15 December 2022
EMA/140777/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adcirca

International non-proprietary name: tadalafil

Procedure No. EMEA/H/C/001021/X/0035/G

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

6MWD	6-Minute walking distance
ADR	adverse drug reactions
AE	Adverse event
ANCOVA	Analysis of Covariance
AUCss	Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state
BCS	Biopharmaceutical classification system
bpm	Beats per minute
CFU	Colony Forming Units
CI	Confidence interval
cm	Centimetres
Cmax,ss	Maximum plasma concentration at steady-state
CQA	Critical Quality Attribute
CRS	Chemical reference substance
DMD	Duchenne muscular dystrophy
DoE	Design of experiments
E-R	Exposure-response
ED	Erectile dysfunction
ECG	Electrocardiogram
EM(E)A	European Medicines (Evaluation) Agency
ER	Exposure–response
ERAs	Endothelium receptor antagonists
ES	Epoprostenol sodium
EU	European Union
FMECA	Failure mode effect and criticality analysis
GMP	Good Manufacturing Practices
GSK	GlaxoSmithKline
HDPE	High density polyethylene
HPAH	Heritable pulmonary arterial hypertension
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IDMC	Independent Data Monitoring Committee
IPAH	Idiopathic pulmonary arterial hypertension
ITT	Intent-to-Treat
kg	Kilograms
L	Litre
LEVDP	Left ventricular end diastolic pressure
LFTs	Liver function tests
LS	Least Squares
m	Metre
m^2	Square metres

MAA	Marketing Authorisation Application
MCID	Minimal clinically important difference
mg	Milligram
MIAH	Manufacturer and Importer Authorisation Holder
min	Minute
mL	Millilitre
mmHg	Millimetres of mercury
MMRM	Mixed Model with Repeated Measures
mPAP	Mean pulmonary arterial pressure
ng	Nanogram
NMT	Not more than
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAR	Proven acceptable range
PBPK	Physiologically Based Pharmacokinetic
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure
PDE-5(i)	Phosphodiesterase-5 inhibitor
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PopPK	population PK
PP	Polypropylene
pPAH	paediatric pulmonary arterial hypertension
PVR	Pulmonary vascular resistance
QbD	Quality by design
QD	*Quaque Die* (once daily)
QoL	Qality of life
QP	Qualified Person
QTPP	Quality target product profile
RA	Right atrial
RH	Relative humidity
RV	Right ventricular
s(ec)	Seconds
SC	Sildenafil citrate
SDAC	Statistics and Data Analysis Centre
SE	Standard error
SF-10	Short Form 10
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count

TAPSE	Tricuspid annular plane systolic excursion
TRJ	Tricuspid regurgitant jet
TYMC	Total Combined Mould And Yeasts Count
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
UV-Vis	Ultraviolet-visible
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

Eli Lilly Nederland B.V. submitted on 16 December 2021 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form associated with a new strength (2 mg/ml oral suspension) grouped with a type II variation (C.I.6.a) to include paediatric use (from 6 months to 17 years) based on study 4 (H6D-MC-LVHV [LVHV]) - A 24-week placebo-controlled efficacy and safety study with an open-label long-term extension phase. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The paediatric indication is applicable to the new and all existing presentations. The Package Leaflet and Labelling are updated accordingly. Furthermore, the PI is brought in line with the latest QRD template and editorial changes have been implemented. The RMP (version 9.1) is updated in accordance.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

- Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008 - Extensions of marketing authorisations.
- Article 7.2(b) of Commission Regulation (EC) No 1234/2008 – Group of variations.

According to Annex III of Regulation (EC) No 1234/2008, this grouped application comprises:

- Extension of marketing authorisation – Annex I - Addition of a new pharmaceutical form (2 mg/mL oral suspension).
- Type II variation: C.I.6.a – Addition of a therapeutic indication in paediatric patients with PAH from 6 months to less than 18 years

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0376/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0376/2020 was completed.

The PDCO issued an opinion on compliance for the PIP <PIP P/0376/2020. However, as Adcirca is not patent protected, the reward of supplementary protection certificate extension cannot be applied.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on 21 July 2016 (EMA/CHMP/SAWP/476106/2016). The Scientific advice pertained to clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: Bruno Sepodes

The application was received by the EMA on	16 December 2021
The procedure started on	20 January 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 April 2022
The CHMP Co-Rapporteur's Critique Assessment Report was circulated to all CHMP and PRAC members on	25 April 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	19 May 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	09 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	13 October 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	11 November 2022

The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 November 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Adcirca on	15 December 2022
The CHMP adopted a report on similarity of Adcirca with Opsumit (macitentan), Adempas (riociguat) and Trepulmix (treprostinil sodium) on (see Appendix on similarity)	19 May 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Adcirca is currently authorised in the EU as 20 mg film-coated tablets for oral use for the following indication:

> ADCIRCA is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

The Marketing Authorisation Holder (MAH) *submited an application for Adcirca (tadalafil) for the following proposed new indication for paediatric pulmonary arterial hypertension (PAH) specifically:*

"Treatment of paediatric patients aged 6 months to 17 years old with PAH classified as WHO functional class II and III. Efficacy in patients ≥ 6 years in terms of improvement of exercise capacity has been shown in IPAH and PAH associated with surgical repair of at least 6-month duration of simple congenital systemic to pulmonary shunt."

Paediatric PAH is a rare and complex condition associated with significant morbidity and mortality. The aetiology of PAH in the paediatric population is predominantly idiopathic (idiopathic pulmonary arterial hypertension *(*IPAH)) or associated with congenital heart disease.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Accurate estimates of the prevalence and incidence of PAH in children do not exist. However, it is believed to be significantly lower in children than in adults (1 to 2 adults per million).

It has been estimated that about 0.5 per million children are diagnosed with IPAH yearly, which accounts for about 50% of all paediatric pulmonary arterial hypertension (pPAH).

2.1.3. Aetiology and pathogenesis

WHO defined 5 different groups of pulmonary hypertension based upon different causes. Pulmonary arterial hypertension refers to WHO Group 1.

PAH disease aetiologies are described in the following table. The more frequent aetiologies in children are idiopathic, heritable, associated with connective tissue disease and associated with congenital heart disease. Persistent Pulmonary Hypertension of the Newborn remains in the PAH group but has been moved to a subgroup (Subgroup 1'' within group 1), as it is considered to be a specific entity with a more transient course in most cases.

GROUP 1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable (familial)
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.4.1. Eisenmenger's syndrome
Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.
1.4.4.2. PAH associated with prevalent systemic-to-pulmonary shunts
• Correctable
• Non-correctable: Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.
1.4.4.3. PAH with small/coincidental defects
Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.
1.4.4.4. PAH after defect correction
Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.
1.4.5 Schistosomiasis

GROUP 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

GROUP 1". Persistent pulmonary hypertension of the newborn

BMPR2 = bone morphogenetic protein receptor, type 2; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance;

Source: Galie et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2015; 46: 903–75

2.1.4. Clinical presentation, diagnosis

Although the clinical presentation of pPAH may vary according to the aetiology, the most frequent symptoms are dyspnoea, fatigue, chest pain, dizziness, syncope, cyanosis, palpitations and irritability. Progression of the disease may lead to right cardiac failure, cardiac failure, oedema, haemoptysis, cerebrovascular accidents from paradoxical emboli, cardiac arrhythmias, Eisenmenger syndrome and thrombocytopenia. The WHO functional class system was implemented for disease evaluation of

patients with PAH to define the disease severity of symptoms and disease impact on day-to-day activities.

Overall, for paediatric patients with PAH, the median age at diagnosis is about 7 years. Without appropriate treatment, median survival rate after diagnosis of IPAH in children is about 10 months. The prognosis of children with PAH has improved over time due to new therapies and off-label use of adult PAH specific therapies being administered to paediatric patients.

2.1.5. Management

Therapies that are currently approved for the treatment of PAH in adults, in various geographies around the world, include prostacyclin and its analogues (epoprostenol, treprostinil, iloprost and beraprost), endothelin receptor antagonists (ERAs; bosentan, macitentan and ambrisentan), PDE5 inhibitors (sildenafil and tadalafil), soluble guanylate cyclase stimulator (riociguat) and selective prostacyclin receptor agonist (selexipag). Due to limited clinical data in children, treatment decisions are often extrapolated from adult studies. However, various therapies have been used to treat PAH in children. Most of these are based upon prior studies in adults.

The use of PDE5 inhibitors, including sildenafil and tadalafil, has become very common in the treatment of paediatric patients with PAH and has become standard of care in pPAH.

In the EU, bosentan, sildenafil and ambrisentan are approved for paediatric patients with PAH.

In the US, bosentan is the only approved drug for the treatment of paediatric patients with PAH.

Sildenafil and tadalafil are the only PDE5 inhibitors that have been approved for the adult PAH indication in the US, EU and Japan.

2.2. About the product

Tadalafil is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

Tadalafil belongs to the pharmacotherapeutic group of urologicals, drugs used in erectile dysfunction (ATC code: G04BE08).

Tadalafil is currently approved in the EU as 20 mg film-coated tablets for oral use for the treatment of pulmonary arterial hypertension (PAH) adult patients classified as WHO functional class II and III, to improve exercise capacity (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

The claimed the therapeutic indication in paediatric population was:

Treatment of paediatric patients aged 6 months to 17 years old with PAH classified as WHO functional class II and III. Efficacy in patients ≥ 6 years in terms of improvement of exercise capacity has been shown in IPAH and PAH associated with surgical repair of at least 6 month duration of simple congenital systemic to pulmonary shunt.

