $V_{max,inh}$. Only one parameter, $V_{max,inh}$ in adults, was impacted by the CYP2C19 status. The predicted AUC_{0-12} values (based on the final model) in the five CYP2C19 PMs were similar to the observed AUC_{0-12}, indicating that the final model described the CYP2C19 PM data well.

Clearance. The predicted total clearance (linear plus nonlinear) versus time at a concentration of 5 mg/liter across different age groups is presented in Fig. 3. In adolescents and adults, the ratio of nonlinear to linear clearance was reduced from 2.5 at 1 h after initiation of treatment to 0.49 during maintenance treatment, while in children, the estimated reduction in the ratio was less because of the smaller degree of V_{max} inhibition (reduction from 2.5 at 1 h to 0.90 during maintenance treatment). It can be seen that V_{max} is fully inhibited at its maximum [$V_{max,1} \cdot (1 - V_{max,inh})$] during maintenance dosing. For adults classified as CYP2C19 PM or HEM, the nonlinear clearance was predicted to be fully blocked ($V_{max,inh}$ = 100%; V_{max} = 0) based on the final model, so the total clearance is linear and does not depend on the drug concentration.

Oral bioavailability. Although the potential effects of multiple covariates (i.e., weight, age, CYP2C19 status, and formulation) on oral bioavailability (F1) were evaluated, none of them was identified as having a significant impact on the interindividual variability in F1. Weight and age have been found to be statistically significant covariates for F1 when children's data from study 3 alone were analyzed, but in the integrated analysis that included wider age and weight ranges, no tested function of age and weight was found to be significant for F1.

The typical bioavailability was predicted to be 64% in all age groups, and no study effect on bioavailability could be identified. It is acknowledged that the oral bioavailability may have been underestimated in adults, since the k_a approached infinity (and therefore was fixed at a high value, 100 h^{-1}), and at the same time, the Alag was estimated close to the first observation time point in adults (approximately 1 h). Thereby, part of the area under the curve during the first hour after dosing may have been artificially omitted, which could contribute to an underestimation of the exposure in adults following oral treatment.

Simulations in children. At first, different dosing regimens were simulated to predict the total exposures (AUC_{0-12}) in children from the recent study 3.

(i) First i.v. dose on day 1. As shown in Fig. 4a, although the simulated median AUC_{0-12} (11.3 µg · h/ml) in children receiving a 9-mg/kg i.v. loading dose was slightly lower than the adult reference (6 mg/kg i.v.; median AUC_{0-12}, 13.4 µg · h/ml), the distribution of AUC_{0-12} in children substantially overlapped with that in adults due to the higher interindividual variability in children. A 10-mg/kg i.v. dose was projected to provide an average exposure closer to the adult reference, but more children at 10 mg/kg i.v. would have higher voriconazole exposures than adults compared

TABLE 3 Voriconazole population PK parameter estimates for the final model based on i.v. and oral data

