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ORIGINAL ARTICLE

Pharmacokinetics and safety of tadalafil in a paediatric population with pulmonary arterial hypertension: A multiple ascending-dose study

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Aims: To evaluate the pharmacokinetics and safety of once-daily (QD) tadalafil in paediatric patients with pulmonary arterial hypertension (PAH) to establish an appropriate dose range for further research.

Methods: This was an open-label, multicentre, international, multiple-ascending-dose study. Patients aged ≥2 years were enrolled into 1 of 3 cohorts based on body weight: heavy-weight (≥40 kg), middle-weight (25 to <40 kg), and light-weight (<25 kg). Each patient received tadalafil QD for 10 weeks: 5 weeks at a low dose, then 5 weeks at a high dose. The doses for each cohort were intended to produce plasma tadalafil concentrations within the range produced by 5–10 mg (for the low dose) or 20–40 mg (for the high dose) of tadalafil in adults with PAH. Area under the plasma concentration–time curve during 1 dosing interval (AUC_τ), maximum concentration, and apparent clearance were assessed throughout the trial, as were safety and tolerability.

Results: The study enrolled 19 patients aged 2–17 years, weighing 9.9–76.0 kg. Tadalafil's median (range) steady-state AUC_τ at the high dose was 7243 (3131–13 088) ng•h/mL across all patients. Concentrations were higher in no bosentan-treated patients than in bosentan-treated patients, but both populations were within the range of respective adult patients taking 20–40 mg QD. Tadalafil had an acceptable safety profile consistent with the known safety profile of tadalafil in adults.

Conclusions: Tadalafil 40 mg QD for patients ≥40 kg, and 20 mg QD for patients <40 kg and aged ≥2 years, are suitable for further research in paediatric patients with PAH.

KEYWORDS

paediatric, pharmacokinetics, phosphodiesterase type 5 inhibitor, pulmonary arterial hypertension, tadalafil

The authors confirm that the Principal Investigators for this paper are Dr Nagib Dahdah and Dr Domein Bonnet and that they have direct clinical responsibility for patients.

1 | INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vasculopathy that can lead to right ventricle failure and death.[1] PAH is associated with reduced levels of cyclic guanosine monophosphate (cGMP), caused by impaired release of nitric oxide due to little or no expression of nitric oxide synthase in the vascular endothelium of pulmonary arteries.[2] The effects of cGMP are mediated in part by phosphodiesterases.[3,4] Phosphodiesterase 5 (PDE5) is the predominant phosphodiesterase isoenzyme in the pulmonary vasculature; it normally degrades cGMP, and therefore inhibiting PDE5 increases endogenous cGMP, which relaxes pulmonary vascular smooth muscle cells and dilates the pulmonary vascular bed.

Several therapeutic options exist worldwide for the treatment of PAH in adults. Tadalafil 40 mg once daily (QD), a potent and selective PDE5 inhibitor administered orally, was approved for the treatment of PAH in adults. Pulmonary Arterial Hypertension Response to Tadalafil (PHIRST) was a global Phase 3 study that evaluated tadalafil for 16 weeks in adult PAH patients. Tadalafil 40 mg QD was well tolerated and associated with improved exercise capability,[5,6] and, based on this study, tadalafil was approved for use in adults to treat PAH in adults. Despite the progress of treatment in adults, approved therapies for PAH in children are lacking. Currently, the therapies approved in adults are often used off-label in children[7] and, therefore, there is a need to evaluate the safety and efficacy of such treatments in paediatric patients with PAH for clinicians to take an informed decision about this treatment option. Weight-adjusted tadalafil doses of 1.0 ± 0.4 mg/kg/day[8] and 0.991 ± 0.540 mg/kg/day[9] have had favourable safety profiles in paediatric patients with PAH.[8,9] Here, we report the pharmacokinetics (PK) and safety of QD tadalafil treatment in paediatric patients with PAH to establish an appropriate dose range for further clinical research.