The approved indication is:

Paediatric population

Treatment of paediatric patients aged 2 years and above with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III.

This extension of the marketing authorisation also concerns the approval of a new pharmaceutical form (2 mg/mL oral suspension) intended to treat paediatric patients who require 20 mg of tadalafil or less and are not able to swallow the already authorised 20 mg film-coated tablets.

2.3. Type of Application and aspects on development

On 1 October 2008, Tadalafil Lilly was 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]). This authorisation was based on the authorisation granted to Cialis in 2002 ('informed consent'). The name of the medicine was changed to Adcirca on 21 October 2009.

On 30 November 2009, the European Commission approved the change of the indication of Adcirca (previously known as Tadalafil Lilly) from the treatment of erectile dysfunction in adult males (20 mg on demand, maximum once per day) to the treatment of pulmonary arterial hypertension (PAH) in adults classified as WHO functional class II and III (40 mg [2 x 20 mg] once daily). For further information as regards this variation procedure (EMEA/H/C/1021/II/0001), please see: https://www.ema.europa.eu/en/documents/variation-report/adcirca-h-c-1021-ii-0001-epar-assessment-report-variation_en.pdf

The safety and efficacy of tadalafil for the treatment of PAH in adults have been investigated in a 16-week placebo controlled study (Study H6D-MC-LVGY [LVGY]) which demonstrated that tadalafil 40-mg once-daily dosing is effective in the treatment of adult patients with PAH and is associated with an increase in exercise capability.

This application for tadalafil (Adcirca) EMEA/H/C/001021 is an extension of Marketing Authorisation to register a new pharmaceutical form (2 mg/mL oral suspension), grouped with a Type II variation for adding a therapeutic indication in paediatric patients from 6 months to 17 years old with pulmonary arterial hypertension.

2.4. Quality aspects

2.4.1. Introduction

This extension application introduces a new pharmaceutical form and is grouped with an extension of the therapeutic indication to paediatric patients.

The finished product is presented as oral suspension containing 2 mg/mL of tadalafil as active substance.

Other ingredients are: xanthan gum; microcrystalline cellulose; carmellose sodium; citric acid; sodium citrate; sodium benzoate (E211); silica, colloidal anhydrous; sorbitol (E420), liquid (crystallising); polysorbate 80; sucralose; simethicone emulsion 30 % (containing simethicone, methylcellulose, sorbic acid, purified water); artificial cherry flavour (contains propylene glycol (E1520)); and purified water.

The product is available in a polyethylene terephthalate (PET) bottle with a peelable seal and child-resistant polypropylene (PP) closure containing 220 mL of oral suspension.

Each carton contains one bottle, and a low-density polyethylene (LDPE) 10 mL graduated syringe with 1 mL graduations and an LDPE press-in-bottle adaptor.as described in section 6.5 of the SmPC.

2.4.2. Active Substance

No additional information was provided on the active substance to what has been previously approved apart from an update of module 3.2.S.2.1 (address clarifications for existing manufacturing sites) and submission of a new module 3.2.S.5 (reference standards).

The current specification of tadalafil active substance is acceptable for manufacturing of the finished product and there is no need for addition of other parameters. The acceptance criterion for the particle size is suitable for the oral suspension.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a white to practically white aqueous suspension containing 2 mg/mL tadalafil.

Co-packaged with the bottle containing the oral suspension is a 10 mL low-density polyethylene oral syringe with 1 mL graduation. The syringe is CE-marked. In addition, a low-density polyethylene press-in bottle adaptor which mates with the bottle and the syringe is provided. A declaration of conformity with current EU Regulation for medical devices is provided.

The aim of formulation development was to achieve a once-daily administration form suitable for paediatric patients to treat patients with pulmonary arterial hypertension. Pharmaceutical development of the finished product contains QbD elements, but no design space is claimed. The quality target product profile (QTPP) formed the basis for the design of the finished product. Definition of the QTPP allowed identification of potential critical quality attributes (CQAs).

The active substance tadalafil is a BCS Class 2 compound according to the Biopharmaceutics Classification System with low solubility and high permeability. As the *in vivo* absorption of Class 2 substances is typically dissolution rate-limited, particle size of the active substance is an important parameter that can affect the dissolution rate and the formulation of suspensions. The particle size of the approved active substance is suitable for use in the oral suspension. The active substance contains two chiral centres and is prepared as a single enantiomer. Stability studies conducted during development of the oral suspension have shown that the enantiomer is stable.

To develop the oral suspension formulation, a prototype formulation-screening study was conducted using the excipients of the commercial product and several other excipients. A range of concentrations was studied to determine the appropriate excipients. The prototype suspensions were packaged in amber PET bottles and stored at 25 ºC / 60 % RH and 40 ºC / 75 % RH. Results demonstrated that the active substance is stable with the chosen excipients. Antimicrobial effectiveness testing was also conducted for the prototype formulations. The formulations containing sodium benzoate passed while formulations containing the parabens did not pass (see also further details below).

The lead formulation was selected due to faster dissolution, good stability over 6 months at 25 ºC / 60 % RH and 40 ºC / 75 % RH as well as for having satisfactory appearance, texture and processability. The selected excipients demonstrated very good chemical and physical stability. The excipients

enabling the suspension formulation are Avicel RC-591 and xanthan gum aided by the addition of silica (colloidal silicon dioxide). Avicel RC-591 allows the suspension to be re-dispersed and dispensed via an oral syringe. Xanthan gum is a protective colloid that increases viscosity and structure and in conjunction with Avicel RC-591 forms a long-lasting suspension. Silica acts as a flocculating agent and prevents hard packing of the particles to aid in re-dispersion. The viscosity of the suspension increases upon standing which helps to keep the solids suspended. Simethicone emulsion 30 % is added to eliminate foam and prevent foam formation.

The oral suspension is aqueous-based and packaged in a multiple use container, thus requiring addition of a preservative to protect from growth of microbial organisms. Sodium benzoate was selected as the preservative due to its high solubility, preservative effectiveness and compatibility with tadalafil at an acidic pH. The antimicrobial effectiveness of sodium benzoate was studied at three different concentrations within the pH range. The proposed level of sodium benzoate ensures robust antimicrobial effectiveness throughout the product shelf-life. The level is within the acceptable intake of 0 – 5 mg/kg as stated in the "*Questions and answers on benzoic acid and benzoates used as excipients in medicinal products for human use*". Sodium benzoate is an excipient with a known physiological effect and is thus also listed in section 2 of the SmPC.

The remaining excipients used, and their characteristics were also discussed and the suitability and the amount of each of each excipient has been justified. Sweeteners and flavour are added to the formulation for better taste. Sorbitol liquid (crystallising) contains 110.25 mg/mL of sorbitol. As sorbitol is a source of fructose, the package leaflet includes information for patients with the rare genetic disorder of hereditary fructose intolerance as discussed in the guideline "*Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use*". The artificial cherry flavour contains propylene glycol. The amount of propylene glycol is below the limit indicated in the "*Questions and answers on propylene glycol used as an excipient in medical products for human use*". As excipients with a known physiological effect sorbitol and propylene glycol are listed in section 2 of the SmPC. The theoretical sodium content from all contributing excipients (carmellose sodium, sodium citrate and sodium benzoate) is below 1 mmol of sodium per a 20 mg dose (10 mL) and therefore below the threshold for reporting in section 2 of the SmPC.

In response to a multidisciplinary Major objection raised during the procedure, the applicant presented justification regarding the suitability of the excipients used in the formulation for paediatric patients, in line the "*Guideline on pharmaceutical development of medicines for paediatric use",* in particular also regarding the use of sodium benzoate at a concentration of 2.1 mg/mL. The amount of each excipient was adequately justified based on the clinical dosing strategy. As regards quality, the use sodium benzoate as a preservative is acceptable due to the risk of contamination of the oral suspension during multiple use. The Major objection was, therefore, considered resolved.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of simethicone emulsion (which complies with USP) and artificial cherry flavour (which complies to in-house specifications). The flavouring agents comply with Regulation (EC) No. 1334/2008.

During formulation development, prototype formulations were evaluated against the identified CQAs and other attributes including particle size distribution, viscosity, sedimentation and taste acceptance which are controlled by the qualitative and quantitative unit formula as well as the process equipment and parameters. Pre-formulation and prototype formulation data was used to define the unit formula and multivariate design of experiments (DoEs). The results from the DoE studies improved the formulation by reducing product quality attribute risks and increasing patient safety. The data on the compatibility of the active substance with the excipients guided the initial qualitative formula and quantitative targets for many excipients and the quantitative level for sorbitol. The formula was further

developed to improve the taste. The studies conducted to optimise the formulation are discussed in detail.

The rheological properties were investigated. Adcirca oral suspension is thixotropic (shear thinning). Early formulations demonstrated that high viscosities could impact the dissolution rate and therefore, adjustments were made to the formulation to decrease the viscosity and ensure rapid dissolution. The current formulation has demonstrated rapid and complete dissolution while maintaining sufficient viscosity to support the uniformity of the suspension during manufacturing and for up to an hour after shaking in the bottle.