Parameter	Typical value (%RSE[a])	Interindividual variability	SD[b] (%RSE[a])
K_m (μg/ml)		$K_m,i = K_m \cdot \exp(\eta_{\text{km-}Vmax1})$	
$\theta_{Km}/\theta_{STDY1,ped}$	1.15 (28)/−0.382 (21)	$\omega_{Km\text{-}Vmax,1}$	1.36 (21)
$V_{max,1}$ (mg/h/70 kg[c])		$V_{max,1},i$[e]	
$\theta_{Vmax,1}$	114 (16)	$\omega_{Km\text{-}Vmax},1/\omega Vmax1,ped$	1.36 (21)/0.239 (78)
$\theta_{STDY1,ped}$	−0.382 (21)	$\theta_{Vmax,scale,adol}$	0.208 (49)
		$\theta_{Vmax,scale,adult}$	0.584 (10)
$V_{max,inh}$[d]			
$\theta_{Vmax,inh}/\theta_{AGE<12}$	1.50 (9.3)/−0.390 (39)		NS[g]
T_{50} (h)			
θ_{T50}	2.41 (6.6)		NS
CL (liter/h/70 kg[c])		$CL,i = CL \cdot \exp(\eta_{CL} \cdot (1 + \theta\eta_{CLnotSTDY5,adult} \cdot notSTDY_{5,adult}))$	
θ_{CL}	6.16 (13)	$\omega_{CL}/\theta\eta_{CLnotSTDY5,adult}$	0.435 (18)/1.70 (14)
V_2 (liter/70 kg)		$V_2,i = V_2 \cdot \exp(\eta_{V2})$	
θ_{V2}	79.0 (3.1)	ω_{V2}	0.136 (21)
V_3 (liter/70 kg)		$V_3,i = V_3 \cdot \exp(\eta_{V3})$	
θ_{V3}	103 (6.0)	ω_{V3}	0.769 (15)
Q (liter/h/70 kg[c])		$Q,i = Q \cdot \exp(\eta_Q)$	
$\theta_Q/\theta_{QnotSTDY5,adult}$	15.5 (6.8)/0.637 (16)	ω_Q	0.424 (22)
F1		$\text{logit}(F1,i) = \text{logit}(F1) + ETATR,i$[f]	
θ_{F1}	0.585 (13)	$\omega_{FnotSTDY5,adult}$	1.67 (19)
		$\omega_{FSTDY5,adult}$	0.686 (18)
		$\theta_{BC\text{-}F}$	0.367 (42)
K_a (h^{-1})		$K_a,i = K_a \cdot \exp(\eta_{ka} \cdot notSTDY_{5,adult})$	
$\theta_{ka}/\theta_{STDY4,adol}$	1.19 (20)/−0.615 (32)	ω_{ka}	0.898 (35)
$\theta_{STDY5,adult}$	100 FIX		
Alag (h)			
$\theta_{Alag}/\theta_{QnotSTDY5,adult}$	0.949 (0.4)/−0.874 (4.4)		NS
Residual error	W[h] $= \theta_{STDY1,ped} \cdot STDY_{1,ped} + \theta_{STDY2,ped} \cdot STDY_{2,ped} + \theta_{STDY3,4,ped,adol} \cdot STDY_{3,4,ped,adol} + SQRT(\theta_{STDY5,adult}^2 + \theta_{STDY5,adult,oral}^2 \cdot Oral) \cdot STDY_{5,adult}$		
$\theta_{STDY1,ped}$	0.593 (7.2)	$\theta_{STDY5,adult}$	0.0912 (3.6)
$\theta_{STDY2,ped}$	0.425 (5.9)	$\theta_{STDY5,adult,oral}$	0.132 (15)
$\theta_{STDY3,4,ped,adol}$	0.365 (4.3)		
$W,i = W \cdot \exp(\eta_{RE} \cdot notSTDY_{5,adult})$			
ω_{RE}	0.456 (12)		

[a] %RSE, percent relative standard error (equal to SE/parameter estimate × 100) (for variability terms, this is the %RSE of the variance estimate). SE was computed based on a limited nonparametric bootstrap ($n = 10$).
[b] SD, standard deviation of random effects (ω).
[c] Note that a power function of 0.75 was applied for clearance terms, i.e., the relationship to weight is not linear.
[d] $V_{max,inh} = \exp(\theta_{Vmax,1} + \theta_{STDY1,ped})/(1+ \exp(\theta_{Vmax,1} + \theta_{STDY1,ped}))$. $V_{max,inh} = 100\%$ if the adult is a CYP2C19 HEM or PM.
[e] $V_{max,1},i = V_{max,1} \cdot \exp(\eta_{Vmax1,ped} \cdot STDY_{1–3,ped} + \eta_{Km\text{-}Vmax1} \cdot \theta_{Vmax,scale,adol} \cdot STDY_{4,adol} + \eta_{Km\text{-}Vmax1} \cdot \theta_{Vmax,scale,adult} \cdot STDY_{5,adult})$.
[f] Box-Cox transformation. $ETATR,i = (EXPETA,i^{\theta BC\text{-}F} - 1)/\theta_{BC\text{-}F}$; $EXPETA,i = \exp(\eta_{FnotSTDY5,adult}) \cdot notSTDY_{5,adult} + \exp(\eta_{FSTDY5,adult}) \cdot STDY_{5,adult}$.
[g] NS, not supported in the model.
[h] W, standard deviation of residual error (on a log scale).

with children at 9 mg/kg i.v. Therefore, to minimize potential overexposure of a small percentage of children, a 9-mg/kg i.v. loading dose was considered appropriate to match the 6-mg/kg i.v. loading dose in adults.