What is already known about this subject

- Pulmonary arterial hypertension (PAH) is a progressive pulmonary vasculopathy that can lead to right ventricle failure and death.
- Several therapeutic options exist worldwide for the treatment of PAH in adults
- Approved therapies for PAH in children are lacking, and therefore approved therapies for PAH in adults are often used off label in children

What this study adds

- Based on tadalafil exposure in paediatric patients with PAH, doses suitable for further clinical research are 40 mg daily for paediatric patients ≥40 kg and 20 mg daily for patients <40 kg body weight and aged ≥2 years.
- The safety profile of tadalafil in the study population is consistent with that in the adult population

2 | METHODS

Study LVIG (ClinicalTrials.gov identifier: NCT01484431, phase 1b/2a) was an open-label, multicentre, international, multiple-ascending-dose study to evaluate the PK and safety and to establish an appropriate dose for further clinical research of tadalafil administered orally as a tablet or suspension to children with PAH, either idiopathic (including hereditary) or associated with collagen vascular disease or congenital heart defects after surgical repair. Eligible patients were aged 6 months to <18 years, with PAH established by resting mean pulmonary artery pressure ≥25 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and a pulmonary vascular resistance ≥3 Wood units via right heart catheterisation, and had World Health Organization functional class value of I, II or III. Patients were either not on PAH-specific therapy or were receiving endothelin receptor antagonists (ERA), specifically bosentan or ambrisentan for ≥12 weeks prior to screening. The study was conducted in 2 parts. In Period 1, patients were evaluated for PK and safety/tolerability of tadalafil during the first 10 weeks of treatment. Patients continued into Period 2 for at least 2 years for safety evaluation; Period 2 is ongoing and beyond the scope of this manuscript. All patients were divided into 3 cohorts based on body weight: heavy weight (HW; ≥40 kg), middle weight (MW; 25 to <40 kg), and light weight (LW; <25 kg). Each patient received tadalafil QD for 10 weeks: 5 weeks at a low dose and then 5 weeks at a high dose (Table 1). This study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines; the International Conference on Harmonisation (ICH) GCP Guideline [E6]; and applicable local laws and regulations. The local ethics review committees approved the protocol, and written informed consent was obtained from legal guardians prior to a patient's participation.

The goal of the study was to determine and test doses that would produce comparable adult exposure in paediatric patients with the theory that achieving this goal would produce similar therapeutic results. Doses selected for each cohort were intended to produce plasma tadalafil concentrations within the range of those produced by 5–10 mg (for the low dose) or 20–40 mg (for the high dose) of tadalafil in adults with PAH. The tadalafil doses predicted to produce target exposures in paediatric patients were determined by simulations based on allometric principles[10,11] using a population PK model developed from the dose–response study in adult patients with PAH (PHIRST study, data on file). Apparent clearance (CL/F) and apparent volume of distribution (V/F) in adults were used to predict paediatric CL/F and V/F by calculating a body/weight ratio and then applying allometric exponents (0.75 and 1, respectively) including parameter values both with and without bosentan for a variety of paediatric weights. These results were then used to conduct dose–exposure simulations in S-PLUS (TIBCO Spotfire S+) using a 1-compartment oral absorption population PK model assuming the same interpatient variability obtained from the adult model overlaid with simulations of

TABLE 1 Actual doses of tadalafil received by weight group and ERA treatment

			Period 1	
Weight cohort	**Patient No.**	**ERA**	**Low dose (mg)**	**High dose (mg)**
Light weight **<25 kg (*n* = 6)**	1	Bosentan	4	10
	2	Bosentan	4	20
	3	None	4	15
	4	Ambrisentan	4	20
	5	None	2	8
	6	None	4	20
Middle weight **25 to <40 kg (*n* = 7)**	7–9	Bosentan	5	20
	10	Bosentan	5	10
	11	None	5	15
	12 & 13	None	5	20
Heavy weight **≥40 kg (*n* = 6)**	14–16	Bosentan	10	40
	17	Ambrisentan	10	40
	18	None	10	20
	19	None	10	40

ERA, endothelin receptor antagonist; Period 1, patients evaluated for PK and safety/tolerability of tadalafil during the first 10 weeks.

adult exposure. In the PHIRST study, the adult patients who benefited most from tadalafil treatment received ≥20 mg tadalafil once daily regardless of the PK influence of bosentan and other disease- or patient-specific factors. Therefore, the simulations were used to predict the tadalafil dose, which would yield exposures in paediatrics at the high dose similar to those in adults receiving tadalafil 20 or 40 mg QD, but not exceeding the 40-mg QD maximum dose (with bosentan: median AUC = 9600 ng*h/mL, range = 5906–17 306 ng*h/mL; without bosentan: median AUC = 14 825 ng*h/mL, range = 10 017–26 792 ng*h/mL). Doses expected to achieve the plasma tadalafil concentrations per the objective of the study were specified in the protocol, but as permitted by the protocol, the planned low and/or high dose(s) could be revised for patients based on emerging data during the study.