Sedimentation rate and re-dispersibility were studied throughout development of the suspension to ensure homogeneity of the product prior to dispensing a dose. Although settling of the suspension does occur over an extended period, the re-dispersibility results demonstrate that the suspension is easily re-dispersed to a homogeneous suspension by shaking the bottle according to the instructions in the SmPC.

A ready-to-use oral suspension was developed to support a relative bioavailability study compared to approved 20 mg Adcirca film-coated tablets. Slight modifications were made to the quantitative composition after the relative bioavailability study to ensure appropriate pH and buffer capacity to enable in-use microbiological control. The formulation proposed for marketing is the same as used during Phase 1b/2/3 clinical trials and for primary stability studies.

The commercial manufacturing process was developed using a QbD approach. The manufacturing development has been evaluated through the use of risk assessments and design of experiments to identify the critical process parameters. Risk analysis was performed using the failure mode effect and criticality analysis (FMECA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. No critical process parameters have been identified for the ranges indicated in the proven acceptable ranges (PARs). No design spaces are proposed for the manufacturing process, as all combinations of PARs studied for each unit operation resulted in finished product with acceptable quality.

Dosing device

During clinical trials, the dosing device used to measure and dispense the ready-to-use oral suspension was a commercially available CE marked delivery device system consisting of a press-in bottle adaptor and a conically tipped oral syringe.

For marketing, a commercially available CE marked press-in bottle adaptor in combination with a CE marked 10 mL blunt end oral syringe was selected. Graduation markings every 1 mL for the oral dosing syringe allow flexibility of dosing to support the possible 2 mL, 3 mL, and 10 mL doses. The delivery device system has met the requirements for *Ph. Eur. 2.9.27 Uniformity of Mass of Delivered Doses from Multidose Containers* for the three primary stability batches at both the low dose (2 mL) and high dose (10 mL).

Compatibility of the oral suspension with nasogastric tubes

The oral suspension can be also administered via nasogastric tubes of silicone or polyurethane materials. A study to confirm the compatibility of the oral suspension with nasogastric tubes of either polyurethane or silicone has been conducted. Different volumes of the oral suspension were tested: 0.5 mL and 1.0 mL, delivered with a syringe of 1 mL (used for clinical trial only) and 2.0 mL, 3.0 mL and 4.0 mL, delivered with a syringe of 5 mL (used for clinical trial only). The content of each volume of oral suspension was tested after dispensation into either polyurethane or silicone tubing, followed by a

flush of 1 mL, 2 mL or 3 mL of NaCl 0.9 % solution. The obtained mean assay value (n = 3) were all between 94.9 – 99.8 %, except for a delivered dose of oral suspension of 0.5 mL, which is not a dose to be used. The stability of finished product in the silicone or polyurethane tubing, respectively, was tested for 0 – 30 minutes and no loss of active substance was observed. No related substances were detected, but the preservative content decreases significantly in polyurethane tubing.

The primary packaging is an amber polyethylene terephthalate (PET) bottle of 240 mL with a peelable seal and child-resistant polypropylene (PP) closure. The material complies with Ph. Eur. and EU regulations. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Medical devices

A CE-marked 10 mL low density polyethylene oral syringe with 1 mL graduation is co-packaged. Additionally, a low-density polyethylene press-in bottle adaptor which mates with the bottle and the syringe is provided. A declaration of conformity with current EU Regulation for medical devices has been provided.

The oral suspension can be also administered via nasogastric tubes of silicone or polyurethane materials.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of five main steps: mixing of the ingredients, active substance dispersion, pH adjustment, filling and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been described in detail.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. There are no critical process parameters for the manufacture of tadalafil oral suspension. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications shown in Table 5 include appropriate tests for this kind of dosage form: identity tadalafil (HPLC, UV), identity sodium benzoate (HPLC, UV), assay tadalafil (HPLC), degradation products (HPLC), description (visual), pH (Ph. Eur.), assay sodium benzoate (HPLC), uniformity of mass delivered doses from multidose containers (Ph. Eur.), and microbiological testing for microbial enumeration and specified microorganism (Ph. Eur.).

The finished product specification includes all relevant test parameters for an oral suspension and complies with Ph. Eur. and EU/ICH guidelines. All proposed acceptance criteria have been sufficiently justified. Limit established for impurities are set in line with ICH Q3B (R2).

Sufficient justification has been provided for the absence of routine testing for parameters such as re-dispersibility, relative density, density, viscosity, particle size distribution and dissolution.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using an ICP-MS method was provided, demonstrating that each relevant elemental

impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "*Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products*" (EMA/409815/2020) and the "*Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products*" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial-scale batches confirming the consistency of the manufacturing process and its ability to manufacture the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.3.4. Stability of the product

Stability data from three commercial-scale batches of finished product stored for up to 18 months under long term conditions (30 ºC / 35% RH) and for up to six months under accelerated conditions (40 ºC / NMT 25% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. The stability study was carried out under low relative-humidity conditions to demonstrate the suitability of the finished product packaging (8-ounce amber PET bottle, a semi-permeable container.) Therefore, the expected water loss from the container closure system was evaluated in addition to physical, chemical, and microbiological stability. The analytical procedures used are stability indicating. No significant trend has been observed and all results remained within specification. The potency of the finished product increases with time during storage at the low humidity conditions due to water loss but is expected to meet the proposed shelf-life specification.

In addition, stability data from eight batches of oral suspension used for clinical trials and manufactured by an earlier development process were provided. The batches have the same unit formula as the commercial formulation and were manufactured at a batch size similar to the commercial process. The product was packaged in similar 8-ounce PET bottles and stability data cover the proposed shelf life. Data is available for 36 to 48 months at 25°C / 60% RH and demonstrate that the product is stable. All results remained within specification and no significant trends were observed.

Water loss was monitored during stability studies to determine the amount of water egress from the 8-ounce amber PET bottle. At the 40 °C / NMT 25% RH storage condition, the water loss was is acceptable in line with ICH Q1A(R2) on *Stability testing of New Drug Substances and Products*.

In addition, one batch was exposed to light as defined in the ICH Guideline on *Photostability Testing of New Drug Substances and Products*. In the photostability study, the stability of the oral suspension outside of the immediate packaging as well as in the amber PET bottle was studied and no changes

were observed as a result of direct exposure to simulated sunlight conditions. Thus, the finished product is photostable.

Result from stress testing were also presented. The studies were conducted using one primary stability batch and investigated stability against thermal stress when packaged in the primary container proposed for marketing. No adverse changes to the physical or chemical stability were observed after storage for 14 days at low temperature (range of -20 to <1 °C) or at high temperature (70 °C). In addition, the product was subjected to thermal stress in 5 freeze/thaw cycles and no negative trends were observed.

In-use stability studies were performed using a primary stability batch at the initial timepoint, and a clinical batch aged to 24 months (representing in-use at the end of shelf-life). The study simulated real time dosing and rinsing using the delivery system (bottle adapter and syringe) to demonstrate antimicrobial effectiveness of the preservative system as well as the chemical and physical stability during usage. The in-use stability data from these studies as well as supporting studies demonstrated stability up to at least 110 days after first opening of the bottle followed by daily dosing.

Based on available stability data, the proposed shelf-life of 2 years and without special storage conditions as stated in the SmPC (section 6.3) are acceptable. The bottle should be stored upright. The shelf life after first opening of the bottle is 110 days.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, a multidisciplinary Major Objection was raised in relation to the suitability of the excipients used for paediatric patients, which was satisfactorily resolved as discussed above. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Toxicology, safety pharmacology and Absorption, Distribution, Metabolism and Excretion (ADME) studies to support administration of tadalafil in adult patients have been submitted in previous applications. For the proposed indication of this extension application for the treatment of paediatric patients with PAH, the MAH submitted toxicology data from a juvenile rat study.

2.5.2. Pharmacology

No additional pharmacology studies have been conducted for this application which is considered acceptable by the CHMP.

2.5.3. Pharmacokinetics

No additional pharmacokinetic studies have been conducted for this application which is considered acceptable by the CHMP.

2.5.4. Toxicology

The new toxicological data submitted by the MAH were obtained from a juvenile animal study, to investigate the potential toxic effects on the paediatric population. The studies performed included a repeat dose toxicity study in juvenile rats (PND14-PND90) and a toxicokinetic analysis performed in a satellite group.

2.5.4.1. Reproductive and developmental toxicity

The purpose of the juvenile rat study (JAS) was to evaluate potential adverse effects of long-term oral administration of tadalafil on neonatal growth and development in juvenile male rats when treated from Postnatal Day (PND) 14 through PND 90 followed by a 30-day recovery period. In addition, a toxicokinetic assessment of plasma levels of tadalafil was performed in satellite animals. PND14 was chosen for dosing initiation because the developmental stage of rats at this age corresponds to the neurological developmental stage of human infants at approximately 6-months to 1 year of age.

There were no tadalafil-related effects on survival noted at any dose level. There were 7 unscheduled deaths during the dosing period (including control animals). The causes of death were determined to be inflammatory genitourinary tract disease, suspected gavage error, or head trauma.

Based on the lack of adverse tadalafil-related effects on survival, clinical observations, body weight, food consumption, clinical pathology, organ weights, and histopathology noted at any dose level during the dosing and recovery periods, the no-observed-adverse-effect level (NOAEL) for male systemic toxicity was considered to be 1000 mg/kg, the highest dose level evaluated. In addition, no adverse effects on developmental landmarks and neurobehavioral endpoints were observed at 60, 200, or 1000 mg/kg.