(ii) Steady-state i.v. dosing regimen. Similarly, although the simulated median $AUC_{0\text{-}12}$ (24.3 μg · h/ml) in children receiving 8 mg/kg i.v. q12h was lower than the adult reference (4 mg/kg i.v. q12h; median $AUC_{0\text{-}12}$, 37.9 μg · h/ml), the distribution of $AUC_{0\text{-}12}$ in children substantially overlapped with that in adults due to higher interindividual variability in children (Fig. 4b). A 9-mg/kg i.v. dose was projected to provide an average exposure closer to the adult reference, but more children at 9 mg/kg i.v.

TABLE 4 Voriconazole pharmacokinetic parameter estimates for typical subjects with different weights

Parameter	Typical value	IIV (CV%)[a]
K_m (μg/ml)	1.15	136
$V_{max,1}$ (mg/h)[b]		
70-kg adult	114	79
55-kg adolescent	95.1	28
45-kg adolescent/child	81.8	28/24
20-kg child	44.6	24
$V_{max,inh}$ (%)[c]		
Adult PM/HEM	100	NS
Adult UM/EM	82	
Adolescent	82	
Child	75	
T_{50} (h)	2.41	NS
CL (liter/h)[b]		
70-kg adult	6.16	44
55-kg adolescent	5.09	75
45-kg adolescent/child	4.38	75
20-kg child	2.38	75
V_2 (liter) 70-kg subject	79.0	14
V_3 (liter) 70-kg subject	103	77
Q (liter/h)[b,e]		
70-kg adult	15.5	42
55-kg adolescent	21.2	42
45-kg adolescent/child	18.2	42
20-kg child	9.92	42
F (%)[c]	64	–[d]
Alag (h)		
Adult	0.949	NS
Adolescent/child	0.120	NS
K_a (h^{-1})		
Adult	100 FIX	
Adolescent	0.458	90
Child	1.19	90
Residual error (%)		
Adult, i.v.	9	NS
Adult, oral	16	NS
Adolescent	36	46
Child	37–59	46

[a] IIV (CV%), interindividual variability (expressed as percent coefficient of variation). The model for IIV estimation also included covariance between K_m, $V_{max,1}$, CL, V_3 and Q. For adolescents and adults, IIV for K_m and IIV for $V_{max,1}$ were 100% correlated. NS, not significant.

[b] The values reflect the effect of allometric scaling.

[c] $V_{max,inh}$ and F were modeled on the logit scale $[\exp(\theta)/(1 + \exp(\theta))]$, where θ estimates were 1.50 ($V_{max,inh}$ for adults/adolescents), 1.11 ($V_{max,inh}$ for children) and 0.585 (F), respectively.

[d] The variability in F was Box-Cox transformed; $TR\eta_i = ((\exp(\eta_i))^{0.367} - 1)/0.367$; $\text{logit}(F_i) = \text{logit}(F) + TR\eta_i$. The SD of η_i was estimated at 0.686 in adults and at 1.67 in children and adolescents.

[e] There was a statistically significantly higher Q in children and adolescents (per-kg basis) than in healthy adults.

q12h would have higher voriconazole exposure than adults compared with children at 8 mg/kg i.v. q12h. To minimize potential overexposure of a small percentage of children, 8 mg/kg i.v. q12h was considered appropriate to match 4 mg/kg i.v. q12h in adults.

(iii) Steady-state oral dosing regimen. The simulated median $AUC_{0\text{-}12}$ (15.1 μg · h/ml) in children receiving 9 mg/kg orally q12h was slightly higher than the adult reference (200 mg orally q12h; median $AUC_{0\text{-}12}$, 11.7 μg · h/ml), and the distribution of $AUC_{0\text{-}12}$ values in children substantially overlapped with that in adults due to higher interindividual variability in children (Fig. 4c). Since this was to match a step-down oral maintenance dose of 200 mg orally q12h in adults, use of 9 mg/kg orally q12h could minimize potential undetectable levels in children. Except for one child, the 9-mg/kg q12h oral dose would not provide exposures in children weighing >40 kg that were much higher than the range observed in adults receiving 200 mg orally q12h (data not shown). Nonetheless, as a precautionary measure to ensure no potential overexposure in heavy children, an upper limit was proposed based on the simulations at different dosing caps (i.e., 300, 350, and 400 mg). A 350-mg cap would provide the geometric mean $AUC_{0\text{-}12}$ that