Even though the population PK analysis of the adult study PHIRST did not find weight to be a significant covariate in patients ≥40 kg, based on discussions with regulatory authorities, all patients were stratified into 3 body-weight cohorts. Stratification by body weight would ensure a more appropriate distribution of body size while maintaining a broad association with age. Likewise, due to disease pathophysiology and disease conditions, this population may not follow normal male and female paediatric growth charts, thus, weight stratification could account for the potential modest divergence in body weight and age pattern due to underlying disease or across geographies. Typically, in the current study, HW patients were aged >12 years, MW patients were aged between 6 and 12 years, and LW patients were aged <6 years. The 25-kg threshold for the lightest weight-group was also considered as a respective age below which most children would be unable to swallow tadalafil tablets and instead were administered an oral 2-mg/mL tadalafil suspension, whereas HW and MW patients were treated with commercially available tadalafil tablets. Once the paediatric weight ranges were identified, fixed low or high tadalafil doses based upon PK simulation were selected for each weight cohort for the protocol.

Serial blood samples were collected for evaluation of tadalafil PK in plasma on Day 1 after the first low dose, on Day 14 at steady state after the 14th low dose, and on Day 49 at steady state after the 14th high dose. Sampling times were predose and 2, 4, 8, 12 and 24 hours postdose. In each patient, the high dose was selected to produce tadalafil concentrations within the range of those produced by 20–40 mg of tadalafil in adults with PAH. The escalation from low dose to high dose was selected in each individual patient from the tadalafil concentration data on Day 1 and Day 14 and on the safety data and any clinically significant physical signs or safety laboratory results through about 4 weeks after the start of low-dose treatment. In most cases, the high dose was chosen from the PK/safety results of the low dose, which included the steady-state AUC it produced, the target AUC at the high dose, and knowledge of tadalafil's dose proportionality. For the first patients in the MW and LW cohort, a more conservative high dose was chosen for safety considerations (these were Patients 1 and 10 in Table 1).

Tadalafil concentrations were measured at Q^2 Solutions (Ithaca, NY, USA) using a validated liquid chromatography tandem mass spectrometry method with lower and upper quantification limits of 0.5 and 500 ng/mL, respectively. The interassay accuracy (relative error) during validation ranged from −2.98% to 0.63%; the interassay precision (relative standard deviation) during validation ranged from 1.49% to 4.97% (data on file).

2.1 | Analyses

Evaluation of individual profiles during the study was based on PK parameter estimates calculated using standard noncompartmental methods of analysis (Phoenix WinNonlin Professional Network Edition, Version 6.3.0.395). Individual profiles were analysed during the study to evaluate dose escalations in individual patients and to evaluate (as data became available) the appropriateness of the starting

doses for subsequent patients. Final noncompartmental analyses included all data from all enrolled patients who received at least 1 dose of tadalafil and had an evaluable PK profile. Interim analyses conducted during the trial for dose escalations used nominal sampling times; the final analysis used actual sampling times. The tadalafil PK data in the paediatric study population were compared with the historical PK data in adults with PAH.[5]

2.2 | Study assessments

The primary parameters for noncompartmental PK analyses were area under the plasma concentration–time curve during 1 dosing interval (AUC_τ), maximum plasma concentration (C_{max}), and apparent plasma clearance of drug after extravascular administration at steady state (CL_{ss}/F). Safety and tolerability were evaluated in all patients who received at least 1 dose of tadalafil and were reported as treatment-emergent adverse events (TEAEs) by monitoring vital signs, physical examination, laboratory tests, adverse events and 12-lead electrocardiogram.

