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ARTICLE

Physiologically based pharmacokinetic modeling of tadalafil to inform pediatric dose selection in children with pulmonary arterial hypertension

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Abstract

Tadalafil, a phosphodiesterase 5 inhibitor, is being investigated as a treatment for pulmonary arterial hypertension (PAH) in children aged 6 months to less than 18 years. Tadalafil pharmacokinetic (PK) data in children less than 2 years old are unavailable, therefore a physiologically based pharmacokinetic (PBPK) model was developed to enable estimation of tadalafil doses in children less than 2 years old. The model was verified in adults and extended for use in children by modifying CYP3A-mediated intrinsic clearance to include CYP3A7. To account for co-dosing of the commonly prescribed moderate CYP3A4 inducer bosentan, predicted exposures were increased by a factor of 1.54 based on changes in exposure in adults with PAH. This factor was predictable using a bosentan PBPK model. The tadalafil model was verified in children aged greater than or equal to 2 years by comparing predicted and observed exposures. Tadalafil doses for children less than 2 years old were calculated as target area under the concentration curve from zero to 24 h ($AUC_{0–24}$)/predicted $AUC_{0–24}$, with target $AUC_{0–24}$ of 10,000 ng*h/ml based on adult 40 mg single dose exposures determined in patients without bosentan background treatment. These doses were 2 mg, 3 mg, 4 mg, and 6 mg, respectively, for children aged birth to less than 1 month, 1 month to less than 6 months, 6 months to less than 1 year, and 1 to less than 2 years. Due to uncertainties in CYP maturation, a nonmechanistic steady-state volume scalar, and lack of PK data in children less than 2 years old, accumulation of tadalafil to steady-state in children less than 2 years was not verifiable. Safety of proposed doses is supported by postmarketing research and investigator-led trials.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Tadalafil pharmacokinetic (PK) data is available in children age 2 years to less than 18 years, but none is available in children younger than 2 years to guide dosing in this patient population.

WHAT QUESTION DID THIS STUDY ADDRESS?

In children in age groups from birth to less than 2 years, what doses are expected to result in efficacious and safe tadalafil exposures? How does co-therapy with bosentan affect the PK of tadalafil in children?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Recommended doses of tadalafil in children less than 2 years old are suggested based on physiologically based pharmacokinetic (PBPK)-predicted exposures matched to adult 40 mg single dose exposures. Verified PBPK models of tadalafil and bosentan are presented in support of tadalafil pediatric dose estimation.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Using the PBPK model framework has enabled recommendation of doses to guide initial tadalafil therapy in children from birth to less than 2 years. Verified tadalafil and bosentan PBPK models can be used for making predictions in other drug-drug interaction scenarios.

INTRODUCTION

Tadalafil (Cialis, Adcirca) is a potent and selective phosphodiesterase type 5 (PDE5) inhibitor approved for erectile dysfunction, pulmonary arterial hypertension (PAH), and benign prostatic hypertrophy (BPH) in adults. The 35-hour terminal half-life ($t_{1/2}$) of tadalafil in adult patients with PAH enables once daily administration for this condition. Approved treatments for PAH in children at least 1 year of age include the endothelin receptor agonist (ERA) bosentan in the United States and European Union and the PDE5 inhibitor sildenafil in the European Union. In children, PAH therapies are often used in combination: for example, bosentan plus sildenafil.[1,2] An extensive review of treatments for PAH in pediatric patients is presented in a consensus statement by the European Pediatric Pulmonary Vascular Disease Network.[2] Tadalafil is a CYP3A4 substrate based on in vitro data[3,4] and clinical drug-drug interaction (DDI) studies conducted in adults with the strong CYP3A4 inhibitor ketoconazole,[5] the strong CYP3A4 inducer rifampicin,[5] and the moderate CYP3A4 inducer bosentan.[6] Despite the effect of bosentan, a dose adjustment to achieve efficacious exposures of tadalafil in adults is not provided in labeling.[7]

Exposure matching in pediatric patients is an approach to select doses based on the difference between exposures in children and adults; it requires that pediatric exposure data be available. For tadalafil, pharmacokinetics (PK) in 19 pediatric patients with PAH aged 2 to less than 18 years at study start have been reported[8] (NCT01484431). Tadalafil has also been explored as a treatment for Duchenne muscular dystrophy in boys 7 to 14 years old but did not meet its primary end point in improving exercise capacity; this study included sparse PK sampling at steady-state[9] (NCT01865084). Contributing to the body of PK data on tadalafil are a study with sparse PK sampling in pediatric patients with PAH aged 2 to 18 years at study entry[10] (NCT01824290) and the PHIRST-1 study (NCT00125918), where one 14-year-old patient was included.[11] Additional reports of tadalafil use in children and small observational trials with inconsistent dosing based on physician choice support the safety of tadalafil in pediatric patients, but without accompanying PK sampling to support exposure matching in children less than 2 years old. These studies include a postmarketing study of chronic tadalafil administration in Japanese patients, where a subset of participants were less than 2 years old ($N = 120$) with PAH-related conditions (associated with PAH, familial PAH, idiopathic PAH, persistent pulmonary hypertension of the newborn, and pulmonary hypertension).[1] Initial doses administered to patients aged less than 1 year ranged from 0.2 to 20 mg (median 3 mg; $N = 79$) and doses to patients aged 1 to less than 2 years ranged from 0.8 to 20 mg (median 5 mg; $N = 41$). Median tadalafil dose at last administration for patients aged less than 1 year was 5 mg and for patients aged 1 to less than 2 years was 7 mg, both with the same ranges and N as for initial doses. The duration of tadalafil administration ranged from 3 to 1156 days (median 231 days) for ages 0 to less than 1 year and ranging from 4 days to 921 days (median 316 days) for ages 1 to less than 2 years. Multiple smaller studies that support the safety of tadalafil include a study of tadalafil in children with PAH ($N = 33$) aged 4–18 years who received an average dose of 1 mg/kg tadalafil once daily for varying numbers of months,[12] a study of pediatric patients aged 3 months to 2 years ($N = 21$) with a large septal defect and PAH who received tadalafil 1 mg/kg/day for up to ~ 5 weeks,[13] and a study of pediatric patients aged 6 to 19 years (mean age 10.11 years; $n = 18$) with Tetralogy of Fallot who received 1 mg/kg tadalafil for 8 weeks.[14] Tadalafil is currently under investigation as a once-daily treatment for PAH in pediatric patients 6 months to less than 18 years old.

