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EMA/82737/2020
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

tadalafil

Cialis

Procedure no: EMEA/H/C/000436/P46/047

Tadalafil Lilly

Procedure no: EMEA/H/C/004666/P46/002

Adcirca

Procedure no: EMEA/H/C/001021/P46/021

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 2 October 2019, the MAH submitted the completed paediatric study H6D-MC-LVIG for Adcirca and Cialis, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Tadalafil is an orally administered and selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) currently approved by the European Commission for the treatment of erectile dysfunction in adult males (both on demand [general recommended dose 10 mg] and once daily [QD; general recommended dose 5 mg]) under the brand name Cialis. Tadalafil was also approved, under the brand name Adcirca (previously Tadalafil Lilly), for the treatment of pulmonary arterial hypertension (PAH) in adults classified as WHO functional class II and III, to improve exercise capacity (general recommended dose 40 mg). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

As determined by prior studies with tadalafil in adults, area under the curve (AUC) increases proportionally with doses up to 20 mg, but increases only about 50% as the dose increases from 20 mg to 40 mg. The disproportionality between 20 mg and 40 mg is likely attributable to absorption and/or absorption-rate limitations at the higher dose. Concomitant bosentan therapy increased the apparent clearance of tadalafil by 75%, resulting in a 35% decrease in exposure in patients receiving 40 mg tadalafil.

The MAH stated that study H6D-MC-LVIG (LVIG) – "A Multiple Ascending Dose Study of Tadalafil to Assess the Pharmacokinetics and Safety in a Pediatric Population with Pulmonary Arterial Hypertension" is part of a clinical development program.

The extension application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by December 2021.

Study H6D-MC-LVIG is part of an EU Paediatric Investigation Plan (PIP) for tadalafil targeted to grant indications for the treatment of pulmonary arterial hypertension and the treatment of persistent pulmonary hypertension of the newborn (PPHN) (EMA Decision number P/0395/2018; PIP number EMEA-000452-PIP02-10-M05). The following table summarizes all the studies inluded in the PIP number EMEA-000452-PIP02-10-M05:

Clinical studies

Study Title	Study Number	Date of Completion	Date of Submission of Final Study Report
6HD-MC-LVIF: Open-label, randomised, single-dose trial in healthy adult subjects to evaluate bioavailability of a tadalafil suspension (2 mg/ml) compared to marketed tadalafil film-coated tablets.	Study 2	March 2010	The final study report has not been submitted to the EMA under Article 46 as this was not a pediatric study.
6HD-MC-LVIG: Open-label multicentre, 2-period, multiple ascending dose trial to evaluate pharmacokinetics and safety of tadalafil administered orally in children from 6 months to less than 18 years with pulmonary arterial hypertension (PAH) with an open-label long-term extension.	Study 3	April 2019	Included in this submission.
6HD-MC-LVHV: Randomised multicentre, double-blind, add on, 2-period study to evaluate efficacy and long-term safety of tadalafil administered once daily as a tablet or suspension to children from 6 months to less than 18 years of age with PAH with an open-label long-term extension.	Study 4	Period I: May 2019 Period II: March 2021	
Modelling and Simulation Study: Pharmacokinetic (PK) and exposure-response (ER) modelling and simulation study to support tadalafil dose recommendation for treatment of paediatric pulmonary arterial hypertension (PAH)	Study 7	November 2019	
Efficacy Extrapolation Study: Extrapolation study to evaluate the efficacy of tadalafil in paediatric pulmonary arterial hypertension (PAH) based on the change in 6 Minute Walking Distance (6MWD) observed in Study LVHV	Study 8	November 2019	

2.2. Information on the pharmaceutical formulation used in the study<ies>

Tadalafil is currently authorised in the European Union to be used in adults as 2.5 mg, 5 mg, 10 mg, and 20 mg tablets.

Study H6D-MC-LVIG was performed by administering tadalafil QD orally as the authorized tablets or as an oral suspension (2.0 mg tadalafil/mL) developed for use in younger children (Light-weight cohort patients).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study H6D-MC-LVIG – "A Multiple Ascending Dose Study of Tadalafil to Assess the Pharmacokinetics and Safety in a Pediatric Population with Pulmonary Arterial Hypertension".

2.3.2. Clinical studies

Study H6D-MC-LVIG (LVIG) – "A Multiple Ascending Dose Study of Tadalafil to Assess the Pharmacokinetics and Safety in a Pediatric Population with Pulmonary Arterial Hypertension"

Description

Study LVIG is a phase 1b/2, multicentre, international, 2-period, open-label, multiple ascending dose trial to evaluate the pharmacokinetics (PK) and safety of tadalafil administered orally as a tablet or suspension to children from 6 months to less than 18 years with pulmonary arterial hypertension (PAH) with an open-label long-term extension.

Methods

Objectives

Period 1 (10 weeks period to assess PK and safety):

- Primary objective:
  - To characterize the PK of tadalafil in a paediatric population with PAH and establish an appropriate dose range for further clinical research.

- Secondary objectives:
  - To assess the tolerability and safety of tadalafil in a paediatric population with PAH,
  - to compare the PK profile of tadalafil in a paediatric population with historical adult data from Study LVGY,
  - to determine appropriate dose ranges for use in the evaluation of efficacy and safety of tadalafil, and
  - to clinically assess the palatability of the tadalafil suspension in the Light-weight cohort patients.