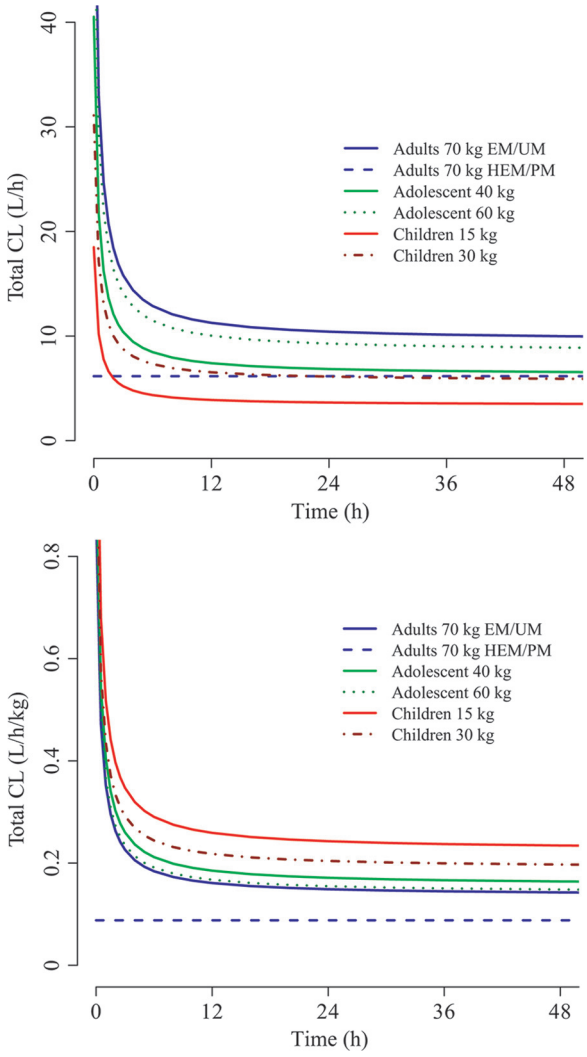

FIG 3 Predicted total clearance (linear plus nonlinear) at a concentration of 5 mg/liter versus time from start of treatment for typical subjects.