Over time, sponsor companies and regulators have gained confidence in physiologically based pharmacokinetic (PBPK) modeling applications and more specifically pediatric PBPK; PBPK is particularly valuable in cases where conducting clinical studies is logistically impractical or unethical, or when extrapolation to a different population is possible based on demonstrated confidence in the data and the approach.[15-17] Recent examples of these methods include work by Lang and colleagues, who conducted a literature review to inform their combined PBPK/pharmacodynamic modeling for ivabradine, a drug used to treat chronic heart failure in children, as a CYP3A4 substrate and victim of inhibition DDIs.[15] Their approach included a comparison of CYP3A4 ontogeny (maturation) functions from Salem[18] and Upreti[19] using the Simcyp® population-based absorption, distribution, metabolism, and excretion (ADME) simulator. Similarly, Salerno and colleagues used custom CYP3A4, CYP3A5, and CYP3A7 maturation functions in the PKsim PBPK framework to model dose adjustments for the PDE5 inhibitor sildenafil in children coprescribed fluconazole for fungal infections.[20] Maturation functions used in that publication were based on work from Lacroix,[21] Stevens,[22] and Treluyer[23] for CYP3A4, an assumption that pediatric CYP3A5 abundance equaled adult CYP3A5 abundance at all ages, and based on the work of Lacroix[21] and Stevens[22] for CYP3A7. Likewise, the current effort utilizes Simcyp maturation functions based on the Salem function for CYP3A4 and a meta-analysis from three sources for CYP3A7.[22-24] The objectives of this work were to support safe and efficacious dosing of tadalafil in young children with PAH by predicting recommended doses of tadalafil and understanding the effect of bosentan cotreatment in pediatric subjects less than 2 years old using PBPK modeling.

METHODS

All Lilly sponsored tadalafil pediatric trials referenced were registered in clinicaltrials.gov, conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and approved by an ethics review board. Informed consent was obtained from adults, and consent of children was obtained from a parent or legal guardian; children may also have been required to give documented assent.

Modeling strategy

The model of tadalafil disposition in adults was developed and applied to pediatric populations in Simcyp version 18 (Certara, Princeton, NJ). The Simcyp Healthy Volunteer and Pediatric Populations were used in adult and pediatric simulations, respectively. All simulations were conducted using a fixed seed value of 1, and where coefficient of variation was an input, the value was 30%. The approach to developing the PBPK model to predict doses of tadalafil in young children (<2 years old) is depicted in Figure 1.

Development of the tadalafil model for adults

The tadalafil model for adults was developed using physicochemical properties, in vitro data, and clinical data, with Simcyp inputs shown in Table 1.

Bioavailability (F; the product of Fa, fraction escaping metabolism at the gut wall [Fg], and hepatic availability [Fh]) was ~ 0.8, assuming Fa = 0.8, Fg = 1 based on slow

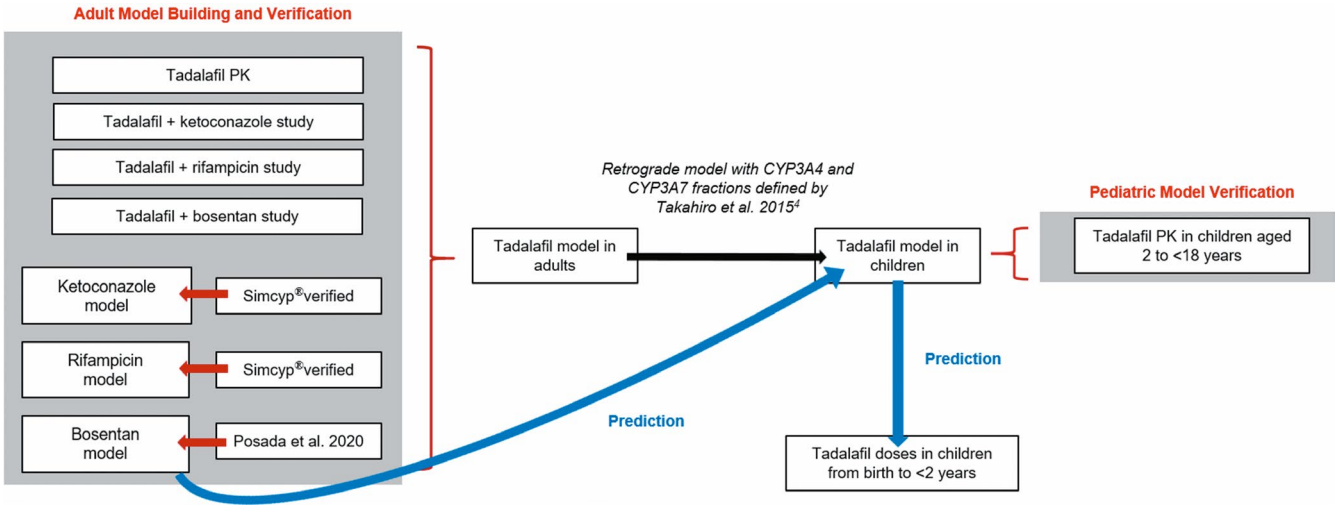

FIGURE 1 Strategy for pediatric PBPK model development to inform tadalafil dose predictions in children aged from birth to less than 2 years. PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic

TABLE 1 Simcyp input parameters for tadalafil in adults

Parameter name	Value	Rationale and source
Physicochemical properties and binding		
Molecular weight	389.4	Calculated from structure
cLogP	1.64	Chemaxon
Compound type	Neutral	No ionizable groups
$f_{u,p}$	0.06	Measured in-house and supported by measured ex vivo samples from children[25]
B:P	0.55	1-hematocrit; verified with concentrations of radioactivity in blood and plasma at early timepoints in study LVAA[5]
Absorption		
F_a	0.8	At least 80% absorbed based on 16% (adjusted for total recovery) of radioactive dose measured in feces from 0 to 48 h.
k_a (h^{-1})	1.86	PopPK analysis of erectile dysfunction patient data[26]
P_{eff} (10^{-4} cm/s)	1.67	Calculated using in-house model based on MDCK data
f_{uGut}	1	Assumed
Q_{gut} (L/h)	7.38	Modified from P_{eff}-based value (9.04) by retrograde calculator to reconcile forward and backward calculations of Fg in retrograde model.
Distribution model type: Full PBPK model		
V_{ss} (L/kg)	0.73	Predicted by method 1 with Kp scalar of 2.19. $V_{ss}/F = 63.8$ L[26]; therefore $V_{ss} = 51.04$ L assuming F = 0.8 and body weight = 70 kg.
Elimination pathways		
fm CYP3A4	0.75	AUC ratio of 4.1 with ketoconazole[5] assume that all interaction is at the liver so AUC ratio = 1/(1-fm).
rCYP3A4 CL_{int} (µL/min/pmol)	0.04415	CL/F = 1.99 L/h[26]; therefore CL = 1.59 L/h, assuming F = 0.8. CL_{int} calculated using Retrograde Model Reverse Translational Tool in Simcyp version 18.
Additional HLM CL_{int} (µl/min/mg)	1.904	Accounts for remaining clearance as calculated by Retrograde Model Reverse Translational Tool in Simcyp version 18.
Renal clearance	0	<0.1 to 0.3% of dose excreted unchanged in urine[5]

Abbreviations: AUC, area under the concentration curve; B:P, blood to plasma concentration ratio; cLogP, logarithm of the octanol water partition coefficient; CL, clearance; $CL_{int,}$ intrinsic clearance; CYP, cytochrome P450 enzyme; F, absolute bioavailability; F_a, fraction absorbed; f_m, fraction of the drug metabolized; f_{uGut}, fraction unbound in the gut; $f_{u,p}$, fraction unbound in plasma; HLM, human liver microsomes; k_a, absorption rate constant; K_p scalar, a factor applied to adjust predicted partitioning into tissues; MDCK, Madin-Darby canine kidney; P_{eff}, effective permeability; PopPK, population pharmacokinetics; Q_{gut}, hybrid term including both villous blood flow and permeability through the enterocyte membrane; V_{ss}, volume of distribution at steady-state.

CYP3A4-mediated intrinsic clearance (CL_{int}), and Fh = 0.97 (calculated as 1- [CL/B:P]/Qh, where Qh was assumed to be 90 L/h). Simulation trial designs for tadalafil in adults are presented in Table S1.

Extension of the tadalafil model for use in children

Other than the inputs describing the tadalafil metabolic CL_{int}, all input parameters for the model of tadalafil disposition in children were the same as for adults. A maturation profile, labeled the "fast" ontogeny in Simcyp, where abundance increases from 0 to adult levels about 1 month after birth, was selected for the nonspecific additional human liver microsomal (HLM) CL_{int} pathway.

Stevens and colleagues report that CYP3A7 represents 64 to 100% of the total CYP3A protein in children aged from birth to 6 months.[22] CYP3A7 rapidly decreases as CYP3A4 rises over the first few months after birth.[21,22] CYP3A4 and CYP3A7 abundances at selected ages were calculated from data provided in Simcyp version 18 using Equation 1 and Equation 2, as shown in Figure S1.

$$\text{Fraction of adult abundance} = F_{\text{birth}} + \frac{\left(\text{Adult}_{\text{Max}} - F_{\text{birth}}\right)\text{Age}^{n}}{\text{Age}_{50}^{n} + \text{Age}^{n}} \quad (1)$$

$$\text{Abundance at age} = \text{Fraction of adult abundance} \times \text{adult enzyme specific abundance} \quad (2)$$

Where F_{birth} is the fraction of adult enzyme-specific abundance present at birth (0.11 for CYP3A4; 33 for CYP3A7), $\text{Adult}_{\text{Max}}$ is the maximal fraction of adult abundance (1.06 for CYP3A4, 0 for CYP3A7), Age_{50} is the age at which half the $\text{Adult}_{\text{Max}}$ is reached (0.64 for CYP3A4; 0.141 for CYP3A7), n is a slope factor (1.91 for CYP3A4; 2.76 for CYP3A7), and adult enzyme specific abundance

is (137 pmol/mg for CYP3A; 5 pmol/mg for CYP3A7). The CYP3A4 abundance curve is modified from the Salem function[18] to reflect postnatal age rather than the originally reported postmenstrual age (email communication from Trevor N. Johnson, PhD, 17 May 2021).

CL_{int} inputs were then modified to incorporate CYP3A7-mediated metabolism. The adult rCYP3A4 CL_{int} input of 0.04415 μl/min/pmol was multiplied by the adult CYP3A4 abundance of 137 pmol/mg to give total CYP3A-mediated HLM CL_{int} in adults of 6.05 μL/min/mg. It was assumed that, in children, the CYP3A-mediated HLM CL_{int} is the same as in adults, and that activity is directly related to enzyme abundance. The total CYP3A-mediated HLM CL_{int} was separated into CYP3A4 and CYP3A7 components, as informed by tadalafil recombinant CYP data.[4] Relative activity factors are not available to account for differences in expression between the expressed enzymes and human liver microsomes. However, based on the reported K_m of tadalafil for CYP3A4 being much lower than the K_m for CYP3A7,[4] the affinity of tadalafil for CYP3A4 is much greater (about 30 times) than for CYP3A7. By calculating $1/(K_{m,CYP3A4}/K_{m,CYP3A7})$ and assuming equal abundance of CYP3A4 and CYP3A7, only around 3% of tadalafil entering the liver will be metabolized by CYP3A7. The total CYP3A-mediated HLM CL_{int} was split by these fractions, and the recombinant CYP CL_{int} inputs were back calculated as HLM CL_{int} per pathway (μl/min/mg) divided by CYP-specific abundance (pmol/mg). For CYP3A4, HLM CL_{int} was 5.9 μl/min/mg divided by 137 pmol/mg to give a pediatric recombinant CL_{int} input of 0.0428 μl/min/pmol CYP3A4, and for CYP3A7, HLM CL_{int} was 0.2 μl/min/mg divided by 5 pmol/mg to give a pediatric recombinant CL_{int} input of 0.0363 μl/min/pmol CYP3A7.

All simulations in the pediatric population (birth to <18 years) were conducted using a tadalafil dose of 1 mg. Simulation trial designs for children are presented in Table S2.