Period 2 (open-label extension of at least 2 years to assess long-term safety):

- To evaluate long-term safety while providing continued access to tadalafil for paediatric patients who completed Period 1.
- To evaluate clinical worsening (CW), defined as any of the following:
  - death,
  - lung or heart transplantation,
  - atrial septostomy or potts shunt,
  - hospitalization for PAH progression,
  - new onset syncope,
  - initiation of new PAH therapy, or increase in dose of existing PAH specific
  - concomitant therapy (for example, ERA or beraprost),
  - increase of 1 or more in World Health Organization (WHO) Functional Class (except for patients already in Class IV) only for patients unable to perform the 6-minute walk (6MW) test, or
  - worsening of WHO functional class (Attachment 4 of the protocol amendment d) by 1 or more for patients who could perform a 6MW test and who had a decrease of ≥20% in the 6MW distance (for those patients who were ≥6 years of age).
- To evaluate the cardiopulmonary hemodynamic changes from baseline (Period 1) to the end of a 3 month treatment in Period 2 as assessed by echocardiography.

Study design

Study LVIG was a phase 1b/2, multicentre, international, 2-period, open-label, multiple ascending dose trial to evaluate the pharmacokinetics (PK) and safety of tadalafil administered QD orally as a tablet or

suspension to paediatric subjects with pulmonary arterial hypertension (PAH) in order to identify appropriate doses of tadalafil to be investigated in further clinical research. Eligible patients were 6 months to <18 years of age at the time of screening and were stratified into 3 weight cohorts (Heavy-weight, ≥40 kg; Middle-weight, ≥25 kg to <40 kg; and Light-weight, <25 kg).

The study consisted of a 10 weeks period (Period 1), where tadalafil was administered during 5 consecutive weeks for each of the considered low and high dose in 2 sequential steps, followed by a long-term extension of at least 2 years (Period 2).

Period 1 (PK and safety): The 5-week treatment duration at each dose (low and high) during Period 1 was selected to ensure sufficient time to reach steady state and allow time to process PK samples and analyze data in each patent prior to schaduled dose escalation. Dose escalation from the low- to the high-dose level for each patient during Period 1 began 5 weeks after the start of treatment.

While the Heavy- and Middle-weight cohorts began simultaneously, the Light-weight cohort was enrolled only after completion and external Data Safety Monitoring Board (DSMB) data review of the Middle-weight cohort.

Period 2 (long-term safety): The patients participating in Period 1 were permitted to enroll in the open-label extension Period 2.

Study population /Sample size

Inclusion/ Exclusion Criteria

Key inclusion/exclusion criteria for this study were the following:

Inclusion criteria

- 6 months to <18 years of age at screening.
- Currently had a diagnosis of PAH that was at least one of the following:
  - idiopathic (including hereditary),
  - related to collagen vascular disease,
  - related to anorexigen use,
  - associated with surgical repair, of at least 6-month duration, of a congenital systemic-to-pulmonary shunt (for example, atrial septal defect, ventricular septal defect, and patent ductus arteriosus).
- Had a history of the diagnosis of PAH established by a resting mean pulmonary artery pressure ≥25 mm Hg, pulmonary artery wedge pressure ≤15 mm Hg, and a pulmonary vascular resistance ≥3 Wood units via right heart catheterization.
- Had a WHO functional class value of I, II or III at the time of enrollment.
- Patients with PAH either naïve to PAH-specific therapy or receiving ERAs. If on an ERA (that is, bosentan or ambrisentan), must have been on a maintenance dose, with no change in dose (other than weight-based adjustments) for ≥12 weeks prior to screening and had a screening aspartate transaminase (AST) or alanine transaminase (ALT) <3 times the upper limit of normal.

Exclusion criteria

- Patients with pulmonary hypertension related to conditions other than specified above, including but not limited to chronic thromboembolic disease, portal pulmonary hypertension, left-sided heart disease or lung disease and hypoxia were excluded.
- History of left-sided heart disease.
- Unrepaired congenital heart disease.
- Concurrent PDE5 inhibitor therapy or has received PDE5 inhibitor therapy within 24 hours prior to study drug dosing.
- Diagnosed with retinal disorder (e.g. Hereditary retinal disorders, retinopathy of the preterm and other retinal disorders).

Sample size

As eligible patients were stratified into 3 weight cohorts (Heavy-weight, ≥40 kg; Middle-weight, ≥25 kg to <40 kg; and Light-weight, <25 kg), Study LVIG was planned to enter approximately 24 patients into this study to ensure that a minimum of 15 patients (at least 5 in each body-weight cohorts, of which ≥2 were not currently receiving ERA-PAH therapy and ≥3 were treated with ERA) complete the planned progression through low and high doses of tadalafil while taking into consideration anticipated patient dropout rates. Of the 15 completers, at least 3 patients would be ≤6 years of age and at least 2 patients would be ≤2 years of age.

At least 25% of patients were planned to be from Europe.

Treatments

Period 1 (10 weeks period to assess PK and safety):

The dose of tadalafil was escalated in 2 sequential steps. During period 1, the doses selected for each weight cohort were intended to provide tadalafil concentrations within the range of those produced by doses of 5 mg to 10 mg (low dose) or 20 mg to 40 mg (high dose) in adults with PAH (according to tadalafil PK/PD information from Study LVGY).