Therefore, the NOAEL for developmental toxicity/neurotoxicity was considered to be 1000 mg/kg (AUClast at PND 14 and 91 of 337,000 and 61,100 ng•hr/mL, respectively). In addition to the results of the JAS, the MAH also presented an estimation of the safety margin for paediatric population, based on the results of the toxicokinetic analysis (table below).

Table 1 - Margin of Safety for Tadalafil in Paediatric Patients Based on Systemic Exposure

Species	AUC_{0-24hr} (ng•hr/mL)	Exposure Multiple[a]
Human Paediatric ≥40 kg[b] (40 mg/day)	12900	--
Juvenile Rat NOAEL[c]	61100	4.7x
Human Paediatric 25 to <40 kg[b] (20 mg/day)	8550	-
Juvenile Rat NOAEL[c]	61100	7.1x
Human Paediatric <25 kg[b] (20 mg/day)	8555	-
Juvenile Rat NOAEL[c]	61100	7.1x

Abbreviations: AUC = area under the plasma concentration x time curve; NOAEL = no-observed-adverse-effect level.

a Exposure multiple is the AUC_{0-24hr} in rats/AUC_{ss} in paediatric patients.

b The proposed pediatric dose is 40 mg for patients ≥40 kg and 20 mg for patients <40 kg; plasma pharmacokinetics were estimated using the primary phase 2/3 PopPK Model (Table 2.7.2.6).

c NOAEL determined in juvenile toxicity study (WIL-353305); plasma toxicokinetics determined on Day 90.

2.5.4.2. Toxicokinetic data

Table 2 - Toxicokinetic data from the juvenile animal study conducted with tadalfil

Toxicokinetics			
Sample: Plasma	Analyte: Tadalafil	Number of animals: 3/group/time point	
Feeding condition: Fed	Dose frequency: Daily	Assay/Method: LC-MS/MS / 140095VRLC_EII_R2	
Dose (mg/kg):	60	200	1000
PND 14			
C_{max} (ng/mL)	6180	11400	17300
AUC_{0-24} (ng•hr/mL)	119000	201000	337000
SE of AUC_{0-24} (ng•hr/mL)	14300	10300	22600
T_{max} (hr)	12	12	12
PND 90			
C_{max} (ng/mL)	2740	12000	4820
AUC_{0-24} (ng•hr/mL)	31800	81400	61100
SE of AUC_{0-24} (ng•hr/mL)	3840	35200	5120
T_{max} (hr)	4	6	6

2.5.5. Ecotoxicity/environmental risk assessment

The MAH submitted an updated ERA, by including the proposed new indication (PAH in paediatric population). The dose for paediatric patients will be based on body weight categories and the maximum recommended dose will be 40 mg/day.

In accordance with the recommendations as published in "*Questions and Answers document on 'Guideline on the environmental risk assessment of medicinal products for human use*' (EMA/CHMP/SWP/44609/2010, rev1, 2016), and in this particular case, an increase in environmental exposure is generally expected. PECsurfacewater calculated as 0.2 µg L^{-1} is over the action limit value established by the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human use* (EMEA/CHMP/SWP4447/00, 2006) and Phase II-tier A environmental fate and effects analysis was performed by the MAH.

2.5.6. Discussion on non-clinical aspects

The MAH conducted a JAS in rats, in which animals were dosed from PND14 to PND90. This starting age can be considered equivalent to an approximate age of 6 months-1 year in humans.

No tadalafil-related findings were reported in the study and no effects on survival, clinical pathology parameters, developmental landmarks, neurobehavioural endpoints or histopathology were observed at the highest dose level (1000 mg/Kg/day). The toxicokinetic analysis and further estimation of safety margins showed exposure levels 7.1-fold as compared with those obtained at the intended paediatric dose.

Considering that PECsurfacewater of tadalafil is above the action limit value, a Phase II environmental fate and effects analysis was conducted by the MAH.

Based on the log Kow value of 2.32 tadalafil has low bioaccumulation potential, as log Kow does not exceed 4.5. The log Koc value reported by the OECD 121 method suggests that tadalafil has low adsorption to sludge, but it is only an indicative value. The guideline EMEA/CHMP/SWP/4447/00 corr 2, 2006, asks for a batch equilibrium method (OECD 106 or OPPTS 835.1110). Thus, it is necessary to perform a study using a batch equilibrium method, OPPTS 835.1110 or OECD 106 using 2 types of sludges and/or 3 soils types, and the MAH was requested to justify the use of the OECD 302A method.

As such the MAH commits to conduct a study according to OECD 106 and also to update the environmental risk assessment with the measured adsorption Koc values from that study as a follow-up measure.

The adsorption Koc values will be determined in at least 3 soils and 2 sludges as per the Questions and Answers document on the environmental risk assessment guideline (Question 10, EMA/CHMP/SWP/44609/2010 Rev. 1, 2016) (EMA 2016).

2.5.7. Conclusion on the non-clinical aspects

No additional pharmacology or pharmacokinetic studies have been conducted in support of this application which is considered acceptable by CHMP.

Overall, the toxicology programme in juvenile animal study did not reveal adverse tadalafil-related effects on survival, clinical pathology, developmental landmarks, neurobehavioural endpoints or histopathology at any dose level (NOAEL considered 1000 mg/Kg/day). The toxicokinetic analysis and further estimation of safety margins showed exposure levels of 7.1-fold as compared with those obtained at the intended paediatric dose.

A new environmental OECD 106 study will be provided to complete the ERA. The MAH will submit the OECD 106 report and an updated ERA report by 31/03/2025. A letter of commitment has been submitted.

In conclusion, the CHMP considers that the non-clinical data submitted for this extension of indication application is adequate to support the use of Adcirca in the approved paediatric population.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 3 - Overview of Studies in the Clinical Pharmacology Program

Study Code and Description	**PK Patient Population**	**Age**	**Dosing Regimen**	**Study Duration**	**PK Sampling**
LVIG Phase 1b/2, open-label multicentre, multiple ascending dose study to evaluate PK and safety of tadalafil administered orally as a tablet or suspension.	18 paediatric patients with PAH With or without ERA therapy	2.5 to 17.96 years	Tadalafil (2 mg to 40 mg, based upon weight category), supplied as the authorised 2.5 mg, 5 mg, 10 mg, and 20 mg Cialis® tablets Oral tadalafil suspension formulation (2 mg/mL of tadalafil)	Period 1: 10 weeks Period 2: a minimum of 2 years	• Day 1 (Visit 2), Day 14 (Visit 4), and Day 49 (Visit 8): Pre dose and 2-, 4-, 8-, 12-, and 24-hours postdose • A trough PK sample was collected at Visit 10 to evaluate the tadalafil exposure after 3 months of treatment during Period 2
LVHV Phase 3, international, randomised, double-blind, placebo-controlled add-on [in addition to the patient's current ERA] study to explore the efficacy, safety, and PK of tadalafil administered orally QD in paediatric patients with PAH	17 paediatric patients with PAH With ERA therapy (bosentan or macitentan)	6.2 to 17.9 years	For children age ≥2 years, tadalafil 20 mg tablets as: • ≥40 kg: 40 mg QD • ≥25 to <40 kg: 20 mg QD • <25 kg: cohort not enrolled	24 weeks	• Weeks 2, 4, 16, 24 (1 sample per visit)
LVJJ	210	7 to	Maximum daily	48 weeks	• Weeks 4,

Phase 3, multicentre, randomised, double-blind, parallel, 3-arm, placebo-controlled study of tadalafil in patients with DMD	paediatric male patients with DMD No ERA therapy	14 years of age	dose: 20 mg and 40 mg in the 0.3-mg/kg/day and the 0.6 mg/kg/day dose groups given as a combination of 2.5-, 5-, 10-, and 20-mg tablets		12, 24, and 36 (1 sample per visit)

Abbreviations: DMD = Duchenne muscular dystrophy; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PK = pharmacokinetic; QD = once daily.

2.6.2. Clinical pharmacology

No new clinical pharmacology studies were conducted to characterise PK in paediatrics or to support the paediatric PAH indication. PK and PD in paediatric patients were obtained from the studies presented in the table above.

2.6.2.1. Pharmacokinetics

Absorption

The PopPK of tadalafil in paediatric patients aged 2 to <18 years were described by a linear 1-compartment model.

Following oral administration of once daily (QD) dosing, tadalafil was absorbed with a median time to maximum observed plasma concentration (t_{max}) of approximately 4 hours in paediatric patients (2 to <18 years) with PAH and was independent of body weight, similar to what was observed in adult patients with PAH.

Dose has an effect on bioavailability (F). F decreased 14% when the dose increases from 20 mg to 40 mg in paediatric patients. The extent of the difference in F between 20 mg and 40 mg in paediatric patients is similar to that of adults.

Data for the absorption, distribution, metabolism, and elimination of tadalafil in children less than 2 years of age is not available.

To support the new paediatric indication, the MAH has submitted one bioavailability study (LVIF) to evaluate the pharmacokinetics of tadalafil 2 mg/mL as a suspension formulation and to determine the relative bioavailability compared to marketed tablets (20 mg Cialis) in healthy adult subjects in fasting conditions. This was a single-centre, open-label, randomized, 3-period, 3-sequence, crossover, single dose study in healthy male and female subjects. There was a washout period of 7 days between dosing periods.