Target exposure and pediatric doses

Target day 1 area under the concentration curve from zero to 24 h (AUC_{0-24}) is 10,000 ng.h/ml, which corresponds to a predicted single dose exposure for adults on 40 mg tadalafil and not receiving bosentan. In healthy adults on 20 mg tadalafil, the average accumulation from single dose to steady-state is about 1.6,[27] whereas accumulation is 1.3 in the 19 pediatric subjects with PAH (ages 2 to 17 years) whose AUC was calculated on both day 1 and day 14.[8] The median population PK (PopPK) model-estimated adult steady-state AUC_{0-24} for patients on 40 mg tadalafil and not taking bosentan in study LVGY was 14,825 ng.h/ml (post hoc model estimated 5th to 95th percentile 9070 to 27,800 ng.h/ml),[8] and the accumulation ratio is about 1.5. Therefore, an adult patient with an AUC_{0-24} of 14,825 ng.h/ml at steady-state would be expected to have an AUC_{0-24} of about 10,000 ng.h/ml after a single dose. Tadalafil doses were calculated as target AUC_{0-24}/predicted dose-normalized AUC_{0-24}, with a target AUC_{0-24} of 10,000 ng.h/ml.

Verification of exposure matching in children aged 2 to 17 years

Projected pediatric doses were then validated by utilizing available pediatric data. To use all available data, observed exposures in pediatric patients receiving the moderate CYP3A inducer bosentan were increased by a factor of 1.54 (calculated as 1/[1–0.35]) to account for the ~ 35% lower observed exposures when adults with PAH were co-treated with bosentan in study LVGY.[28] Use of a nonmechanistic exposure scaling factor was necessary because bosentan doses were not known.

Testing of assumptions

Two possibilities were explored to understand the effect of rifampicin on tadalafil in the gut. First, the absorption rate constant (k_a) for tadalafil was reduced from 1.86 h^{-1} to 0.84 h^{-1} in the adult population to vary the time over which tadalafil is available for interaction with rifampicin at the gut. Additionally, the Q_{gut} input for tadalafil, as calculated via the retrograde approach in Simcyp, was reduced to in turn reduce the F_g. Additionally, parameters related to the fractional clearance in the various age groups were uncertain and thus were tested by varying relevant input parameters. To understand the impact of the assignment of the fractional CYP3A7 contribution, the fractional contribution of CYP3A7 was increased to 6% and 10% (while proportionally decreasing the contribution of CYP3A4). To understand the impact of maturation of the generic additional HLM CL_{int} pathway, the maturation profile was replaced with a profile where abundance rises from 0 to about 50% of adult levels by 1 year and about 100% of adult levels by 5 years. Next, changes in exposures as predicted using a model of bosentan verified in adults[29] and children (Supplementary Materials Table S4, Figures S2 and S3) were compared to the empirical approach of adjusting observed exposures by a factor of 1.54 to account for induction of CYP3A4 in the absence of bosentan dosing information. Finally, to demonstrate the distribution of recommended doses in a larger population, additional simulations were performed where 1 mg tadalafil was dosed to 1500 pediatric subjects aged birth to less than 2 years with dose calculated as described above (Figure S4).

RESULTS

Model verification: adults

The PBPK model for tadalafil in adults was verified against PK data from multiple adult clinical studies (single dose and at steady-state; Tables 2 and 3) and following inhibition by the strong CYP3A inhibitor ketoconazole, induction by the strong CYP3A inducer rifampicin, and induction by the moderate CYP3A inducer bosentan (Table 3). Predicted/observed values were generally within 0.5–2, except for induced AUC for the rifampicin study. Predicted and observed mean concentration-time curve data following dosing of 5 mg tadalafil once daily for 10 days (study LVAU[5]) and predicted mean and individual observed concentration-time curve data on day 8 following dosing of tadalafil in the presence and absence of rifampicin once daily are shown in Figure 2. The tadalafil model uses a first-order, nonmechanistic absorption model that assumes consistent F_a for all doses. There is a less than proportional increase in maximum concentration (C_{max}) and AUC in adults between 20 mg and 40 mg, which has been attributed to limitations in the extent of absorption.[28] Therefore, the tadalafil model was not expected to accurately represent tadalafil PK in adults at 40 mg, the dose at which the DDI study with the moderate CYP3A inducer bosentan was conducted, so PK parameters are not included in Table 3. However, based on no other known nonlinearities in tadalafil PK, the DDI between 125 mg bosentan q.d. and tadalafil was accurately predicted (Table 3).

Model verification: children and adolescents at least 2 years old

The PBPK model for tadalafil in children and adolescents greater than or equal to 2 years old was verified in 19 patients with PAH ages 2 to less than 18 years by comparing predicted and observed dose-normalized C_{max} and $AUC_{0–24}$ (AUC shown in Figure 3) and predicted and observed concentration time curves (Figure 4). Observed exposures in pediatric patients who were receiving bosentan were increased by a factor of 1.54 to account for the ~ 35% lower observed exposures when subjects are co-treated with bosentan.

Model application: children from birth to less than 2 years old

Doses for tadalafil in pediatric patients less than 2 years old were projected based on predicted exposures following a single dose of 40 mg tadalafil in adults (Table 4). In adults, efficacy was demonstrated at a 40-mg tadalafil dose with and without bosentan use and without dose adjustment despite reduction in exposure related to bosentan. Additionally, no dose adjustments to accommodate reduction in exposure by bosentan are recommended for older pediatric (2 to <18 years) patients, therefore no bosentan-related dose adjustment is proposed for younger children.

Testing of assumptions

Sensitivity analyses were performed to understand the impact of tadalafil absorption rate and extraction at the gut on the interaction, in adults, of tadalafil and rifampicin. Reducing k_a to 0.84 h^{-1} extends median time to C_{max} (T_{max}) from about 0.6 to 2 h and brings the predicted/observed C_{max} and C_{max} ratio to within two-fold, whereas the rifampicin-induced $AUC_{0-\infty}$ remains slightly overpredicted. If the Q_{gut} input, as calculated via the retrograde approach in Simcyp, is modified slightly from 7.38 to 5, predicted geometric mean F_g goes from 0.98 to 0.97. In that case, all predictions from the tadalafil study with rifampicin fall within the 0.5- to two-fold range.