Dose escalation from the low- to the high-dose level for each patient during Period 1 began around Day 36, 5 weeks after the start of treatment. Selection of the high dose in each patient was based on the PK data collected on Days 1 and 14, and on the safety data and any clinically significant physical signs or safety laboratory results up to about 4 weeks after the start of treatment. Safety and PK data were reviewed by both the investigator and the Sponsor before beginning the higher dose regimen. This review could have resulted in refinement of the individual planed dose-escalation regimen. The planned low or high dose for the Light-weight cohort could have been redefined based on the results from a final Middle-weight Period 1 data review.

Period 2 (open-label extension of at least 2 years to assess long-term safety):

At the beginning of Period 2, the starting dose for each patient may have varied depending on the weight cohort and tolerability but did not exceed the dose established for the weight cohort in Period 1. The initial dose for the Light-weight cohort was revised based upon the cumulative PK results from the completed Heavy-weight and Middle-weight cohorts.

For the first 3 months of Period 2, the target dose was intended to deliver a tadalafil exposure comparable to that reported with 20 mg in adults, as long as that dose did not exceed the maximum dose established in Period 1.

After the first 3 months of Period 2, the dose may have been increased (as judged by the investigator), but did not exceed the maximum dose established for the weight cohort in Period 1.

Table LVIG.4.1 shows the planned doses for each weight cohort.

Table LVIG.4.1. Planned Tadalafil Doses by Weight Cohort and Period

	Period 1		Period 2
Study Cohort by Weight	Low Dose	High Dose	Initial Dose
Heavy: ≥40 kg	10 mg	40 mg	20 mg
Middle: 25 kg to <40 kg	5 mg	10 mg	7.5 mg
Light: <25 kg[a]	1 mg	5 mg	3 mg

Abbreviation: QD = once daily.
[a] Tadalafil was administered QD in suspension formulation for Light-weight cohort.

Outcomes/endpoints

Primary endpoints

Tadalafil pharmacokinetics were characterised using population pharmacokinetics (Pop-PK) that includes all enrolled patients.

When evaluating dose escalation in an individual patient during the trial, noncompartmental pharmacokinetic analysis was the primary method of analysis.

PK parameters to be evaluated must include AUC, t1/2 an Cmean at steady state.

PK sampling was conducted on Day 1 (single dose), Day 14 (putative steady state, low dose), and Day 49 (putative steady state, high dose) at timepoints pre-dose, 2, 4, 8, 12, and 24 hours after dosing. One trough PK sample was also collected on the second echocardiography day to evaluate the tadalafil exposure after three months treatment during Period 2.

Additionally, tadalafil concentrations were planned to be collected for patients when reporting an SAE.

Main secondary endpoints

Period 1 (10 weeks period to assess PK and safety):

- Safety and tolerability using spontaneously reported adverse events, clinical laboratory data, vital signs, physical examinations, and ECGs.
- Assessment of clinical worsening as defined in section "Objectives".
- Palatability of the tadalafil suspension was evaluated in the Light-weight cohort only, and the questionnaire was completed after the first dose of low dose (Day 1, Visit 2) and the first dose of high dose (Week 5, Visit 6) for those patients who were at least 3 years of age at screening visit.

Period 2 (open-label extension of at least 2 years to assess long-term safety):

- Safety at each study visit by monitoring treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and reasons for discontinuation. Body weight, height, Intelligence Quotient (IQ). Tanner scale was collected at baseline, one and two years of treatment.
- Testicular integrity toxicity was checked by monitoring changes in serum inhibin B levels in male patients ≥9 years of age. Inhibin B levels in patients below the age of 9 years must be collected in an exploratory manner.

- Tadalafil concentrations and protocol clinical laboratory data were collected for patients when reporting an SAE.
- Changes from baseline to endpoint in haemodynamic parameters collected via echocardiogram was summarised.
- Assessment of clinical worsening as defined in section "Objectives".

Statistical Methods

A Pop-PK approach was used for the final evaluation of the data. The effect of age, body weight, sex, bosentan use (yes/no), and tadalafil dose were explored. Before the final Pop-PK analysis was completed, dose escalation decisions in individual patients were based primarily on noncompartmental analysis of PK data from that patient.

Population

All enrolled patients who took at least 1 dose of study medication and had evaluable PK data were included in the PK data analyses. PK data were summarized using descriptive methodology.

Safety analyses were conducted for all enrolled patients who took study medication, whether or not they completed all protocol requirements. All study drug and protocol procedure AEs were listed, and safety data were summarized using descriptive methodology.

Prior to an individual patient were dose-escalated, the safety and PK data were reviewed to assess the suitability of dose escalation.

Interim analysis/es

After 5 Middle-weight cohort patients have completed the study and prior to the Light-weight cohort patients enrolling into the study, an interim analysis were conducted by a DSMB. The DSMB reviewed all available study data and made recommendations on proposed tadalafil dose levels for the Light-weight cohort.