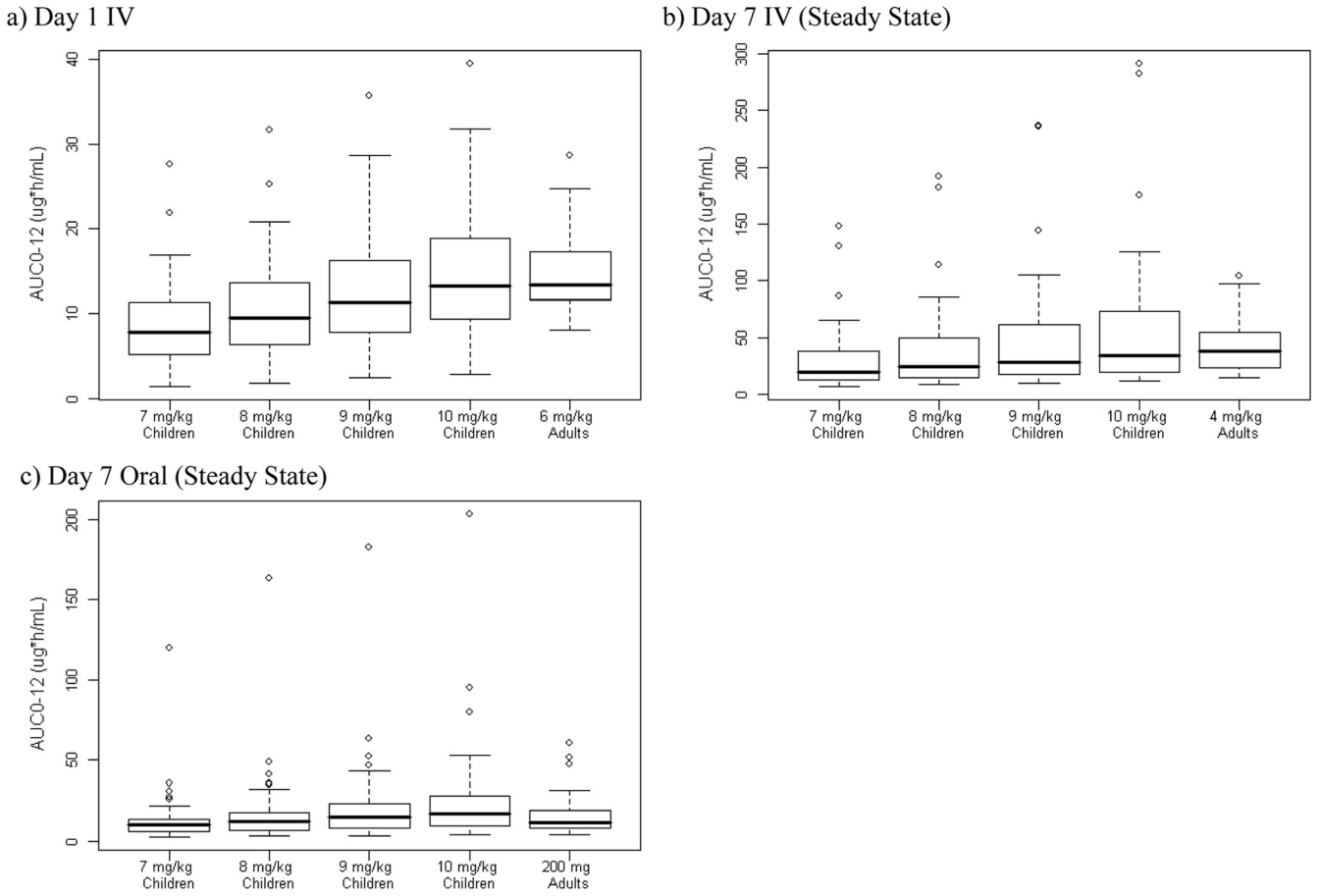

FIG 4 Comparisons of predicted voriconazole exposures ($AUC_{0\text{-}12}$) in children ($n = 40$) in study 3 receiving different dosing regimens to those of adults ($n = 35$) in study 5. Note that the dosing frequency is q12h and the maximum oral dose in children was set to 350 mg q12h. In each diagram, the box represents the interquartile distance, with the median indicated by a solid line in the center of the box; the whiskers represent ≤1.5 times the interquartile range, and outliers are represented by points outside the whiskers.

most closely matches the geometric mean $AUC_{0\text{-}12}$ in adults receiving 200 mg orally q12h. Hence, 9 mg/kg (a maximum of 350 mg) orally q12h in children was selected to match 200 mg orally q12h in adults.

Subsequently, exposures at different dosing regimens were simulated in all children combined from three studies and compared with the adult reference (data not shown). The same dosing recommendations were derived.

Simulations in adolescents. Based on deterministic simulations, one scenario (adolescents 12 to 14 years old weighing <50 kg receiving children's doses, and all other adolescents receiving adult doses) was identified as the best among all 14 scenarios (different combinations of age and weight cutoffs) evaluated, and the comparisons are presented in Fig. 5.

Since the increment of cutoffs for age and weight was small, a few other scenarios also showed acceptable results, which included the scenario of 12 to 14 years old with a 55-kg cutoff. For instance, the geometric mean and median $AUC_{0\text{-}12}$ for the scenario of a 55-kg cutoff were closer to the adult reference than those for the 50-kg cutoff scenario; however, the 95th percentile of $AUC_{0\text{-}12}$ at i.v. steady state for the 55-kg cutoff scenario was much higher than that in adults compared with the 50-kg cutoff scenario (25% versus 4% higher). This indicates a greater potential for overexposure to voriconazole with the 55-kg cutoff scenario. Based on the totality of $AUC_{0\text{-}12}$ distribution, a 50-kg cutoff was considered an appropriate option.

Proposed doses in pediatric subjects. The doses proposed for the pediatric population to match voriconazole exposures in adults are summarized in Table 5. Of note, a previous PK analysis determined that 4 mg/kg i.v. q12h in children could provide voriconazole exposure comparable to that in adults at 3 mg/kg i.v. q12h (15), and this was also confirmed in the current analysis. The predicted exposure parameters for voriconazole in children and young adolescents (12 to 14 year olds weighing <50 kg) at the recommended doses are summarized in Table 6.