For the pediatric modeling, the fractional CYP3A7-mediated CL_{int} was initially assumed to be 3%. When this value was increased to 6% and 10% in the birth to less than

TABLE 2 Predicted and observed geometric mean C_{max} and AUC for tadalafil following single 5 and 20 mg single doses and dosing of 5 mg to steady-state in adults

Dose	5 mg[a]		20 mg[a]		5 mg (SS)[b]	
Parameter	C_{max} (ng/ml) (CV%)	$AUC_{0–24}$ (ng.h/ml) (CV%)	C_{max} (ng/ml) (CV%)	$AUC_{0–24}$ (ng.h/ml) (CV%)	C_{max} (ng/ml) (CV%)	$AUC_{0-\tau}$ (ng.h/ml) (CV%)
Predicted	80 (30)	1159 (29)	319 (30)	4634 (29)	147 (33)	2293 (44)
Observed	103 (25)	1175 (19)	322 (21)	4221 (16)	177 (41)	2741 (55)
Predicted/ observed	0.78	0.99	0.99	1.10	0.83	0.84

Abbreviations: $AUC_{0–24}$, area under the concentration curve; C_{max}, maximum concentration; CV%, percent coefficient of variation.

[a]Study LVBX.[5]

[b]Study LVAU.[5]

TABLE 3 Predicted and observed geometric mean C_{max}, AUC, and C_{max} and AUC ratios for tadalafil with and without ketoconazole 400 mg q.d., rifampicin 600 mg q.d., and bosentan 125 mg b.i.d. in adults

Tadalafil Dose	20 mg[a]			10 mg[b]			40 mg[c]		
Condition	Control	Ketoconazole	Control	Ketoconazole	Control	Rifampicin	Control	Rifampicin	Control	Bosentan
Parameter	C_{max} (ng/ml) (CV%)		$AUC_{0-\infty}$ (ng.h/ml) (CV%)		C_{max} (ng/ml) (CV%)		$AUC_{0-\infty}$ (ng.h/ml) (CV%)		C_{max} (ng/ml)	$AUC_{0-\tau}$
Predicted	319 (30)	344 (30)	9204 (45)	41,357 (54)	143 (27)	111 (30)	4277 (41)	996 (59)	Not applicable[d]	
Observed	548 (24)	670 (30)	13,006 (44)	53,524 (49)	195 (28.5)	105 (28.1)	4017 (40.4)	479 (22.4)		
Predicted/ observed	0.58	0.51	0.71	0.77	0.73	1.06	1.06	2.08		
Predicted ratio	1.1		4.5		0.78		0.23		0.73	0.63
Observed ratio	1.2		4.1		0.54		0.12		0.734	0.59
Predicted/ observed ratio	0.90		1.09		0.48[e]		0.88[e]		1.0[e]	0.89[e]

Abbreviations: $AUC_{0-\infty}$, area under the concentration curve from zero to infinity; C_{max}, maximum concentration.

[a]Study LVEV.[5]

[b]Study LVAZ.[5]

[c]Wrishko et al. 2008.[6]

[d]Not expected to reproduce exposures due to non-mechanistic absorption model that does not account for exposure reductions at 40 mg vs. 20 mg.

[e]Ratio for induction as (Predicted % decrease/observed % decrease).

1 month age group where CYP3A7 is relevant, the predicted dose-normalized AUC_{0-24} substantially decreased as to affect estimated dose (Figure S1). The tadalafil dose was increased to 3 mg in this age group when CYP3A7 contribution was 6%, and it doubled to 4 mg when the CYP3A7 contribution was 10%. Additionally, slowing of the maturation of the nonspecific additional hepatic clearance pathway by replacing the maturation profile with a slower profile (where abundance is about 50% of adult abundance at 1 year) in the birth to less than 1 month age group increased the PBPK-predicted dose-normalized AUC_{0-24} by 7% to 4629 ng*h/ml/mg, and the suggested dose remained at 2 mg.

For dose recommendations in children less than 2 years old, the effect of bosentan on tadalafil exposure was accounted for using an empirically determined factor based on exposure reductions in adults, without regard to the particular bosentan dose administered, as this information was not recorded in study records. To put this empirical factor in context, the bosentan PBPK model was used to predict the effect of bosentan on tadalafil in children, using two study designs. In both designs, bosentan was dosed to steady-state followed by 6 days of tadalafil plus bosentan; day 6 corresponds to about four half-lives of tadalafil in adults with PAH. In the first scenario, bosentan was dosed at 2 mg/kg per the European Medicines Agency (EMA) dosing guidelines[30] in the youngest age group for which bosentan is approved (ages 1 to <2), with a predicted 22% decrease in tadalafil exposure on day 1 of co-dosing and 37% decrease on day 6 of co-dosing. In the second scenario, bosentan was dosed per the dosing guidelines of both the EMA[30] and the US Food and Drug Administration (FDA)[31] in the 12 to less than 18-year-old age group, with a predicted 25% decrease in tadalafil exposure on day 1 of co-dosing and a 39% decrease on day 6 of co-dosing. This additional PBPK modeling suggests that assuming the simple empirical scaling factor of 35% reduced exposures of tadalafil in the presence of bosentan was reasonable.

Suggested doses were confirmed in simulations of a larger pediatric population where tadalafil was dosed to pediatric subjects aged birth to less than 2 years. Median doses (10th–90th percentile) for subjects aged less than 6 months, 6 months to less than 1 year, and 1 to less than 2 years, respectively, were 2.8 mg (2.0–4.3), 4.4 mg (3.2–7.3), and 6.4 mg (4.4–10.6; Figure S4). These values compare well to the values in Table 4 but also show the predicted population variability. The simulations with the larger pediatric population were also used to estimate the percent of children achieving efficacious exposures after a single dose of tadalafil, considering that tadalafil is approved to treat PAH in adults based on efficacy at 40 mg.[7] In this evaluation, the efficacious exposure range

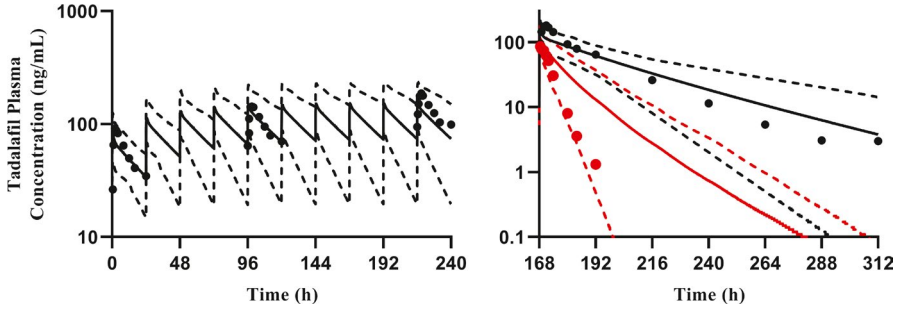

FIGURE 2 Predicted and observed tadalafil concentrations following dosing of tadalafil alone and with rifampicin in adults. Left panel: Tadalafil 5 mg q.d. for 10 days. Right panel: Tadalafil 10 mg alone and following dosing of rifampicin 600 mg once daily for 8 days. Filled black circles represent observed mean concentrations following dosing of tadalafil alone (study LVEV[5] and study LVAZ[5]). Filled red circles represent observed means following dosing of tadalafil with rifampicin. Solid lines represent mean predicted concentrations. Dashed lines represent predicted 5th and 95th percentiles