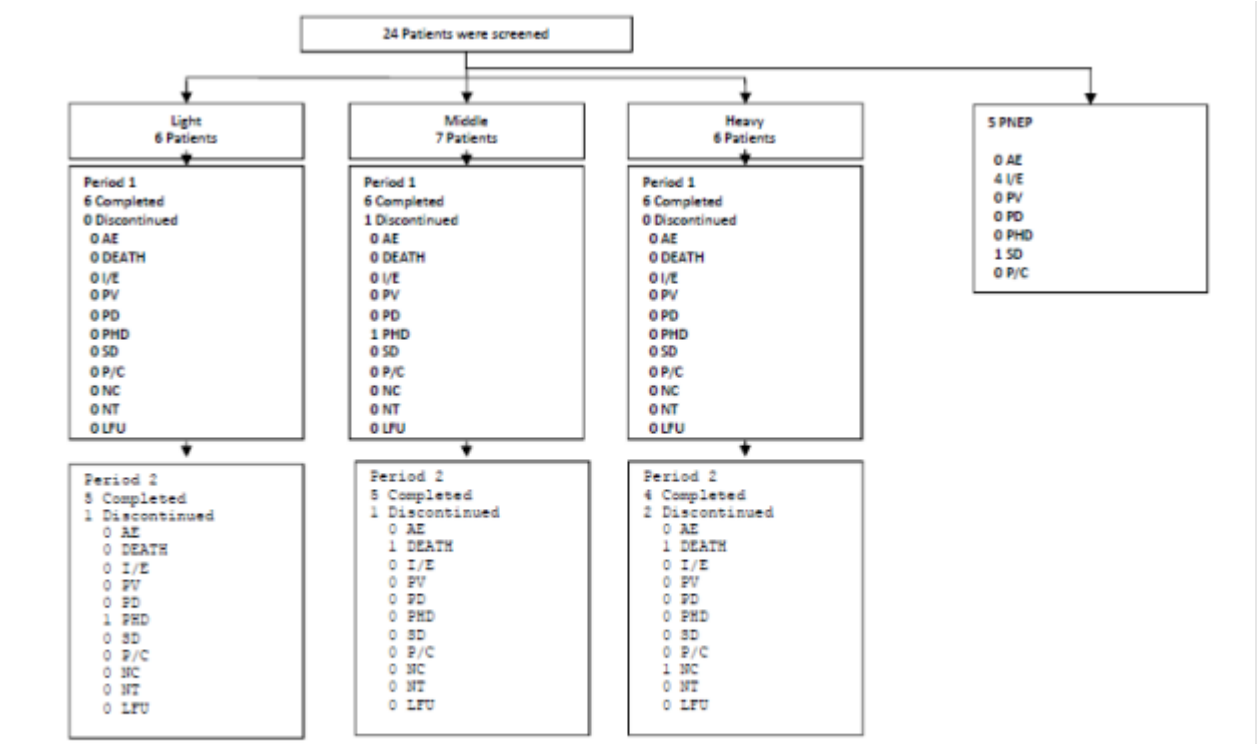
Results

Recruitment/ Number analysed

A total of 24 patients were screened, 5 were not eligible to participate. Nineteen patients, 6 male and 13 female, aged 2.5 to 17 years at the time of enrollment, participated in the study. Twelve of the 19 patients (63%) were enrolled from Europe (France, United Kingdom, Poland, and Spain).

Eighteen of the 19 patients who enrolled in Period 1 of the study were enrolled in Period 2. One female patient in the Middle-weight cohort was terminated early from the study during Period 1 (after Visit 7, Week 6) due to not meeting the required hemodynamic inclusion criterion.

Four patients did not complete Period 2 of the study; 1 during Period 1 (did not meet inclusion criteria) and 3 during Period 2 (2 due to death, 1 in the Middle- and 1 in the Heavy-weight cohort, and 1 due to noncompliance with study drug) and there were a total of 14 paediatric patients who completed both Periods 1 and 2 of Study LVIG. Please see below the patient flow through of Study LVIG.



Abbreviations: AE = adverse event; I/E = entry criteria not met; LFU = lost to follow up; NC = noncompliance with study drug; NT = new treatment required (for PAH); PAH = pulmonary arterial hypertension; P/C = Parent/Caregiver decision; PD = patient decision; PHD = physician decision; PNEP = patients not eligible to participate; PV = protocol violation; SD = Sponsor decision.

Disposition of Patients by Weight Cohort are showed inTable LVIG.6.7.

Table LVIG.6.7. Disposition of Patients by Weight Cohort: Safety Population

	Weight Cohort			
	Light (<25 kg) (N = 6) n (%)	Middle (25 to <40 kg) (N = 7) n (%)	Heavy (≥40 kg) (N = 6) n (%)	Total (N = 19) n (%)
Enrolled	6 (100.0)	7 (100.0)	6 (100.0)	19 (100.0)
Overall				
Completed Study	5 (83.3)	5 (71.4)	4 (66.7)	14 (73.7)
Discontinued Study	1 (16.7)	2 (28.6)	2 (33.3)	5 (26.3)
Reason for Discontinuation				
Death	0 (0.0)	1 (14.3)	1 (16.7)	2 (10.5)
Non-compliance with Study Drug	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.3)
Physician Decision	1 (16.7)	1 (14.3)	0 (0.0)	2 (10.5)
Period 2				
Entered	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)
Completed Period 2	5 (83.3)	5 (83.3)	4 (66.7)	14 (77.8)
Discontinued Period 2[a]	1 (16.7)	1 (16.7)	2 (33.3)	4 (22.2)
Reason for Discontinuation				
Death	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
Non-compliance with Study Drug	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.6)
Physician Decision	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)

Abbreviations: N = number of patients in each cohort; n = number of patients in the category in each cohort.
Note: Percentages for Period 2 are based on the number of patients who entered Period 2 in each cohort.
[a] Completed Period 2 is defined as completing Year 2 (Visit 17) of the study.

Actual doses administered in this study for each enrolled patient are presented in Table LVIG.5.1.