Assessment of trough sample collection timing. Exposure (i.e., $AUC_{0\text{-}12}$ and C_{min}) simulations over 7 days during the i.v. or oral switch period showed that by day 3, i.v. or orally (before the 5th dose), voriconazole exposures in children and adults were close to steady state, as demonstrated by accumulation ratios of approximately 80 to 90% during the i.v. period and within 125% during the i.v. to step-down oral dose switch period (data not shown). The day 3 trough sample was considered acceptable for use in facilitating dose adjustment, since slight under- or overestimation of steady-state exposure (e.g., trough sample collection on day 3) should not pose any significant risk to a patient's safety.

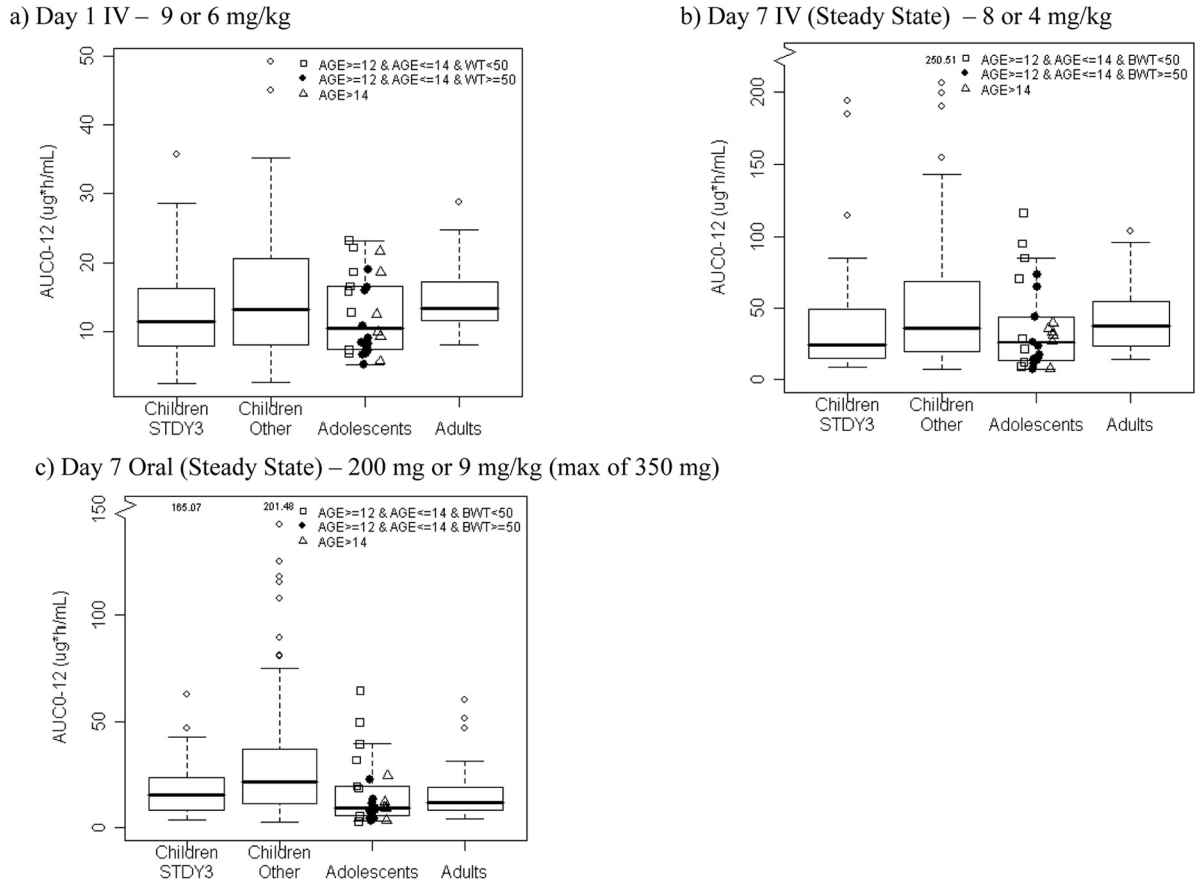

FIG 5 Comparisons of predicted exposures ($AUC_{0\text{-}12}$) in adolescents (cutoffs, 12 to 14 years old and <50 kg) with those in children and adults. Children Other, $STDY_1$ and $STDY_2$; Adolescents, $STDY_4$; Adults, $STDY_5$. The dosing regimens are also presented in Table 5. In each diagram, the box represents the interquartile distance, with the median indicated by a solid line in the center of the box; the whiskers represent ≤1.5 times the interquartile range, and outliers are represented by points outside the whiskers.