The treatment sequences are shown in the table below:

Table 4 – Tadalafil treatment sequence

Sequence	Period 1	Period 2	Period 3
1	20 mg tadalafil tablet (Cialis®) (1 x 20 mg)	20 mg tadalafil suspension (10 mL x 2 mg/mL)	40 mg tadalafil suspension (20 mL x 2 mg/mL)
2	20 mg tadalafil suspension (10 mL x 2 mg/mL)	40 mg tadalafil suspension (20 mL x 2 mg/mL)	20 mg tadalafil tablet (Cialis®) (1 x 20 mg)
3	40 mg tadalafil suspension (20 mL x 2 mg/mL)	20 mg tadalafil tablet (Cialis®) (1 x 20 mg)	20 mg tadalafil suspension (10 mL x 2 mg/mL)

In all 18 subjects, 14 blood samples were drawn at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 hours post-dose.

Pharmacokinetic Variables

Pharmacokinetic parameters of tadalafil were estimated by non-compartmental linear-trapezoidal rule using WinNonlin 5.2.

Primary pharmacokinetic parameters

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Secondary pharmacokinetic parameters

AUC_{0-6}, AUC_{0-12}, AUC_{0-24}, t_{max} and $t_{1/2}$.

Statistical methods

The primary pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} after logarithmic transformation were subjected to an analysis of variance (Mixed Procedure) with fixed factors: period, formulation and sequence, and subject as a random effect.

To assess the bioavailability of both formulations a linear mixed effects model to the natural log-transformed of the primary pharmacokinetic parameters was used to obtain the adjusted geometric mean ratio (and associated 90 %CI) after back-transforming the difference between LS means.

Mean plasma concentration time profiles (linear with ±SD and semi-log) of 20 mg and 40 mg of tadalafil are shown in the figure below (both oral suspension and tablets).

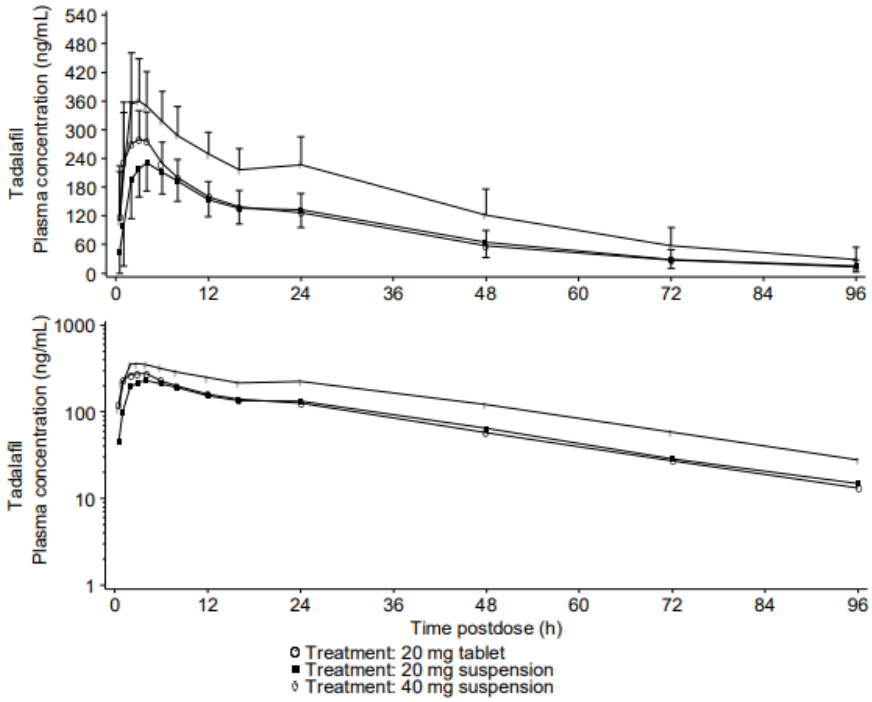


Figure 1 - Mean plasma concentration time profiles (linear with ±SD and semi-log) of 20 mg and 40 mg of tadalafil

The results demonstrate that the suspension formulation is non bioequivalent to the tablet one as the Cmax do not fall within the acceptance limits of 80.00%-125.00%, although it is unclear what is the clinical relevance of this finding.

Distribution

Following oral administration of multiple, once daily 20- or 40-mg doses of tadalafil, the geometric mean V/F is 43.3 L (CV=25.8%) and 101 L (CV= 19.1%), respectively, for paediatric patients aged 2 to <18 years in the weight range of <40 kg and ≥40 kg.

Elimination

The geometric mean CL/F of tadalafil is 3.09 L/h (CV=30.8%) and 2.34 L/h (CV=18.1%) at 40 mg and 20 mg, respectively, in paediatric patients aged 2 to <18 years. Concomitant bosentan use increases CL/F by approximately 50%. The estimates of CL/F and the effect of bosentan on CL/F in paediatric patients are similar to those in adult patients with PAH. The mean terminal $t_{1/2}$ for tadalafil is 24.2 hours and 13.6 hours, respectively, for paediatric patients aged 2 to <18 years with a body weight ≥ 40kg and <40 kg; due to smaller V/F, $t_{1/2}$ for paediatric patients <40 kg is shorter. Bosentan use reduces the $t_{1/2}$ by approximately 42% across weight groups.

Tadalafil is predominantly oxidatively metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for phosphodiesterase 5 (PDE5). Consequently, it is not expected to be clinically active at observed metabolite concentrations and for these reasons the methylcatechol glucuronide was not measured in the paediatric PAH studies.

Dose proportionality and time dependencies

Based on the Primary Phase 2/3 PopPK Analysis in paediatric patients, F decreases with an increase in dose. Due to this effect, there is a lack of dose proportionality between 20 mg and 40 mg and a

nominal dose of 40 mg provides exposures approximating a 20- to 30-mg dose. The magnitude of dose effect on the F is similar to that estimated in adult patients with PAH.

A linear PK model in regard of time adequately described the PK in paediatric patients based on the Phase 2/3 PopPK Analysis, indicating an absence of time-dependent PKs similar to the adult data.

Pharmacokinetics in the target population

In total, the Population Pharmacokinetic (Pop PK) dataset included data from 4 trials, 2 disease indications [PAH and Duchenne muscular dystrophy (DMD)], 247 patients across whose ages ranged from 2 to 18 years at study entry and who weighed between 10.0 and 80.0 kg.

Table 5 – Studies included in the pooled paediatric Pop PK analysis

Dieate / Study	Population	Dosing Regimen	PK / PD Measurements
PAH / H6D-MC-LVHV (Period 1) Phase 3, international, randomized, double-blind, placebo-controlled add-on (in addition to the patient's current ERA) study to explore the efficacy, safety, and Pop PK of tadalafil administered orally once daily in pediatric patients with PAH	• n = 17 • 10 female, 7 male • 6 to 17 years • With ERA therapy (bosentan or macitentan)	For children age ≥2, tadalafil 20 mg tablets as: ≥40 kg: 40 mg qd ≥25 to <40 kg: 20 mg qd Or 2 mg/mL oral suspension <25 kg: 20 mg qd (<25 kg cohort not enrolled)	Baseline: PD Week 2: PK (1-4 hrs postdose) Week 4: PK (trough) & PD Week 8: PD Week 12: PD Week 16: PK (trough) & PD Week 20: PD Week 24: PK(trough) & PD
PAH / H6D-MC-LVIG (Period 1) Phase 1b/2, open-label multicenter, multiple ascending dose trial to evaluate PK and safety of tadalafil administered orally as a tablet or suspension.	• n = 19 • 13 female, 6 male • PAH pediatric patients • 2 to 17 years • With or without ERA therapy	tadalafil 1 mg – 40 mg as tablets or a 2 mg/mL oral suspension [a] ≥40 kg: 10 mg/40 mg qd ≥25 to <40kg: 5 mg/10 mg qd <25kg: 1 mg/5 mg qd	PK: Predose, 2.0, 4.0, 8.0, 12.0, and 24.0 hrs postdose, collected at: Visit 2, Day 1, Visit 4, Day 14, Visit 8, Day 49 and Visit 10, Day 100, trough
PAH / H6D-MC-LVGY This is a Phase 3 randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of tadalafil 2.5, 10, 20, and 40 mg once daily in the treatment of subjects with pulmonary arterial hypertension.	• n = 1, female • age 14 years Note this is primarily an adult study, however, 1 pediatric patient was enrolled and is thus included here.	tadalafil 2.5, 5, 10, 20, 40 mg or placebo given as 2.5, 10 or 20 mg tablets Note the one pediatric subject was on: 2.5 mg qd	Week 4, PK & PD Week 8, PK & PD Week 12, PK & PD Week 16, PK & PD
DMD / H6D-MC-LVJJ Phase 3, multicenter, randomized, double-blind, parallel, 3-arm, placebo-controlled study of tadalafil 0.3 mg/kg and 0.6 mg/kg daily in patients with Duchenne muscular dystrophy. The study consisted of a 48-week double-blind treatment period.	• n = 210 male • 7 to 14 years • No ERA therapy	0.3 mg/kg or 0.6 mg/kg administered as total doses of 5 mg to 40 mg based upon available tablets[b]	PK: Visit 3 (Week 4): 1-3 hrs postdose Visit 4 (Week 12): 6-9 hrs postdose Visit 5 (Week 24): 12-18 hrs postdose Visit 6 (Week36): 24 (± 1) hrs postdose

Abbreviations: DMD = Duchenne Muscular Dystrophy; ERA = endothelin receptor antagonist; n = number of subjects; PAH = pulmonary arterial hypertension; PD = pharmacodynamics; PK = pharmacokinetics;

Final population PK model

The structural population PK model was one-compartment parameterized in terms of F, Ka, CL/F, and V/F with IIV on F, Ka and CL/F. The IIV on V/F was near 0 and was thus fixed to 0. The final population PK model incorporates dose on F, bosentan use on CL and weight on V.