Table LVIG.5.1. Actual Tadalafil Doses Administered

Weight Cohort	Patient #	ERA	Period 1 Low Dose (mg)	Period 1 High Dose (mg)	Period 2 Starting Dose (mg)
Light-weight	[redacted]	Bosentan	4	10	7
		Bosentan	4	20	20
		Bosentan	4	15	15
		Ambrisentan	4	20	20
		None	4	20	20
		None	2	8	8
Middle-weight		Bosentan	5	20	15
		Bosentan	5	20	15
		Bosentan	5	20	7.5
		Bosentan	5	10	7.5
		Ambrisentan	5	15	10
		None	5	20	NA[a]
		None	5	20	15
Heavy-weight		Bosentan	10	40	20
		Bosentan	10	40	20
		Bosentan	10	40	20
		Ambrisentan	10	40	20
		None	10	20	15
		None	10	40	40

Abbreviations: ERA = endothelin receptor agonist; NA = not applicable.

[a] Patient [redacted] was terminated early from the study during Period 1 and did not participate in Period 2.

Baseline data

Period 1 (10 weeks period to assess PK and safety):

For Period 1, the most common PAH etiology was idiopathic in 13 patients (68.42%) followed by associated PAH with persisting or recurring at least 6 months after repair of a congenital systemic-to-pulmonary shunt (5 patients, 26.32% for Period 1). At baseline, a majority of the patients were WHO function class of Class 2 (12 patients, 63.16%) and Class 1 (6 patients, 31.58%). Bosentan use at baseline of study Period 1 was more common (9 patients, 81.82%) than ambrisentan (2 patients, 18.18%) in all weight cohorts.

Period 2 (open-label extension of at least 2 years to assess long-term safety):

For Period 2, the most common PAH etiology was idiopathic in 13 patients (72.22%) followed by associated PAH with persisting or recurring at least 6 months after repair of a congenital systemic-to-pulmonary shunt (4 patients, 22.22%). For Period 2, the majority of patients were WHO functional class of Class 2 (12 patients, 66.67%) and Class 1 (5 patients, 27.78%). Bosentan use at baseline was more common (9 patients, 81.82%) than ambrisentan (2 patients, 18.18%) in all weight cohorts.

Pharmacokinetic and safety results

Results from LVIG Period 1 and interim results from Period 2 through a data cutoff date of 20 April 2017 were presented in the initial LVIG clinical study report (CSR) (07 March 2018). The final results from Period 2 and overall safety assessment from Period 1 and Period 2 data were presented in the LVIG CSR addendum (23 September 2019).

Primary endpoints

Noncompartmental Pharmacokinetics Analyses

The small number of patients in this study (19) were separated into smaller groups according to weight cohort, dose, and bosentan status. Steady-state pharmacokinetic parameters were evaluated on Day 49 (Visit 8) and are presented in Table LVIG.5.2.

Table LVIG.5.2. Summary of Tadalafil Pharmacokinetic Parameters by Weight Cohort and Bosentan Use for Day 49: Pharmacokinetic Population

Site Id/ Patient Id	Age (Years)/Sex/ Weight (kg)	Dose (mg)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{tau} (ng · hr/mL)	CLss/F (L/hr)
Heavy/Bosentan (N=3)						
[redacted]	[redacted]	40	717	1.88	7838	5.10
		40	403	2.00	5831	6.86
		40	610	2.00	8582	4.66
Geometric Mean (CV%)			561 (30.4)	2.00 (1.88-2.00)	7320 (20.4)	5.46 (20.4)
Heavy/Non-bosentan (N=3)						
[redacted]	[redacted]	20	583	2.05	8860	2.26
		40	486	3.98	8912	4.49
		40	749	2.00	11,428	3.50
Geometric Mean (CV%)			NA	2.05 (2.00-3.98)	NA	3.29 (35.9)
Middle/Bosentan (N=4)						
[redacted]	[redacted]	20	600	2.00	5980	3.34
		20	733	2.00	8667	2.31
		20	524	2.00	5939	3.37
		10	248	4.00	3131	3.19
Geometric Mean (CV%)			NA	2.00 (2.00-4.00)	NA	3.02 (18.2)
Middle/Non-bosentan (N=2)						
[redacted]	[redacted]	20	420	4.33	6262	3.19
		15	991	2.00	13,088	1.15
Geometric Mean (CV%)			NA	NA	NA	NA
Light/Bosentan (N=2)						
[redacted]	[redacted]	10	717	1.75	9665	1.04
		20	454	1.80	4254	4.70
Geometric Mean (CV%)			NA	NA	NA	NA
Light/Non-bosentan (N=4)						
[redacted]	[redacted]	8	314	4.00	4300	1.86
		15	418	4.00	3615	4.15
		20	924	2.00	8620	2.32
		20	425	8.00	6647	3.01
Geometric Mean (CV%)			NA	4.00 (2.00-8.00)	NA	2.71 (35.6)

Abbreviations: AUC_{tau} = area under the concentration versus time curve during 1 dosing interval (tau); CL_{ss}/F = apparent plasma clearance; C_{max} = maximum observed plasma concentration; CV% = coefficient of variation; N = number of patients with non-missing values for the indicated variable in each cohort; NA = not applicable; t_{max} = time to maximum observed plasma concentration.
Source: Interim CSR Table 7.1.