DISCUSSION

Model development. The model structure developed in this analysis has additional complexity compared with the previous model (8). The current model includes mixed linear and nonlinear (Michaelis-Menten and time-dependent V_{max}) elimination. These complexities resulted in substantial improvements in the goodness of fit, with a total drop in OFV of more than 400 units.

Voriconazole is known to inhibit its own metabolism, and its major metabolite (voriconazole *N*-oxide) also inhibits these enzymes (similar potencies on CYP2C9 and CYP3A4; lower potency on CYP2C19) (12). It was thought that both voriconazole and its *N*-oxide metabolite would contribute to enzymatic inhibition after voriconazole administration. However, because of model complexity and run times, the assumption was made that the inhibition was independent of the voriconazole dose and concentration, and metabolite concentrations were not included in the modeling. The time-dependent V_{max} was estimated to decrease to a pronounced degree during the first day of administration. The estimated T_{50}, the time at which half of the maximum inhibition occurs, was short (2.4 h), and the maximum fractions of inhibition ($V_{max,\ inh}$) were high: 75% for children and 82% for adolescents and adults.

When the time-dependent V_{max} was included in the model, the estimate of the peripheral volume of distribution (V_3) dropped by approximately 25%, and the ratio between the peripheral and central volumes of distribution was lower than that obtained from the

TABLE 5 Voriconazole doses in children and adolescents providing exposures comparable to those in adults

Group	Matching dose (q12h)			
	Loading dose (i.v.)	Maintenance dose		
		i.v.	i.v.	Oral
Children (2 to <12 yr old) and young adolescents (12 to 14 yr old weighing <50 kg)	9 mg/kg	8 mg/kg	4 mg/kg	9 mg/kg (maximum dose of 350 mg)
Other adolescents (12–14 yr old weighing ≥50 kg and 15–16 years old) and adults	6 mg/kg	4 mg/kg	3 mg/kg	200 mg

TABLE 6 Predicted exposure parameters of voriconazole in immunocompromised children (2 to <12 years old) and young adolescents (12 to 14 year olds weighing <50 kg)

Parameter	Geometric mean (CV%)[a]			
	9 mg/kg i.v. (loading dose)	4 mg/kg i.v. q12h	8 mg/kg i.v. q12h	9 mg/kg orally q12h (maximum of 350 mg)
AUC_{0-12} (μg · h/ml)	11.6 (52)	9.92 (69)	29.2 (99)	15.7 (113)
C_{max} (μg/ml)	2.84 (30)	2.42 (28)	4.90 (64)	2.67 (72)
C_{min} (μg/ml)		0.23 (119)	1.04 (140)	0.48 (175)

[a] Summary statistics were based on pooled data from 40 children in study 3 and on 8 young adolescents weighing <50 kg in study 4. These values were predicted using individual PK parameters and an infusion rate of 3 mg/kg/h for i.v. administration.

previous analysis (1.3 versus 2.7) (8). A likely explanation is that the peripheral volume becomes inflated to accommodate a prolonged half-life when time-dependent elimination is ignored.

The observed difference in the k_a between children (1.19 h^{-1}) and adolescents (0.46 h^{-1}) might be a result of different formulations (POS in children versus tablets in adolescents).

As described above, the oral bioavailability in adults may have been underestimated in this analysis compared with the value (96%) reported previously (12). Although multiple factors (i.e., study, weight, age, CYP2C19 status, and formulation) were evaluated as potential covariates, none of them (except the study on variability) was identified as having a significant impact on oral bioavailability. In the current model-based analysis, bioavailability was estimated when both the concentration and time dependence in PK were considered. This could be a reason why the bioavailability estimated here (64%, with no dependence on age) differed from previous estimates of 96% in adults (12) and 45% in children (8).