Table 6 – Pharmacokinetic and Covariate Parameters from the final population model

	Parameter Description	Population Estimate (%SEE)		Inter-Patient Variability[a] (%SEE)	Population Estimate Bootstrap Median (95% CI)	Inter-Patient Variability Bootstrap Median (95% CI)
	Absorption Rate Constant					
θ_2	Parameter for Ka (hr^{-1})	0.971 (14)	ω_2	163% (17)	0.972 (0.739 – 1.32)	164% (119% – 229%)
	Apparent Clearance[b]					
θ_8	Effect of bosentan on CL	0.803 (18)		NA	0.800 (0.518 – 1.09)	NA
θ_5	Effect of weight on CL	0 FIXED		NA	NA	NA
θ_3	Parameter for CL (L/hr)					
	not taking bosentan	1.89 (2)	ω_3	26% (27)	1.89 (1.81 – 1.98)	25% (15% – 32%)
	taking bosentan (calculated)	3.41		NA	NA	NA
	Apparent Volume of Distribution[c]					
θ_4	Parameter for V (L) for a 70-kg patient	95.9 (4)	ω_4	0 FIXED	95.5 (88.5 – 103)	NA
θ_6	Effect of weight on V	1 FIXED		NA	NA	NA
	Relative Bioavailability[d]					
θ_1	Parameter for F (fraction centered at 15 mg)	1 FIXED	ω_1	18% (35)	NA	18% (12% – 25%)
θ_9	Effect of dose (continuous)	-0.227 (16)		NA	-0.228 (-0.298 – -0.160)	NA
	Residual Error[e]					
θ_7	Additive (ng/mL)	21.2 (25)		NA	21 (7 - 38)	NA
σ_1	Proportional	23% (11)		NA	23% (20% – 26%)	NA

Abbreviations: CI = confidence interval; CL = apparent clearance; CV = coefficient of variation; F= bioavailability; Ka = absorption rate constant; NA = not applicable; NONMEM = nonlinear mixed-effects modeling; SEE = standard error of the estimate reported by NONMEM; V = apparent volume of distribution; WT = weight (kg).

Note: The bootstrap method used was a nonparametric bootstrap.

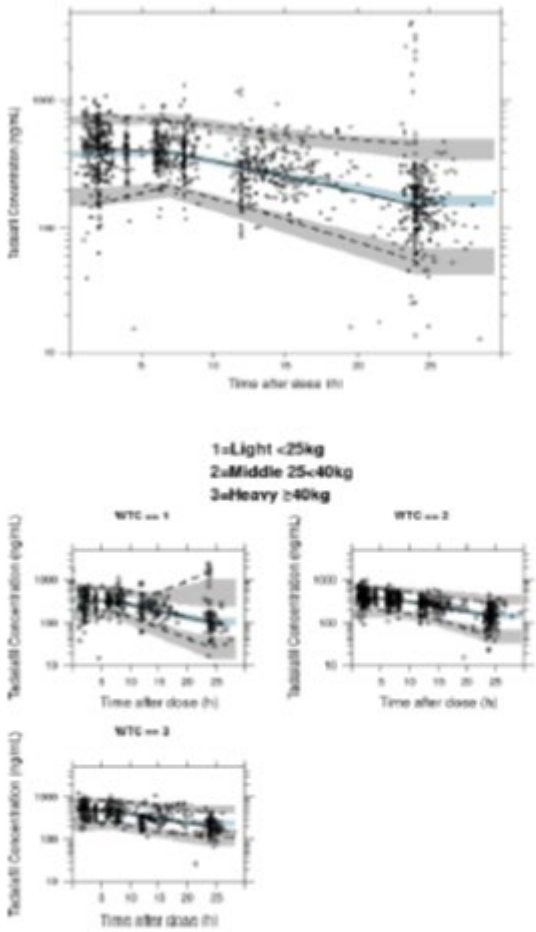
[a] Reported as CV, calculated using equation $100\% \cdot \sqrt{e^{\omega^2} - 1}$, where ω^2 is the variance of the corresponding parameter.

[b] $CL = \theta_{3,TVCL} \cdot (1 - BOS) + \theta_{3,TVCL} \cdot (1 + \theta_{8,BOS}) \cdot (BOS)$ where $\theta_{3,TVCL}$ is the typical value for CL for a patient not taking bosentan, BOS is an indicator variable (0=no, 1=yes) for concomitant bosentan, and $\theta_{8,BOS}$ is the change in CL for patients taking concomitant bosentan.

[c] $V = \theta_{4,TVV} \cdot COV^{\theta_{6,WT}}$, where $\theta_{4,TVV}$ is the typical value for V, COV is the patient's body weight at study entry normalized to a typical weight of an adult (70 kg), and $\theta_{6,WT}$ is the effect of body weight on V fixed to the allometric scaling value of 1.

[d] $F = \theta_{1,TVF} \cdot \left(\frac{DOSE}{15}\right)^{\theta_{9,DOSEF}}$, where $\theta_{1,TVF}$ is the typical value for F and fixed to 1, DOSE is the subject's reported dose, $\theta_{9,DOSEF}$ the effect of dose on F.

Proportional residual error reported as CV using the equation $100\% \cdot \sqrt{\sigma_1}$, and additive residual error reported as $\sqrt{x^2 \cdot \sigma_1}$, where x is the additive error term, θ_7, and σ_1 is the estimate for the residual error term.



Black open circles represent individual observations. The solid black line depicts the median of observed data, while the blue shaded area represents the 90% confidence interval around the median of the simulated data (1000 simulations). The dashed lines represent the observed 5th and 95th percentiles, while grey shaded areas represent simulated 90% confidence interval of the same.
Abbreviations: CL/F = apparent clearance; h = hours; VPC = visual predictive check, WTC = weight cohort.

Figure 2 – Prediction-corrected VPC for the final Pop PK model (upper panel) and stratified by weight cohort (lower panel)

Pediatric model-estimated post-hoc results of key PK parameters are presented in Table P06 for patients taking or not taking bosentan (including 1 subject taking macitentan; subjects on concomitant ambrisentan are included in non-bosentan results). For comparison, tadalafil PK parameters in a typical adult patient were estimated using the final adult (LVGY) Pop PK model and are included in the table. For all subjects, the differences between estimated PK parameter values in subjects not taking or taking bosentan reflect the effect of bosentan in the estimate of CL/F. Tadalafil PK parameters were summarized for each pediatric weight cohort from the pediatric-model post-hoc parameter estimates.

Table 7 – Final model-estimated values of PK parameters by weight cohort at the recommended 20 and 40 mg qd doses with adult reference

Study (n)	Cohort (kg)	Dose (mg)	Weight (kg)[a]	Geometric Mean (Geometric CV%) CL/F (L/hr)	V/F (L)	AUC_{ss} (ng·hr/mL)	$C_{min,ss}$ (ng/mL)	$C_{av,ss}$ (ng/mL)	$t_{1/2}$ (hr)
With concomitant bosentan									
LVGY (n=39)	Typical adult	40	73	4.09 (39.1)	124 (29.5)	9770 (39.1)	263 (61.4)	407 (39.1)	21.0 (54.1)
(n=42)		20	73	2.89 (44.3)	82.7 (35.4)	6920 (44.3)	181 (66.3)	288 (44.3)	19.8 (55.2)
Combined (n=16)[b]	≥40	40	56.6	4.59 (27.2)	98.5 (19.3)	8720 (27.2)	204 (39.7)	363 (27.2)	14.9 (22.9)
(n=6)	25 to <40	20	27.7	3.35 (29.2)	42.5 (19.1)	5970 (29.2)	91 (56.7)	249 (29.2)	8.79 (21.4)
(n=1)	<25	20	11.3	5.42 (NA)	19.7 (NA)	3690 (NA)	6.13 (NA)	154 (NA)	2.51 (NA)
LVHV (n=13)	≥40	40	58.0	4.49 (28.2)	99.5 (20.5)	8910 (28.2)	215 (39.3)	371 (28.2)	15.4 (23.0)
(n=3)	25 to <40	20	27.3	3.63 (38.1)	42.5 (16.5)	5510 (38.1)	79.9 (91.4)	230 (38.1)	8.13 (31.0)
(NA)	<25	20	NA	NA	NA	NA	NA	NA	NA
No bosentan									
LVGY (n=36)	Typical adult	40	73	2.53 (40.6)	116 (30.7)	15800 (40.6)	497 (53.2)	658 (40.6)	31.9 (51.9)
(n=36)		20	73	1.92 (53.5)	82.5 (27.6)	10400 (53.5)	323 (73.3)	434 (53.5)	29.8 (43.2)
Combined (n=5)[b]	≥40	40	63.0	3.09 (30.8)	108 (19.0)	12900 (30.8)	379 (41.8)	539 (30.8)	24.2 (33.3)
(n=13)[b]	25 to <40	20	32.3	2.34 (19.2)	48.8 (10.6)	8550 (19.2)	203 (28.9)	356 (19.2)	14.5 (13.6)
(n=2)[b,c]	<25	20	17.6, 23.9	2.13, 2.59	28.7, 34.2	7710, 9400	175, 183	321, 392	7.66, 11.1
LVHV (NA)	≥40	40	NA	NA	NA	NA	NA	NA	NA
(n=1)[d]	25 to <40	20	39.8	2.68 (NA)	58.7 (NA)	7460 (NA)	175 (NA)	311 (NA)	15.2 (NA)
(NA)	<25	20	NA	NA	NA	NA	NA	NA	NA

Abbreviations: AUC_{ss} = AUC over one dosing interval at ss; CL/F = apparent clearance; $C_{av,ss}$ = the average concentration at ss; $C_{min,ss}$ = the minimum concentration at ss; CV = coefficient of variation; n = number of subjects; NA = not applicable; PK = pharmacokinetics; qd = once daily; ss = steady-state; $t_{1/2}$ = half-life; V/F = apparent volume of distribution.