3 | RESULTS

Nineteen patients (6 HW, 7 MW and 6 LW) aged 2–17 years with PAH were enrolled. Eighteen patients completed the 10-week PK/safety period in accordance with the protocol. One patient in the MW group discontinued prematurely due to physician decision; the data from this patient were included in the PK and safety analyses. The demographics and baseline characteristics are shown in Table 2. The mean age was 10 years; 65% were female and 74% were Caucasian. Twelve patients (67%) had idiopathic PAH and 5 patients (28%) had persistent PAH after surgical repair of congenital heart disease. Prior to and during the PK/safety study period, no changes were made to pre-existing ERA treatment.

3.1 | PK

The doses of tadalafil that the patients received are listed in Table 1. The AUC estimates in individual patients receiving low-dose tadalafil are shown in Figure 1. The average accumulation ratio from single dose to steady state was 1.3 across all 19 patients whose AUC was calculated on both Day 1 and Day 14. Tadalafil concentrations in the no bosentan-treated patients were generally higher than those in the bosentan-treated patients (Figure 1).

The individual plasma tadalafil concentration–time profiles by weight cohort receiving low dose on Day 14 and high dose Day 49 are shown in Figure 2. In all weight cohorts, tadalafil concentrations in the no bosentan-treated patients were generally higher than those in the bosentan-treated patients (Figure 2). A similar effect of

TABLE 2 Demographics and baseline characteristics by weight

	Weight cohort			
	Light <25 kg (*N* = 6)	Middle 25 to <40 kg (*N* = 7)	Heavy ≥40 kg (*N* = 6)	Total (*N* = 19)
Age (y), mean (SD)	5 (2)	11 (4)	15 (2)	10 (5)
Female, *n* (%)	4 (67)	5 (71)	4 (67)	13 (65)
Race, *n* (%)				
American Indian or Alaska native	1 (17)	0	0	1 (5)
Asian	0	2 (29)	1 (17)	3 (16)
Black or African American	1 (17)	0	0	1 (5)
White	4 (67)	5 (71)	5 (83)	14 (74)
Weight in kg, mean (SD)	15 (5)	30 (4)	54 (13)	33 (17)
PAH aetiology, *n* (%)				
Idiopathic	2 (40)	5 (71)	5 (83)	12 (67)
Related to collagen vascular disease	1 (20)	0	0	1 (6)
CHD with surgical repair	2 (40)	2 (29)	1 (17)	5 (28)
WHO functional class, n (%)				
Class I	2 (33)	4 (57)	0	6 (32)
Class II	4 (67)	2 (29)	6 (100)	12 (63)
Class III	0	1 (14)	0	1 (5)
Use of bosentan or ambrisentan, *n* (%)	3 (100)	4 (100)	4 (100)	11 (100)
Bosentan	2 (67)	4 (100)	3 (75)	9 (82)
Ambrisentan	1 (33)	0	1 (25)	2 (18)

CHD, collagen heart disease; n, number of patients with non-missing values for the indicated variable or response in each cohort for each period; *N*, number of patients in each cohort; PAH, pulmonary arterial hypertension; SD, standard deviation; WHO, World Health Organization.

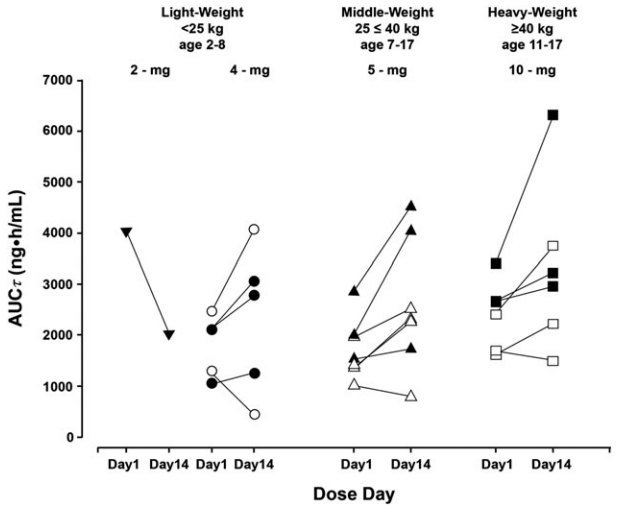

FIGURE 1 Individual tadalafil area under the plasma concentration–time curve during 1 dosing interval (AUC_τ) by weight cohort and study day for each patient's initial dose. Open symbols represent subjects taking concomitant bosentan. Solid symbols represent subjects taking ambrisentan or no endothelin receptor antagonist

bosentan on tadalafil concentrations was found in adult patients with PAH.[12]