Overall, voriconazole exposure in children and adolescents exhibited higher variability than that in adults. Of note, the reference adult study ($STDY_5$) was performed in healthy subjects in a well-controlled setting, while most children and adolescents were hospitalized transplant patients with very low activity who received many concomitant medications and procedures during the study period. Although the identified covariates reduced the unexplained interindividual variability and provided a better description of the observed data, the unexplained variability was still relatively high.

Simulations. As shown in Fig. 5, due to large interindividual variability in voriconazole exposure in children and adolescents, some children and adolescents may have much higher or lower voriconazole exposures at the proposed dosing regimens. For instance, at the 8-mg/kg i.v. maintenance dose, approximately 10 to 20% of children may have overexposure and 10 to 20% may have underexposure. Therefore, these regimens should be considered the initial dosing recommendation, and close monitoring of a patient's tolerability profile and response is highly recommended. Similar to adult dosing instructions, flexible dose adjustment should be implemented for pediatric patients in response to inadequate response or intolerance for voriconazole treatment. For instance, the i.v. dose may be increased or decreased by 1-mg/kg steps; the oral dose may be increased or decreased by 1-mg/kg steps (or by 50-mg steps if the maximum oral dose of 350 mg was used initially).

It should be noted that an 8-mg/kg i.v. maintenance dose will provide voriconazole exposure approximately 2-fold higher than a 9-mg/kg oral maintenance dose in pediatric subjects (Table 6). Hence, it is recommended to initiate the therapy with an i.v. regimen for the treatment of invasive fungal infections, and an oral regimen should be considered only after there is significant clinical improvement.

Practical implementation in clinical practice was taken into consideration for the setup of the dosing strategy in young adolescents. Although the Tanner scale is a better measurement of maturation than age and body weight, the data on pubertal development were not available in this adolescent study. Also, it is likely that these data (Tanner scale) may not always be available when treating this age group in clinical practice. It is acknowledged that a different, intermediate dose (e.g., 6 mg/kg i.v. q12h for young adolescents versus 4 mg/kg in adults and 8 mg/kg in children) may also provide exposure comparable to that in adults. However, the concern is for potential confusion in prescribers when another set of dosing regimens is introduced, since multiple regimens for children and adults already exist. In addition, given the large interindividual variability in pediatric subjects, the regimens proposed will be used as the initial recommendation, and the dose can be adjusted based on the patient's response, tolerability profile, and/or voriconazole trough concentration. Therefore, the practical approach was implemented in this analysis: set up an acceptable age and weight cutoff.

Previously, a good correlation between voriconazole total exposures and trough concentrations at steady state was identified based on the observed data in children, adolescents, and adults (4, 5), and a similar trend was also observed in this analysis.

Of note, in this analysis, all 5 studies were conducted in subjects who were prohibited from receiving inhibitors or inducers of CYP450 enzymes that affect voriconazole exposure. Drug-drug interaction is one of the major factors contributing to the intra- and interindividual variability in voriconazole exposure in the clinical setting, which affects the prediction of voriconazole exposure at a given dose. Therefore, concomitant medications used in a specific patient should be taken into consideration for voriconazole dosing management.

In summary, a two-compartment model with first-order absorption and mixed linear and nonlinear (Michaelis-Menten and time-dependent V_{max}) elimination adequately described the voriconazole data across different age groups. The results of this integrated analysis suggested the following. The predicted total exposure (AUC_{0-12}) in children following a 9-mg/kg i.v. loading dose was comparable to that in adults following a 6-mg/kg i.v. loading dose. The predicted AUC_{0-12}s in children following 4 and 8 mg/kg i.v. q12h were comparable to those in adults following 3 and 4 mg/kg i.v. q12h, respectively. The predicted AUC_{0-12} in children following 9 mg/kg (maximum, 350 mg) orally q12h was compa-

rable to that in adults following 200 mg orally q12h. To achieve voriconazole exposures comparable to those of adults, dosing in 12- to 14-year-old adolescents depends on their weight: they should be dosed like children if their body weight is <50 kg and like adults if their body weight is ≥ 50 kg. Other adolescents (15 to 16 years old, regardless of body weight) should be dosed like adults. The above proposed dosing regimens are being evaluated in ongoing pediatric clinical studies.

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