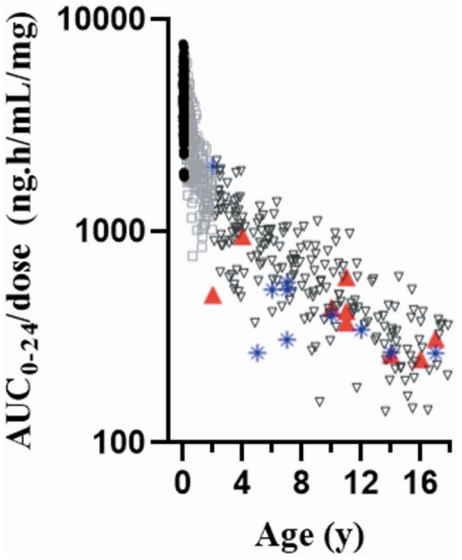

FIGURE 3 Semi-log plot of predicted and observed tadalafil dose-normalized $AUC_{0–24}$ following a single dose to children aged birth to less than 18 years. Observations are from the study reported by Small and colleagues,[8] where filled red triangles (▲) represent adjusted values for subjects on bosentan co-therapy, and blue asterisks (*) represent values from subjects not on bosentan. Predicted values for pediatric patients aged 2 to less than 18 years are represented by open triangles (▽). Open gray squares (□) represent predicted values for simulated patients aged 1 month to less than 2 years, and filled circles (●) represent predicted values for simulated patients aged birth to less than 1 month. $AUC_{0–24}$, area under the concentration curve from zero to 24 h

was considered to be the 10th to 90th percentiles of exposures following a 40 mg dose to adults. About 13% of children less than 6 months old and 21% of children 6 months to less than 2 years old were predicted to have exposures lower than the 10th percentile of the adult efficacious exposure, whereas less than 1% of children aged less than 2 years were predicted to exceed the 90th percentile of the adult efficacious exposure (Table S5).

DISCUSSION

We have developed a PBPK model to support identification of tadalafil doses for the treatment of PAH and related conditions in children less than 2 years old by exposure matching. During the verification of the tadalafil model in adults, certain parameters were slightly over- or underpredicted. In the ketoconazole study, C_{max} in the control and inhibited groups were underpredicted. However, comparison with other studies where a 20 mg dose was administered indicates that a more typical C_{max} for tadalafil would be closer to 350 ng/ml,[27] indicating that the observed C_{max} (548 ng/ml) in the ketoconazole study was on the upper end of the observed values. The PBPK model would thus not be expected to capture the atypical C_{max}. The rifampicin-induced $AUC_{0–\infty}$ for tadalafil was overpredicted, although the observed extent of induction was captured, whereas the magnitude of the tadalafil C_{max} ratio following induction of CYP3A4 by rifampicin was underpredicted. The tadalafil model includes an assumption that F_g is ~ 1. If the Q_{gut} input is modified slightly from 7.38 to 5, predicted geometric mean F_g goes from 0.98 to 0.97. In that case, all rifampicin predicted/observed ratios fall within 0.5 to 2. We do not consider that difference in F_g to be meaningful, and so the Q_{gut} was maintained as the value from the retrograde calculator in Simcyp. Another possibility is that the tadalafil absorption rate is slower in children with PAH than assumed in the model. Although the tadalafil k_a input of 1.86 h^{-1} was justified based on a PopPK analysis performed following dosing up to 20 mg tadalafil (tablet form) to adults with erectile dysfunction,[26] a PopPK analysis performed following dosing up to 40 mg to adults with PAH suggests a k_a value of 0.84 h^{-1}. Additionally, T_{max} was delayed about 1 h when tadalafil was dosed as suspension relative to tablets in healthy adults (data on file), and lower weight children received suspension in the study used for verification of predicted