The AUC in HW patients taking tadalafil 40 mg QD was within the range of AUC in adult patients treated with tadalafil 20–40 mg (Figure 3). Most AUCs of patients in the MW group taking 10–20 mg QD and in the LW group taking 8–20 mg QD were also within the range of AUC in adult patients treated with tadalafil 20 mg to 40 mg, although a few fell below this range (Figure 3). The AUC at steady state at Day 49 for all patients from LVIG were compared with those in adult patients with PAH from the PHIRST study. Tadalafil exposures in the study population were within the range of exposures in adult patients taking 20–40 mg QD (Figure 3), but a given dose tended to produce lower exposure in children than in adults.

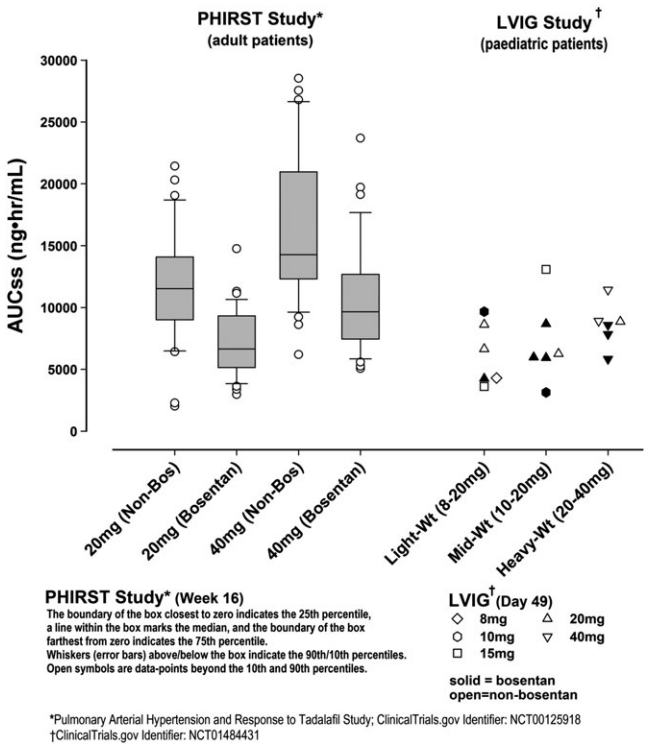

FIGURE 3 Individual tadalafil area under the plasma concentration–time curve (AUCss) by weight cohort at the high dose compared with adult exposures from Pulmonary Arterial Hypertension Response to Tadalafil (PHIRST) study. The boundary of the box closes to zero indicates the 25th percentile, a line within the box marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Whiskers (error bars) above/below the box indicate the 90th/10th percentiles. Open symbols are data points beyond the 10th and 90th percentiles

The individual estimates of CL_{ss}/F were generally higher in patients receiving bosentan during Period 1 (Figure 4; Table 3). Individual PK parameter estimates during high-dose treatment on Day 49 are shown