Based upon noncompartmental results, tadalafil PK appear similar between children and adults. Like adults, with increasing dose, paediatric patients generally had increasing exposure and the time of the maximum observed concentration was about 2 hours. Also similar to adults, in all paediatric weight cohorts, mean tadalafil concentrations in the non-bosentan patients were generally higher than those in the bosentan-treated patients. Likewise, in all weight cohorts on Day 49, the geometric mean AUCtau in patients not on bosentan was higher than the AUCtau in bosentan-treated patients.

Individual estimates of CLss/F were generally higher in patients on bosentan.

Population Pharmacokinetic (Pop-PK) Analyses

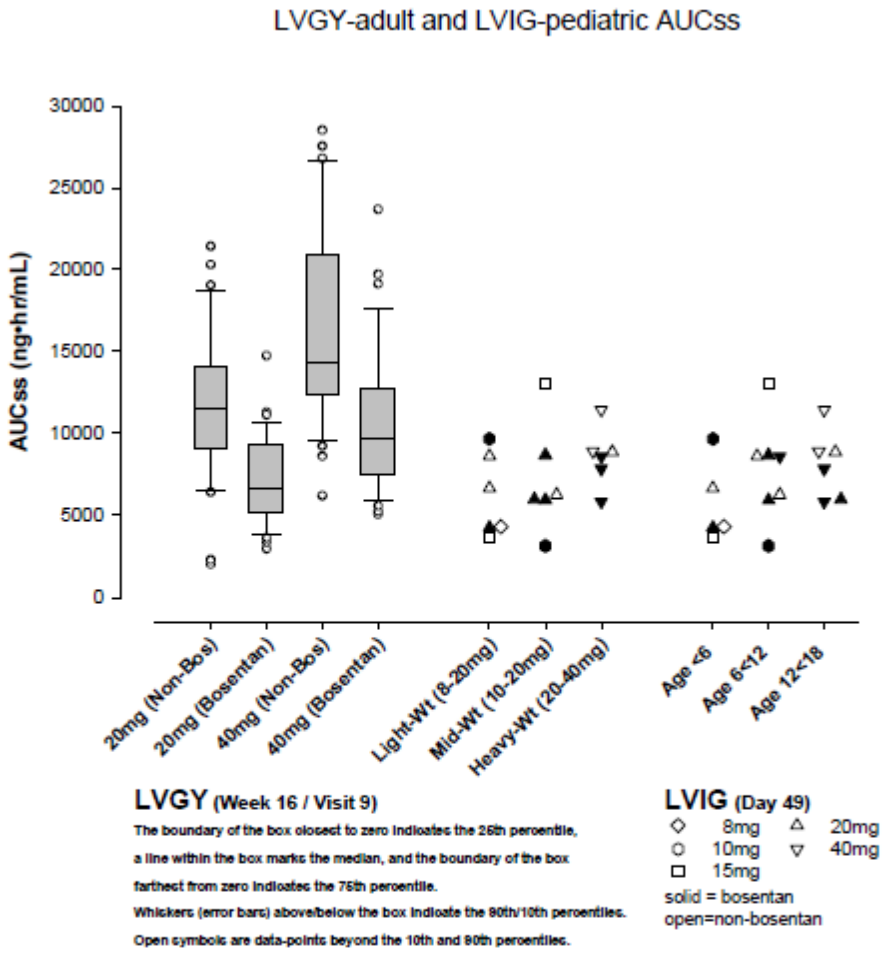
The population PK dataset included data from 19 LVIG patients and data from 305 adult patients in LVGY (69 male and 236 female) administered tadalafil 2.5 mg,10 mg, 20 mg, or 40 mg QD. A 1-

compartment model parameterized in terms of bioavailability (F), absorption rate (Ka), apparent clearance (CL/F), and apparent volume of distribution (V/F) described the data well.

The final population PK model revealed that bosentan increased CL/F and that the magnitude of the effect was similar to that in adult patients with PAH. V/F decreased with decreasing body weight, which resulted in shorter half-lives in patients with lower body weight. Bioavailability decreased with increasing dose and with decreasing age. Additional details are included in a Population PK report of the Interim LVIG CSR.

Comparison with Historical Adult Data from Study LVGY

Figure LVIG.5.2 shows the observed (noncompartmental) AUC at steady state (AUCss) at Day 49 (Visit 8) for LVIG paediatric patients compared to the population PK model-calculated AUCss at the end (Week 16) of the adult LVGY trial. Exposures in the current study were within the range of exposure in adult patients with PAH taking 20 mg QD to 40 mg QD.



Abbreviations: AUCss = area under the concentration curve over one dosing interval at steady state; Bos = bosentan; Wt = weight.
Source: Interim CSR Figure 7.6

Figure LVIG.5.2. **AUC_{ss} in adult PAH patients in Study LVGY and in pediatric patients in the current Study LVIG.**

Secondary endpoints

Deaths, Serious AEs, Discontinuation due to AEs, and Overall AE Profile

There were no deaths in Period 1 and 2 deaths in Period 2; 1 patient in the Middle-weight cohort died due to PAH, and 1 patient in the Heavy-weight cohort died due to cardiac failure. Neither death was related to tadalafil as judged by the investigator.

Overall, 8 patients experienced SAEs (2 [10.53%] in Period 1, and 7 [38.89%] in Period 2). Two patients experienced SAEs of viral infection in Period 1. The remaining SAEs (cardiac failure, gastritis, pyrexia, Type 1 diabetes mellitus, febrile convulsion, presyncope, seizure, and ovarian cyst) were reported during Period 2. One patient had multiple SAEs during study Period 1 and Period 2. None of the SAEs in this study were considered related to tadalafil or study procedures.