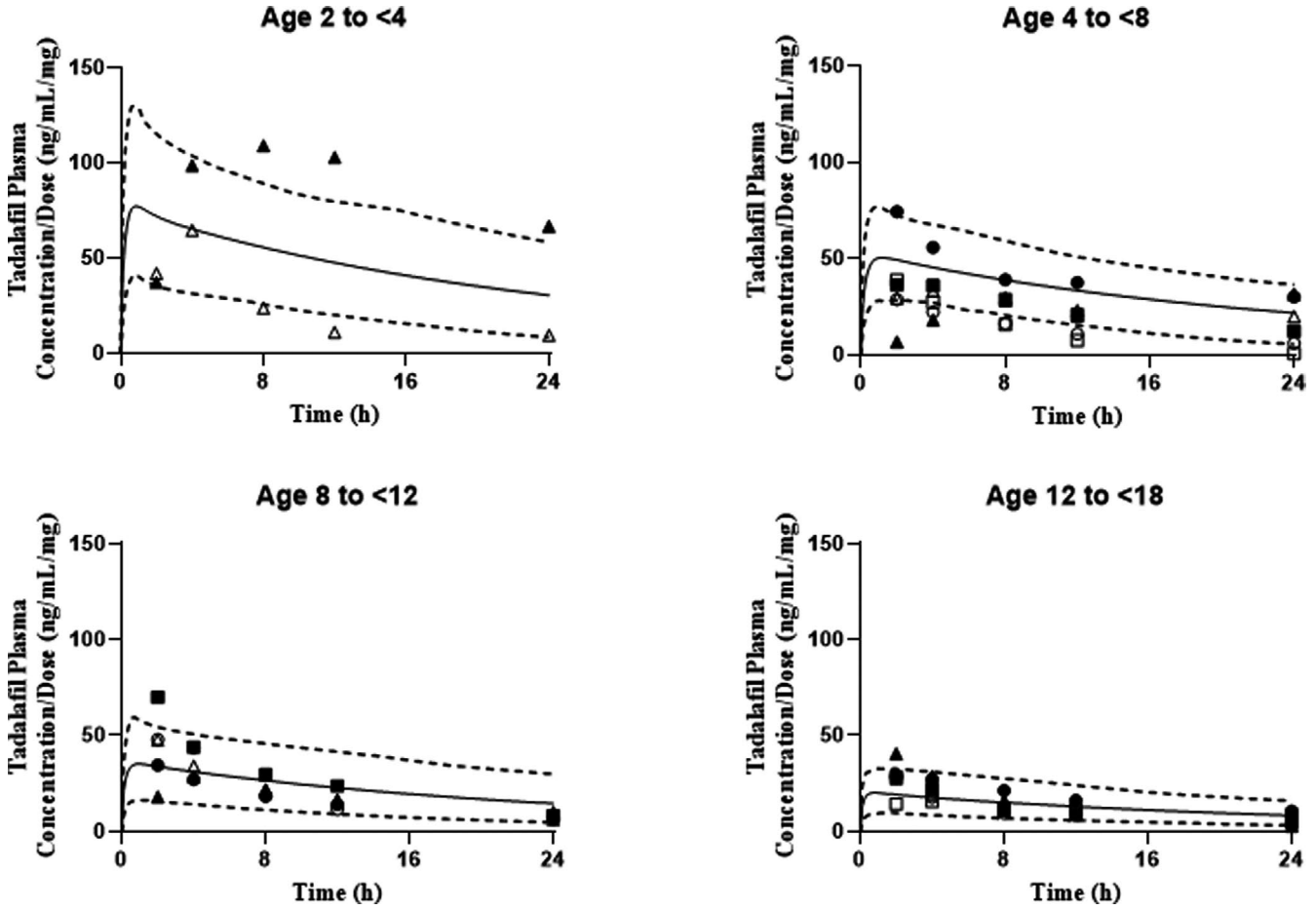

FIGURE 4 Predicted and observed tadalafil dose-normalized concentration-time profiles for children by age group. Solid lines represent predicted mean concentration-time profiles, dashed lines represent the 5th/95th percentiles of the prediction interval. Observations (Small and colleagues[8]) for individual patients are represented by different symbols

TABLE 4 Suggested clinical doses of tadalafil for children from birth to less than 2 years old as predicted by PBPK modeling

Age range	PBPK-predicted mean dose-normalized single dose AUC_{0-24} (ng*h/ml/mg)	Suggested dose (mg)	Target AUC_{0-24} (ng*h/ml)
Birth to <1 month	4308	2	10,000
1 to <4 months	1. 3801	3	10,000
4 to <6 months	3007	3	10,000
6 months to <1 year	2312	4	10,000
1 to <2 years	1626	6	10,000

In simulations, 1 mg tadalafil was dosed pediatric subjects aged birth to <2 years. Dose was calculated as target AUC_{0-24}/predicted individual dose-normalized AUC_{0-24}. Suggested doses were rounded to the nearest milligram.

Abbreviations: AUC_{0-24}, area under the concentration curve; PBPK, physiologically based pharmacokinetic.

exposures in children aged 2 to less than 18 years.[8] It is possible that a combination of suspension dosing to a subset of children and that a difference between healthy/erectile dysfunction and PAH populations contributes to variable absorption. Reducing tadalafil k_a to 0.84 h^{-1} means that tadalafil is primarily absorbed during or after the time of rifampicin absorption (rifampicin median predicted T_{max} 1.88 h), and it therefore reduces the time window during which CYP3A is predicted to be exposed to very high concentrations of rifampicin in the gut where reversible inhibition can temporarily counteract induction. The slowing of the tadalafil absorption increases the ability of rifampicin to lower tadalafil C_{max}. Although the focus of this modeling effort was only on predicting AUC in children, it remains important to confirm curve shape so that factors dependent on peak time and concentration are appropriate in other scenarios. After slowing the absorption of tadalafil with a k_a value of 0.84 h^{-1}, suggested doses in the 4 to less than 6 months, 6 months to less than 1 year, and 1 to less than 2 years age groups round up to the closest milligram doses of 4 mg, 5 mg, and 7 mg, respectively, instead of down to 3 mg, 4 mg, and 6 mg. The slightly

higher doses with the faster k_a value are still within the ranges suggested by the simulations in larger pediatric populations (Figure S4, Table S5). The larger simulations also suggest that targeting the day 1 adult efficacious exposure of 10,000 ng.h/ml is appropriate and that children less than 2 years old are unlikely to be overexposed to tadalafil based on the age-based dosing suggested by the PBPK modeling. However, the simulations with larger populations also suggest that there are some children who may be underexposed on day 1 following the PBPK-based suggested doses. Safety of proposed doses is supported by postmarketing research[1] and investigator-led trials.[12-14]

Recommended doses for tadalafil ranged from 2 mg in the birth to less than 1 month group to 6 mg in the 1 to less than 2 years group. Flat dosing in children less than 2 years old, as opposed to weight-based dosing (mg/kg), is simple for treating physicians and consistent with the finding in patients with PAH aged greater than 2 years, where a specific relationship between weight and exposure was not identified.[8]

The PBPK approach incorporates knowledge on changes in physiology and drug-metabolizing enzyme abundance.[17] This approach enabled development of a model that could be compared with the limited PK data (19 patients aged 2 to <18 at study start) to gain confidence in input parameters and assumptions, followed by extrapolation to younger ages where no PK data is available. The model performed well in the 2 to less than 18-year-old age range, as demonstrated by visual comparison of the observed and predicted exposures in this age range. However, the biggest limitation for the wider application of this model remains the lack of available PK data for tadalafil in children less than 2 years old for verification.