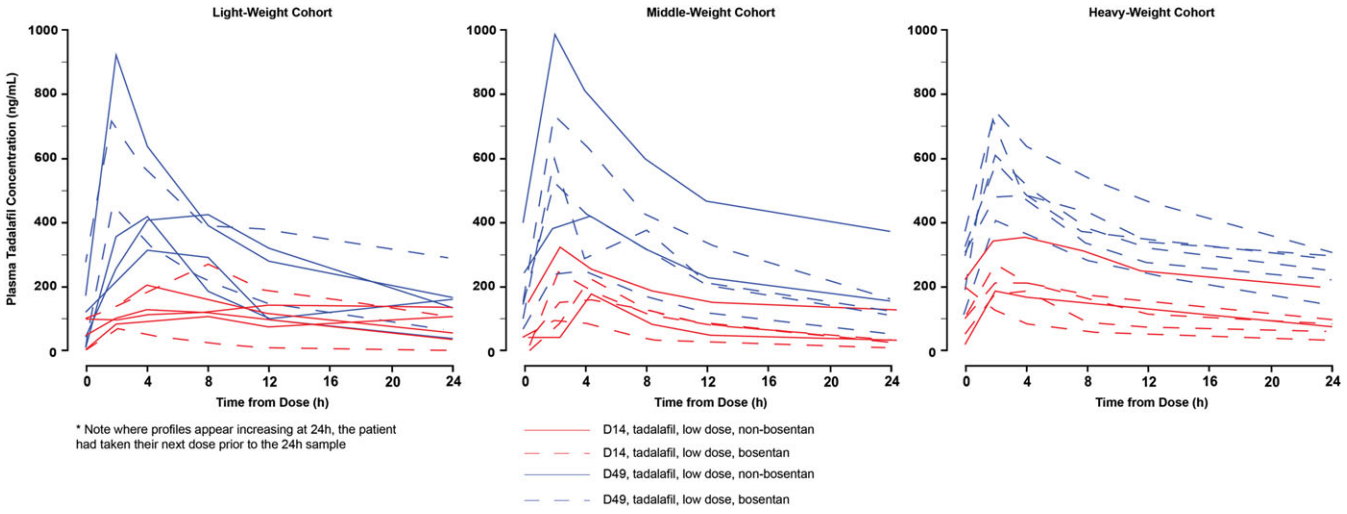

FIGURE 2 Individual plasma tadalafil concentration profiles by weight cohort, study day and bosentan use. Note: Where profiles appear increasing at 24 hours, the patient had taken the next dose prior to the 24-hour sample

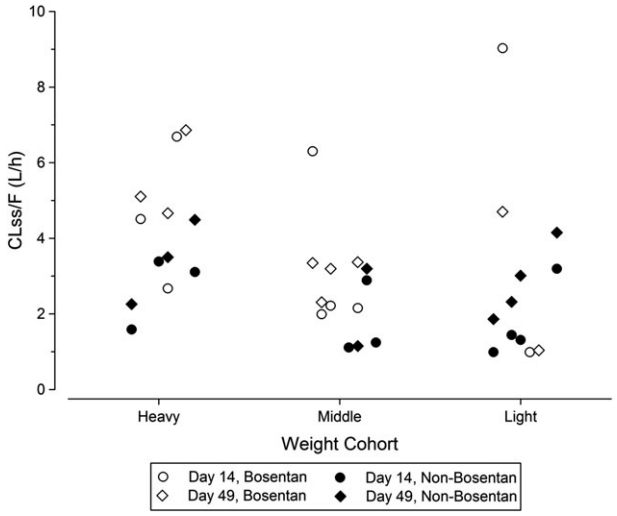

FIGURE 4 Individual tadalafil apparent plasma clearance of drug after extravascular administration at steady state (CLss/F) by weight cohort across all doses

in Table 3. C_{max} and t_{max} were consistent with the known PK of tadalafil.

3.2 | Safety

At the end of the 10-week PK/safety period, 16 patients (5 LW, 6 MW and 5 HW) reported at least 1 TEAE. The most frequently reported TEAEs were pyrexia (*n* = 3), abdominal pain (*n* = 2), headache (*n* = 2), nausea (*n* = 2), pain in extremity (*n* = 2), rash (*n* = 2), and viral infection (*n* = 2; Table 4). Most TEAEs reported were mild (63% [*n* = 12]) or moderate (21% [*n* = 4]) in severity; no adverse event led to a study discontinuation. Two patients (11%; 1 each in MW and HW cohorts) were hospitalised (serious adverse events) with viral infection; neither event was considered to be study drug-related on evaluation by investigators. There were no deaths and no clinically relevant changes from baseline in laboratory parameters, vital signs or electrocardiograms.

4 | DISCUSSION

The target exposure range for paediatric patients in this study was based on efficacy and PK data from the Phase 3 PHIRST study of tadalafil in adult patients with PAH.[5] The primary efficacy endpoint in that trial was 6-minute walk distance, which improved in a dose-dependent manner.[5] Following 16 weeks of tadalafil treatment, the model-predicted increase in 6-minute walk distance was >30 m for the 20-mg and 40-mg doses, regardless of bosentan use. Only the 40-mg dose reached statistical significance in the adult Phase 3 trial; however, the data showed only a small difference in the model-predicted 6-minute walk response between patients taking 20-mg tadalafil and those taking 40-mg tadalafil.