[a] The weight of 70 kg selected for adults is considered a typical value (the median weight of adult patients in Study LVGY was 73 kg). The weights in the pediatric cohorts are the median weight in the subset.

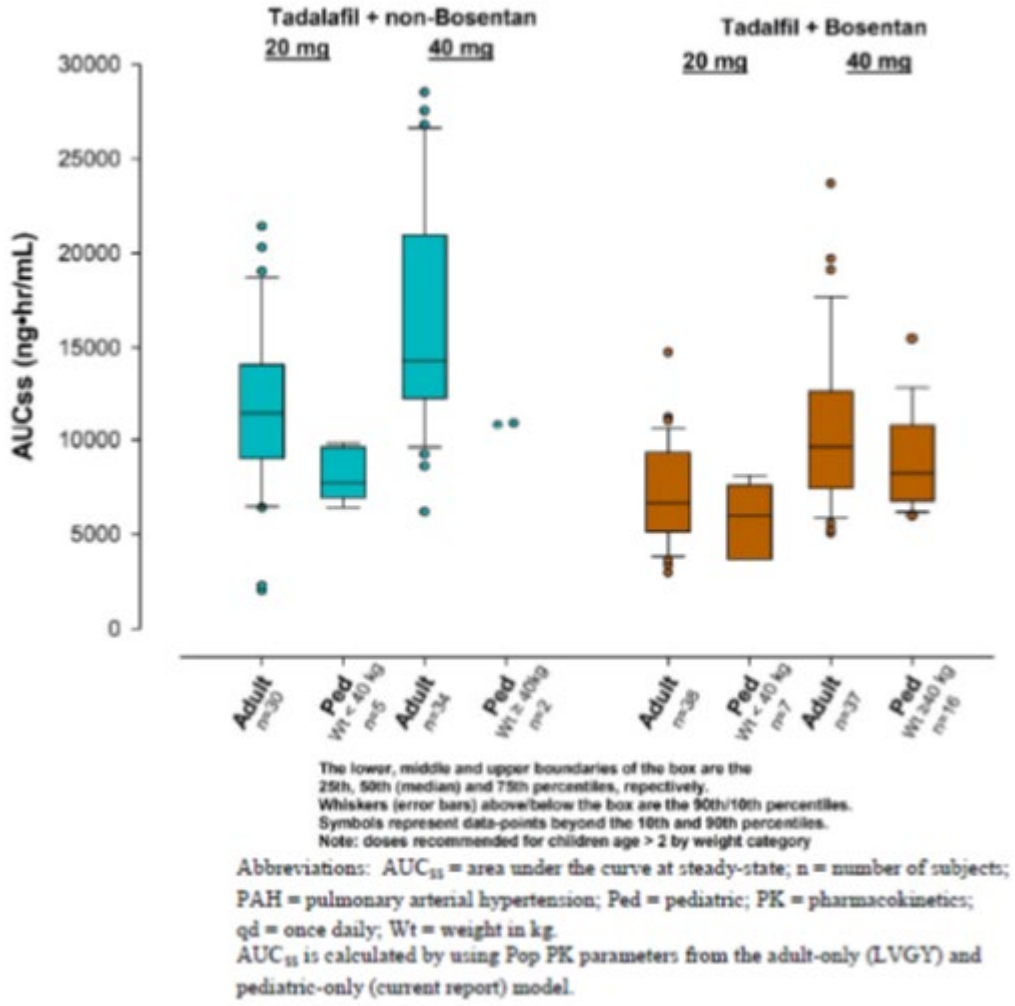
[b] The combined results are from the subset of subjects within the pooled pediatric dataset who were on either 20 or 40 mg tadalafil, for subjects on bosentan this includes patients in LVHV and LVIG, for patients not on concomitant bosentan this includes subjects from LVHV, LVIG, and LVJJ;

[c] n = 2; median, geometric mean and CV% were not calculated, the data listed are individual values.

[d] n = 1; patient's ERA (endothelin receptor antagonist) was macitentan; geometric mean and CV% could not be calculated, the data listed are individual values.

[d] n = 1; patient's ERA (endothelin receptor antagonist) was macitentan; geometric mean and CV% could not be calculated, the data listed are individual values.

Figure P03 shows a comparison among PAH patients with the model estimated post-hoc AUC over one dosing interval at steady state (AUCss) for combined LVIG and LVHV pediatric patients compared to the population-calculated post-hoc AUCss of the adult LVGY trial. The plasma tadalafil concentrations in pediatric PAH patients were comparable to the adult LVGY exposures observed at the therapeutic 20 and 40 mg qd doses of tadalafil. Of note, the pediatric PK concentrations at both 20 and 40-mg generally overlap the concentrations observed at the tadalafil 40-mg approved adult dose.



Abbreviations: AUC_{ss} = area under the curve at steady-state; n = number of subjects; PAH = pulmonary arterial hypertension; Ped = pediatric; PK = pharmacokinetics; qd = once daily; Wt = weight in kg.
AUC_{ss} is calculated by using Pop PK parameters from the adult-only (LVGY) and pediatric-only (current report) model.

Figure 3 – Comparison of steady-state post-hoc model estimated exposure (AUCss) in PAH adults (LVGY) and paediatric patients (LVIG, LVHV) for tadalafil 20 or 40 mg qd either with (right) or without (left) concomitant bosentan

PBPK model

Model development

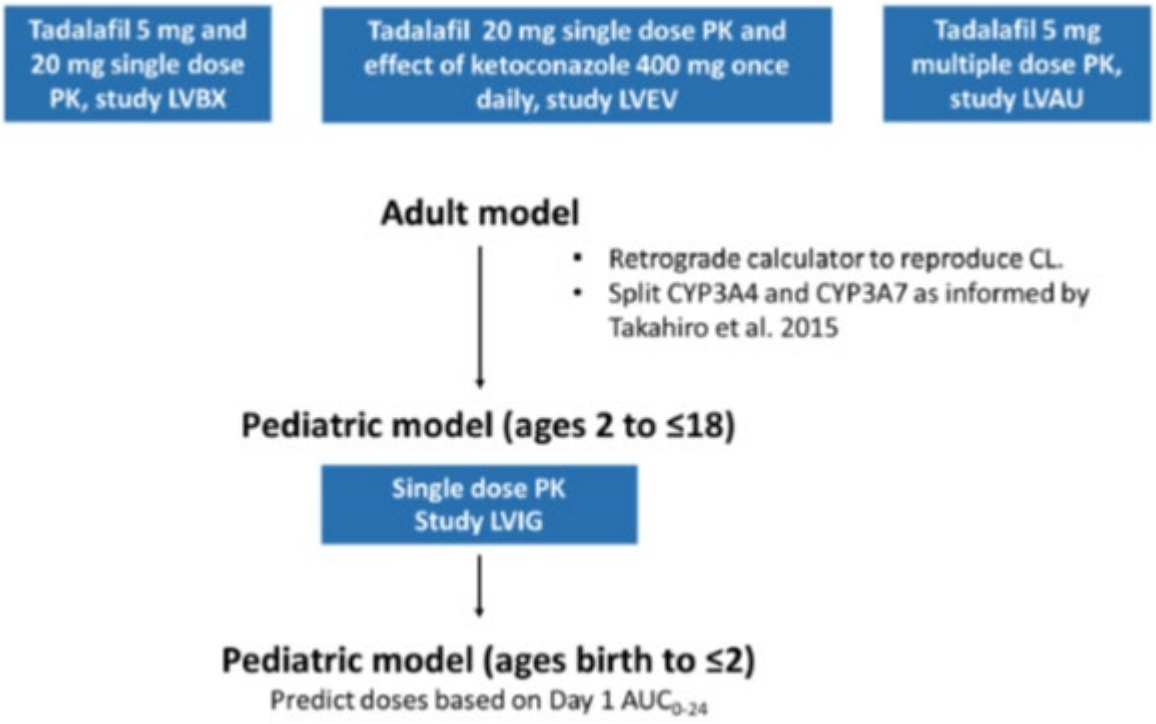


Figure 4 – Strategy to inform paediatric PBPK model for predictions in children aged from birth to <2 years

The model of tadalafil disposition in adults was developed in Simcyp version 18. Absorption was assumed to be first order, with fraction absorbed (Fa) of at least 0.8 based on only 16% of radioactivity (adjusted for recovery) being excreted as unchanged tadalafil in the first 48 hours after dosing (LVAA 1999). The fraction of the drug that escapes first pass metabolism in the intestine (Fg) was assumed to be 1 based on the low intrinsic clearance (CLint) and moderate permeability of tadalafil. Systemic clearance (CL) was assumed to be 75% CYP3A4-mediated metabolism and 25% through another pathway (assigned as additional human liver microsomal CLint) based on the fm (calculated using Equation 3.1, assuming Fg of 1) from the observed AUC ratio of 4.1 with 400 mg once daily ketoconazole (LVEV 2003).