Negative slopes on the plot of AUC_{0-24} versus age (Figure 3) are steepest at the youngest ages and shallower above 2 years of age. Visually, there are inflection points at about 4 to 6 months, when the less active CYP3A7 abundance has reached a minimum,[4] and again at about 1 year, at which point CYP3A4 has increased to about 80% of the abundance in adults (per the Salem function[18]). The relationship between predicted AUC and age depends on the assignment of the fraction of CYP-mediated elimination that is due to CYP3A7, which, in this model, was initially 3%. A sensitivity analysis demonstrates that increasing the relative contribution of CYP3A7 from 3% to 10% is impactful on calculated doses because the assigned CYP3A7 CL_{int} is multiplied by a high CYP3A7 abundance in the birth to less than 1 month age group, thus magnifying any change in the initial assignment. Another consequence of increasing the CYP3A7 contribution is that the y-intercept of the plot of AUC_{0-24} versus age (Figure 3) would be closer to 2000 ng.h/ml than 4000 ng.h/ml. That is, the difference in slopes between age groups on the plot of AUC_{0-24} versus age becomes less distinctive. This analysis demonstrates that confidence in the relative activities of CYP3A4 and CYP3A7 is critical for predicting PK in children less than 1 month old when CYP3A7 is relevant. Hepatic CYP3A4 abundance appears to relate directly to apparent oral clearance (CL/F) of tadalafil from ages greater than 1 month not only because CYP3A4 (no longer CYP3A7) drives the systemic clearance (CL) of tadalafil, but also because there is little to no pre-systemic metabolism of tadalafil by CYP3A4 in the gut. Of note, the default Simcyp CYP3A4 maturation function based on the Salem ontogeny, where CYP3A4 abundance reaches about 80% of adult abundance by 1 year, reproduces tadalafil exposures in children 2 to less than 18 years.[18] The alternative Upreti ontogeny function,[19] where CYP3A4 abundance reaches adult levels at about 1 month and about 150% of adult levels by about 4 months, would underpredict observed exposures and yield higher suggested doses.

Models incorporating metabolism by CYP3A7 are rare.[15,17] Inclusion of metabolism by CYP3A7 requires that in vitro data regarding metabolism by CYP3A7 exists and that there is a driver to predict doses in neonates where CYP3A7 expression is relevant. In the current modeling effort, tadalafil doses in children starting from birth were recommended based on a PBPK model that incorporates CYP3A4 and CYP3A7-mediated metabolism using the default Simcyp maturation functions for both CYPs. Lack of exposure data in very young children hinders the ability to qualify existing maturation functions,[17] and thus very young ages are an area of high uncertainty. Furthermore, due to the use of a nonmechanistic K_p scalar to match observed V_{ss} in adults, there are uncertainties in the translatability of volume (and thus half-life and accumulation ratio) using the PBPK framework. For these combined reasons, only single dose exposures were predicted to recommend doses of tadalafil in pediatric patients less than 2 years.

The children with the lowest weights (<25 kg) used to verify the performance of the tadalafil PBPK model in children aged 2 to less than 18 years were dosed with a suspension formulation of tadalafil.[8] The children in this group were typically less than 6 years old, whereas the older and heavier children were administered tadalafil as tablets. The PBPK modeling assumed that tablet disintegration was not rate-limiting and thus dissolution of tadalafil particles in suspension and the particles in a tablet formulation were equivalent. $AUC_{0-\infty}$ for 20 mg tadalafil dosed as tablet and suspension were bioequivalent (data on file), so the exposure-based dose recommendations herein should be applicable to both formulations.

An additional factor should be considered for older children who might be expected to receive doses of tadalafil of up to 40 mg. The current PBPK model for tadalafil uses a first-order absorption model with an k_a based

on a PopPK analysis of adult data and assumes that F_a is not dose-dependent. Because a mechanistic absorption model was not employed, tadalafil absorption from the gastrointestinal tract is assumed to be consistent across age groups. Tadalafil adult PK are linear with respect to time and dose from 2.5 mg to 20 mg range, and exposure increases in a dose-proportional manner with doses up to 20 mg.[27] There is a less than proportional increase in C_{max} and AUC in adults between 20 mg and 40 mg, which has been attributed to limitations on the extent of absorption.[28] This effect is unaccounted for in this model and could result in pediatric subjects having exposures that differ from predicted exposures if tadalafil absorption is higher or lower than expected at the suggested doses. Regarding absorption rate, the first sample in the available pediatric concentration-time curves was at 2 h, and T_{max} was not well-defined (Figure 4). Therefore, the k_a value derived from adult PK was used to suggest pediatric doses without adjustment due lack of informative data at early timepoints in children.

PAH may be caused by congenital systemic-to-pulmonary (left-to-right) shunt. Although patients with these congenital shunts were not included in the phase III trial of tadalafil in pediatric patients with PAH,[8] 73.4% of the pediatric patients in the postmarketing research trial had this congenital shunt,[1] which may lower cardiac output (CO) and thus affect hepatic blood flow (Q_h). Tadalafil is a low extraction ratio drug with predicted hepatic availability (Fh) of 0.98 in a population aged 1 month to less than 2 years. Low CO would not be expected to affect the hepatic availability of a low extraction drug like tadalafil.

The verification of the tadalafil model performance in children aged 2 to less than 18 years assumed that bosentan reduces tadalafil exposure by 35% regardless of age. Of note, bosentan is approved only in patients greater than 3 years in the United States[31] and in children aged greater than 1 year in EMA countries.[30] Induction of CYP3A-mediated metabolism would be expected to depend on bosentan dose, but bosentan doses were not initially considered in the PBPK modeling because the relevant study had insufficient information; that is, bosentan dose information was not recorded.[8] To reduce uncertainty in the effect of bosentan on tadalafil, however, we used a PBPK model of bosentan, verified in adults and children, to confirm the appropriateness of the factor by which bosentan reduces tadalafil exposure. When dosed according to approved labeling, the predicted effect of bosentan on tadalafil exposure does not appear to be age dependent. This bosentan model may be more widely useful in understanding the effect of bosentan in other DDI scenarios.

In conclusion, a PBPK model for tadalafil has been developed and verified in adults and applied to pediatrics to support safe and efficacious dosing of tadalafil in children less than 2 years old with PAH by predicting recommended doses of tadalafil and understanding the effect of bosentan co-treatment in children less than 2 years old. Future collection of PK data for tadalafil in children less than 2 years old will be necessary for confirmation of the modeling approach in this age group.

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CONFLICT OF INTEREST

All authors are employees and stockholders of Eli Lilly and Company.

AUTHOR CONTRIBUTIONS

J.R., L.F.-S., B.L.M., and G.L.D. wrote the manuscript. J.R., L.F.-S., B.L.M., B.L., and G.L.D. designed the research. J.R., L.F.-S., B.L.M., B.L., and G.L.D. performed the research. J.R., L.F.-S., B.L.M., B.L., and G.L.D. analyzed the data. J.R., B.L.M., and G.L.D. contributed new reagents/analytical tools.

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