There were no discontinuations due to AEs in Period 1 and Period 2.

Treatment-emergent AEs (TEAEs) were reported for all 19 (100.00%) patients overall (Periods 1 and 2 combined); 17 (94.44%) experiencing TEAEs during Period 2 and 16 (84.21%) patients during Period 1. TEAEs were most commonly reported in the SOCs of infections and infestations, nervous system disorders, and respiratory, thoracic, and mediastinal disorders. In overall, AEs possibly related to tadalafil as judged by the investigator were reported in 5 patients (26.32%). Headache was the most commonly reported TEAE considered by the investigator to be possibly related to tadalafil.

Clinical Laboratory Evaluations

Safety laboratory tests (including chemistry, hematology, coagulation and urinalysis) were performed during Period 1 of the study only. Sporadic abnormalities in laboratory parameters were observed during the study; none were considered TEAEs. Inhibin B values increased over time compared to baseline values in male patients both <9 and ≥9 years of age, indicating normal testicular function.

Clinical Worsening and WHO Functional Class

Overall, CW was reported for 7 patients (36.84%). CW events from those 7 patients were all cause mortality (2), Potts shunt (2), hospitalization for PAH progress (2), addition of new PAH specific concomitant therapy or increase in dose of existing PAH specific concomitant therapy (7), syncope (1), and increase of 1 or more WHO functional class and decrease of 20% in 6MW test (2).

At the final endpoint assessment (last post-baseline observation from Visit 17/Year 2 or earlier carried forward):

- For most patients the WHO functional class designation at each patient's endpoint determination was the same as at the baseline.
- Five patients were discontinued early during the study and their WHO functional classes at the discontinued visit were no change (3 patients), improved (1 patient), and worsened (1 patient) compared with their WHO functional class from baseline.
- Improvement in WHO functional class from baseline was observed in 2 patients (2 patients shifted from Class 2 to Class 1)
- Worsening of WHO functional class was observed in 5 patients (2 patients had shifted from Class 1 to Class 2, 1 patient shifted from Class 1 to Class 3, and 2 patients had shifted from Class 2 to Class 3).

Vital Signs

Blood pressure and heart rate were collected during Period 1 of the study only, which included intensive measurements during two visits (at the first dosing date of low dose and the first dosing date of high dose.

Electrocardiograms

ECGs were performed during Period 1 of the study only. There were no clinically meaningful changes from a safety point of view.

Physical Characteristics Analysis

- **Eye examinations**: Eye examinations (including patient medical history, external eye examination and retinal examination using an ophthalmoscope) were performed at baseline, Visit 9 (Week 10) of Period 1, and Visit 17 (Year 2) of Period 2. One patient in the Light-weight cohort had a clinically significant eye examination (left eye) at Visit 17 (Year 2) of Period 2; the finding was not recorded as a TEAE and no further details were provided. However, a mild TEAE of dermoid cyst (left upper eyelid) was recorded for this patient previously. It was unknown if this TEAE was related to study drug.
- **Tanner Scores**: Changes from baseline in Tanner scores occurred with the greatest frequencies in males in the Heavy-weight cohort and were not unexpected with this paediatric population.
- **Intellectual ability and cognitive functioning assessment (IQ)**: Measured from study baseline to end of study Period 2.

Echocardiograms

Echocardiography was performed at baseline (Period 1) and at the end of 3-month treatment in Period 2 (Visit 10). Statistical analysis on cardiopulmonary hemodynamic change was not performed. However, compared with baseline, the echocardiograms from Visit 10 showed numeric increase of tricuspid annular plane systolic excursion (cm) and decreased of maximal tricuspid regurgitation jet velocity (cm/s) and left ventricular eccentricity index. There were no clinically meaningful changes from a safety point of view.

Palatability

Six patients enrolled in the Light-weight cohort, of whom 3 patients performed Palatability Questionnaire after the first treatment of low dose and the first treatment of high dose; overall, they categorized the tadalafil suspension as acceptable or very acceptable, not bitter, and as having varying degrees of sweetness.

2.3.3. Discussion on clinical aspects

Tadalafil is an orally administered and selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) currently approved by the European Commission for the treatment of erectile dysfunction in adult males (both on demand [general recommended dose 10 mg] and once daily [QD; general recommended dose 5 mg]) under the brand name Cialis. Tadalafil was also approved, under the brand name Adcirca (previously Tadalafil Lilly), for the treatment of pulmonary arterial hypertension (PAH) in adults classified as WHO functional class II and III, to

improve exercise capacity (general recommended dose 40 mg). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

The hereby submitted study (H6D-MC-LVIG) is part of an EU Paediatric Investigation Plan (PIP) for tadalafil targeted to grant indications in the paediatric population for the treatment of pulmonary arterial hypertension and the treatment of persistent pulmonary hypertension of the newborn (PPHN) (EMA Decision number P/0395/2018; PIP number EMEA-000452-PIP02-10-M05). The primary objective of Study H6D-MC-LVIG (LVIG) was to characterize the PK of tadalafil in a paediatric population with PAH and establish an appropriate dose range for further clinical research in the Phase 3 Study LVHV wich is also part of the PIP number EMEA-000452-PIP02-10-M05. Key secondary objectives were to assess the tolerability and safety of tadalafil in paediatric patients with PAH and to compare the PK profile of tadalafil in paediatric patients with historical adult data from Study LVGY.