Evaluation of the PK results in this study was challenging because the study population size was small (*n* = 19) and was divided into smaller groups according to weight cohort, dose and bosentan status. The patients in the HW cohort received 10 mg for the first 5 weeks and were dose-escalated to 20 or 40 mg for the second 5 weeks. The AUCs calculated during the high-dose treatment were generally within the range of AUCs reported in adult patients taking 20–40 mg of tadalafil. As paediatric patients in the HW cohort demonstrated PK similar to that in adults in the Phase 3 study, the 40-mg

TABLE 3 Tadalafil pharmacokinetic parameters by weight cohort and bosentan use on day 49

		Dose (mg)	C_{max} (ng/mL)	t_{max} (h)	AUC_τ (ng·h/mL)	CL_{ss}/F (L/h)
HW	Bosentan (*n* = 3)	40	717	1.88	7838	5.1
		40	403	2	5831	6.86
		40	610	2	8582	4.66
	No Bosentan (*n* = 3)	20	583	2.05	8860	2.26
		40	486	3.98	8912	4.49
		40	749	2	11 428	3.5
MW	Bosentan (*n* = 4)	20	600	2	5980	3.34
		20	733	2	8667	2.31
		20	524	2	5939	3.37
		10	248	4	3131	3.19
	No Bosentan (*n* = 2)	20	420	4.33	6262	3.19
		15	991	2	13 088	1.15
LW	Bosentan (*n* = 2)	10	717	1.75	9665	1.04
		20	454	1.8	4254	4.7
	Non-Bosentan (*n* = 4)	8	314	4	4300	1.86
		15	418	4	3615	4.15
		20	924	2	8620	2.32
		20	425	8	6647	3.01

AUC_τ, area under the plasma concentration–time curve during 1 dosing interval; CL_{ss}/F, apparent plasma clearance of drug after extravascular administration at steady state; C_{max}, maximum plasma concentration; HW, heavy weight; LW, light weight; MW, middle weight; n, number of patients; t_{max}, time to maximum plasma concentration.

TABLE 4 Treatment-emergent adverse events by preferred term and weight cohort: Events occurring in ≥2 patients

	Weight cohort			
Study period 1, *n* (%)	Light <25 kg (*N* = 6)	Middle 25 to <40 kg (*N* = 7)	Heavy ≥40 kg (*N* = 6)	Total (*N* = 19)
TEAEs	5 (83)	6 (86)	5 (83)	16 (84)
Pyrexia	2 (33)	1 (14)	0	3 (16)
Abdominal pain	1 (17)	1 (14)	0	2 (11)
Headache	0	1 (14)	1 (17)	2 (11)
Nausea	1 (17)	1 (14)	0	2 (11)
Pain in extremity	0	1 (14)	1 (17)	2 (11)
Rash	1 (17)	1 (14)	0	2 (11)
Viral infection	0	1 (14)	1 (17)	2 (11)

n, the number of patients with at least 1 treatment-emergent adverse event from the corresponding row label; *N*, number of patients in each cohort; TEAE, treatment-emergent adverse event. Percentages are based on the *N* of the corresponding column.

dose of tadalafil (the approved dose for adult patients with PAH) could be recommended for HW paediatric patients in future studies.

As the current trial progressed, additional challenges were faced during dose escalation, whereby tadalafil exposures in the paediatric patients were generally lower than those predicted before the trial. The modelling and simulations that predicted the low and high doses in each weight cohort incorporated allometric scaling based on adult data, but assumed a typical weight effect as body size decreased into the range of younger paediatric patients. These simulations had predicted substantial reductions in doses as weight decreased from the HW to the MW and LW cohorts. Following completion of the MW cohort, the simulations based upon adults were updated to incorporate the HW and MW PK data and the low dose for the LW cohort was redefined to a higher than planned dose. However, upon completing the trial, the current study data suggest that there is not an allometric relationship between weight and tadalafil exposure for paediatric patients (aged 2–17). Starting with the reasonable assumption of allometric principles influenced the low doses and the direction of the MW and LW dose escalations.

Patients in the MW cohort received 5 mg during the first 5 weeks and then were dose-escalated to 10 or 20 mg for the subsequent 5-week period. The individual AUCs in the MW cohort during the high-dose treatment were generally within the range of AUCs reported in adult patients receiving 20–40 mg of tadalafil in the adult Phase 3 trial. However, the 20-mg dose was the highest dose tested in this cohort and was the highest dose for which safety data are available, and therefore 20 mg is the highest dose that can currently be recommended for MW paediatric patients in future studies.

Patients in the LW cohort received 2 or 4 mg during the first 5 weeks and the dose was escalated to 8–20 mg for the second 5-week period. The individual AUCs in this cohort during the high-dose treatment were also generally within the range of AUCs reported in adult patients receiving 20–40 mg of tadalafil in the adult Phase 3 trial. However, the 20-mg dose was the highest dose tested in this cohort and was the highest dose for which safety data were available, and therefore 20 mg is also the highest dose that can be recommended for LW paediatric patients (aged ≥2 years) in the paediatric Phase 3 studies.

The current analysis suggests, that based on the conservative approach taken to target the median adult AUC during dose escalation, the paediatric doses chosen for further research are appropriate but produce AUCs in the median-to-lower part of the adult 20–40 mg/day AUC range. We believe that being in this part of the range will not affect efficacy in paediatric patients because the increase in 6-minute walk distance in adults is very similar between the 20 and 40-mg/day doses, although only the 40-mg dose was significant at $P < .01$ (for 20 mg, $P = .028$).[5]

This study does not specify dosing for patients aged <2 years because no patient <2 years was enrolled and therefore no PK data are available for that age range. Moreover, the major elimination pathway for tadalafil is metabolism by cytochrome P450 (CYP)3A4, which is lowest at birth and then increases.[13,14] It is possible that tadalafil is also metabolised by CYP3A7, which typically has similar substrate specificity as CYP3A4, although affinities can differ.[15,16] The activity of CYP3A7 is highest at birth and then diminishes until age about 2 years, at which point its activity is very low.[14] Given the different directional changes in the activities of these enzymes from birth, and the potentially different affinities of the enzymes for tadalafil, the data from this study cannot be simply extrapolated to ages younger than those assessed in the study. To predict exposure in patients younger than 2 years would be likely to require physiologically based PK modelling that could account for these differences in enzyme activities.

Tadalafil had an acceptable safety profile in the study population and was generally consistent with the known safety profile of tadalafil in the adult population, including the events associated with the underlying disease state. There were no trends in the incidence of AE during the low- or high-dose portions of Period 1. Tadalafil was well tolerated and no patient from any weight cohort was discontinued due to AEs.

5 | CONCLUSION

Tadalafil was well tolerated and the overall safety profile from this study was consistent with the known safety profile of tadalafil. Given the overall considerations of tadalafil dose and the current study

results, tadalafil exposure in paediatric patients with PAH who take 40 mg QD and weigh ≥40 kg, or who take 20 mg QD and weigh <40 kg and are aged ≥2 years are within the range of AUC in adult patients treated with 20–40 mg QD. These doses are suitable for further clinical research.

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COMPETING INTERESTS

D.S. is a retired employee of Eli Lilly and Company and owns Lilly stock. He is currently employed by Intarcia Therapeutics, Inc., Boston, MA, USA. N.D. is a paediatric cardiologist at CHU Ste-Justine, Montreal, Canada, and Professor of Pediatrics at the University of Montreal, Canada. He has no competing interests to declare in association with Eli Lilly and Company. D.B. is a paediatric cardiologist at Necker-Enfants malades, University Paris Descartes, Paris, France. He is a steering committee member for tadalafil trials in paediatric pulmonary hypertension and has received fees for advisory boards. L.F.-S., J.L. and B.L. are employed by Eli Lilly and Company and own Lilly stock.

CONTRIBUTORS

D.S., L.F.-S. and B.L. were involved in the conception and design, analysis and interpretation of data, drafting and critical revision of the manuscript, while D.B. and N.D. were involved in acquisition of data, analysis and interpretation of data and critical revision of the manuscript. J.L. was involved in analysis and interpretation of data, drafting and critical revision of the manuscript.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

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