Study LVIG was a phase 1b/2, multicentre, international, 2-period, open-label, multiple ascending dose trial to evaluate the pharmacokinetics (PK) and safety of tadalafil administered QD orally as the authorized tablets (2.5 mg, 5 mg, 10 mg, and 20 mg) or as a suspension (2.0 mg/mL) to paediatric subjects with pulmonary arterial hypertension (PAH). Eligible patients were 6 months to <18 years of age at the time of screening and were stratified into 3 weight cohorts (Heavy-weight, ≥40 kg; Middle-weight, ≥25 kg to <40 kg; and Light-weight, <25 kg). The doses selected for each weight cohort were intended to provide tadalafil concentrations within the range of those produced by doses of 5 mg to 10 mg (low dose) or 20 mg to 40 mg (high dose) in adults with PAH (according to tadalafil PK/PD information from Study LVGY).

Study LVIG consisted of a 10 weeks period (Period 1), where tadalafil was administered during 5 consecutive weeks for each of the considered low and high dose in 2 sequential steps, followed by a long-term extension of at least 2 years (Period 2).

Nineteen patients, 6 male and 13 female, aged 2.5 to 17 years at the time of enrollment, participated in the study. The lack of enrolled patients between age of 6 months to 2.5 years, appears to negatively impact on the findings as no clinical safety or PK data is available for this age range.

During Period 1, patients in the Heavy-weight cohort (≥40 kg, N = 6) received a dose of 10 mg in the first 5 weeks of treatment and were then escalated to doses of 20 mg to 40 mg for the second 5-week period, whereas patients in the Middle-weight cohort (25 to <40 kg, N = 7) received a dose of 5 mg in the first 5 weeks of treatment and were then escalated to doses of 10 mg to 20 mg for the second 5-week period. Patients in the Light-weight cohort (<25 kg, N = 6) received a dose of 2 mg or 4 mg in the first 5 weeks of treatment and were escalated to doses of 8 mg to 20 mg for the second 5-week period. Based upon noncompartmental results, tadalafil PK appear similar between children and adults. Addionally, the noncompartmental AUC calculated during the high-dose treatment (Day 49) in all paediatric weight cohorts were generally within the range of AUC reported in adult patients taking 20 mg to 40 mg of tadalafil (Study LVGY).

No new safety signals were identified in this study. The overall safety profile in Study LVIG was generally consistent with the known safety profile of tadalafil and events associated with the underlying disease state. Tadalafil was well tolerated and no patients were discontinued due to AEs from any weight cohort.

There were 2 deaths, both in Period 2. Neither death was related to tadalafil as judged by the investigator. There were no discontinuations due to AEs. Overall, 8 patients experienced SAEs (2 [10.53%] in Period 1 and 7 [38.89%] in Period 2). None of the SAEs in this study were considered related to tadalafil or study procedures.

For Periods 1 and 2 combined (overall), AEs possibly related to tadalafil, as judged by the investigator, were reported in 5 patients (26.32%), with the highest frequency occurring in the Light-weight cohort (3 of 6 patients). One patient in the Middle-weight and 1 patient in the Heavy-weight cohort had AEs considered possibly related to tadalafil. Headache was the most commonly reported TEAE considered by the investigator to be possibly related to tadalafil.

There were no trends in the incidence of AE during the low- or high-dose portions of Period 1. There were no clinically meaningful trends or changes from baseline in vital signs, ECGs, or eye examinations. Sporadic abnormalities in laboratory parameters were observed during the study; none were considered TEAEs. There were no clinically relevant mean changes from baseline to end of study (Period 1) in laboratory parameters in any of the 3 weight cohorts. There were no clinically significant trends observed from inhibin B, Tanner scores, or IQ testing based on the available data.

For most patients the WHO functional class designation at each patient's endpoint determination was the same as the baseline WHO functional class designation. Five patients were discontinued early during the study and their WHO functional classes at the discontinued visit were no change (3 patients), improved (1 patient), and worsened (1 patient) compared with their WHO functional class from baseline.

Overall, CW was reported for 7 patients (36.84%); no CW was recorded for 12 patients (63.16%).

The long-term safety observed in patients with PAH in this study was as expected in paediatric patients with PAH treated with tadalafil. The continued administration of tadalafil to patients with PAH did not appear to negatively impact the safety of these patients.

Six patients enrolled in the Light-weight cohort, of whom 3 patients performed the Palatability Questionnaire after the first treatment of low dose and the first treatment of high dose; overall, they categorized the tadalafil suspension as acceptable or very acceptable, not bitter, and as having varying degrees of sweetness. However, the assessment of the palatability of the tadalafil suspension should be interpreted with caution due to the scarcity of subjects performing the Palatability Questionnaire.

3. CHMP overall conclusion and recommendation

Given the overall considerations of PK of tadalafil in a paediatric population with PAH, exposure-response relationship, safety profiles at the doses studied, doses of 40 mg QD in the Heavy-weight group and 20 mg QD in the Middle-weight and Light-weight groups, age 2.5 years or older, are appropriate for futher testing in the Phase 3 Study LVHV.

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a extension prior any conclusion on product information amendments is made. The MAH should commit to submit this extension application by December 2021.

☐ **Not fulfilled:**

4. Additional clarification requested

None.