Table 8 – Simcyp input parameters for tadalafil in adults

Property	Value	Source
Molecular weight	389.4	Calculated from structure
cLogP	1.64	Chemaxon
Compound Type	Neutral	No ionizable groups
fu	0.06	Measured
B:P	0.55	1-hematocrit; verified with concentrations of radioactivity in blood and plasma at early timepoints in study LVAA (1999)
Fa	0.8	At least 80% absorbed based on ^{14}C study LVAA (1999); 16% (adjusted for recovery) of radioactivity was excreted unchanged in feces between 0 to 48 hours. This was assumed to be unabsorbed drug.
ka (h^{-1})	1.86	PopPK analysis of erectile dysfunction patient data (Troconiz et al. 2007)
P_{eff} (10^{-4} cm/s)	1.67	Calculated using Lilly model based on MDCK data
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 (Troconiz et al. 2007); therefore V = 51.04 L assuming F is 0.8 and assuming body weight is 70 kg.
Elimination Pathways		
fm CYP3A4	0.75	Based on observed AUC ratio of 4.1 with ketoconazole in study LVEV (2003)
rCYP3A4 CL_{int} (µL/min/pmol)	0.04415	CL/F = 1.99 L/h (Troconiz et al. 2007); therefore CL = 1.59 L/h, assuming F is 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	Study LVAA (1999): <0.1 to 0.3% of dose excreted unchanged in urine

Abbreviations: AUC = area under the concentration curve, B:P = blood to plasma ratio, cLogP = logarithm of the octanol water partition coefficient, CL = clearance, CL_{int} = intrinsic clearance, CYP = cytochrome P450 enzyme, F = absolute bioavailability, Fa = fraction absorbed, fm = fraction of the drug metabolized, fu = fraction of the drug unbound, HLM = human liver microsomes, ka = absorption rate constant, MDCK = Madin-Darby canine kidney, P_{eff} = effective permeability, V_{ss} = volume of distribution at steady state.

The PBPK model of tadalafil disposition in pediatric subjects aged 2 to <18 was developed for adults in Simcyp version 18. Simulations employed the Pediatric population rather than an adult Healthy Volunteers population. PopPK-predicted Vss reported in Troconiz et al. (2007) was reproduced in the pediatric model using a PBPK approach. The distribution model choice was full PBPK, and Vss was predicted using Simcyp method 1 (Poulin method) with a Kp scalar of 2.19.

Takahiro and colleagues (2015) have demonstrated that tadalafil is metabolized by CYP3A4, CYP3A5, and CYP3A7. In the model of tadalafil in adults, all CYP3A-mediated metabolism is assumed to occur via CYP3A4. This assumption is appropriate as adult Caucasians do not express CYP3A7, and CYP3A5 is only expressed in a small subset of individuals. The expression of CYP3A5 was considered negligible in the pediatric model, as in the adult model. However, pediatric subjects do express CYP3A7. CYP3A7 levels at birth are much higher than adult CYP3A4 levels. Stevens and colleagues report that CYP3A7 represents 64% to 100% of the total CYP3A protein in children aged from birth to 6 months (Stevens et al. 2003). CYP3A7 rapidly decreases as CYP3A4 levels rise (Lacroix et al. 1997; Stevens et al. 2003). CYP3A4 and CYP3A7 abundances at selected ages were calculated from data provided in Simcyp version 18) using Equation 3.2 and Equation 3.3. Values at selected ages are compared to CYP3A4 abundance in adults in Table P08.

Table 9 – Comparison of CYP3A4 and CYP3A7 abundances at selected ages as compared to adult CYP3A4 abundance

Age (years)	Age (months)	Age (days)	CYP3A4 abundance (pmol/mg HLM protein)	CYP3A7 abundance (pmol /mg HLM protein)	CYP3A4 + CYP3A7 abundance (pmol/mg HLM protein)	CYP3A4 abundance in adults (pmol/mg HLM protein)
0.003	0.04	1	15.1	165	180	137
0.086	1.0	31	17.8	131	149	
0.33	4.0	120	43.7	14	58	
0.50	6.0	183	65.1	4.9	70	
1.0	12.0	365	106	0.74	107	
2.0	24.0	730	132	0.11	132	

Abbreviations: CYP = cytochrome P450 enzyme, HLM = human liver microsomes.

CLint inputs were modified to incorporate CYP3A7-mediated metabolism, as explained below and shown in Table P09.

Table 10 – Calculation of CYP3A4 and CYP3A7 Recombinant Clint inputs for Tadalafil pediatric model

	Adult Recombinant CL_{int} Input (µL/min/pmol)	Fractional Total CYP3A-mediated HLM CL_{int}	CYP-specific liver abundance (mg HLM protein)	HLM CL_{int} per Pathway (µL/min/mg)	Pediatric Recombinant CL_{int} Input (µL/min/pmol)
CYP3A4 in adult population	0.04415	1	137	6.05	NA
CYP3A4 in pediatric population	NA	0.97	137	5.9	0.0428
CYP3A7 in pediatric population	NA	0.03	35.4	0.2	0.0363

Abbreviations: CL_{int} = intrinsic clearance, CYP = cytochrome P450 enzyme, HLM = human liver microsomes, NA = not applicable.

Table 11 – Simcyp input parameters for tadalafil simulations in children ages 2 to <18

Property	Value	Source
Molecular weight	389.4	Calculated from structure
cLogP	1.64	Chemaxon
Compound Type	Neutral	No ionizable groups
fu	0.06	Measured
B:P	0.55	1-hematocrit; verified with concentrations of radioactivity in blood and plasma at early timepoints in study LVAA (1999)
Fa	0.8	At least 80% absorbed based on ^{14}C Study LVAA (1999); 16% (adjusted for recovery) of radioactivity was excreted unchanged in feces between 0 to 48 hours. This was assumed to be unabsorbed drug.
ka (h^{-1})	1.86	Population PK analysis of erectile dysfunction patient data (Troconiz et al. 2007)
P_{eff} (10^{-4} cm/s)	1.67	Calculated using Lilly model based on MDCK data
Distribution model type		Full PBPK Model
V_{ss} (L/kg)	0.73	Predicted by Method 1 with Kp scalar of 2.19 to match value in tadalafil adult model
Elimination Pathways		
fm CYP3A4	0.75	Based on observed AUC ratio of 4-fold with ketoconazole in study LVEV (2003)
rCYP3A4 CL_{int} (µL/min/pmol)	0.0428	Modified from Adult CYP3A4 input (Table 3.4) to account for CYP3A7 expression in children
rCYP3A7 CL_{int} (µL/min/pmol)	0.0363	Modified from Adult CYP3A4 input (Table 3.4) to account for CYP3A7 expression in children
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	Study LVAA (1999): <0.1 to 0.3% of dose excreted unchanged in urine

Abbreviations: AUC = area under the concentration curve, B:P = blood to plasma ratio, cLogP = logarithm of the octanol water partition coefficient, CL = clearance, CL_{int} = intrinsic clearance, CYP = cytochrome P450 enzyme, F = absolute bioavailability, Fa = fraction absorbed, fm = fraction of the drug metabolized, fu = fraction of the drug unbound, HLM = human liver microsomes, ka = absorption rate constant, MDCK = Madin-Darby canine kidney, P_{eff} = effective permeability, V_{ss} = volume of distribution at steady state.

Model verification

The PBPK model for tadalafil in adults was verified using data from multiple clinical studies following single 5 and 20 mg doses of tadalafil to adults, maximum plasma concentration (Cmax) and AUC0-24 were well-predicted, as shown in Table P11.

Table 12 – Summary of predicted and observed C_{max} and AUC_{0-24} for single doses of 5mg and 20mg tadalafil administered to adults, with observed data from study LVBX

Dose (mg)	Parameter	Predicted [geometric mean (CV%)]	Observed [geometric mean (CV%)]	Predicted/Observed
5	C_{max} (ng/mL)	80 (30)	103 (25)	0.78
5	AUC_{0-24} (ng*h/mL)	1159 (29)	1175 (19)	0.99
20	C_{max} (ng/mL)	319 (30)	322 (21)	0.99
20	AUC_{0-24} (ng*h/mL)	4634 (29)	4221 (16)	1.10

Abbreviations: AUC_{0-24} = area under the concentration time curve from time 0 to 24 hours, C_{max} = maximum concentration, CV% = coefficient of variation.

Following dosing of 5 mg tadalafil to steady state in adults, both Cmax and AUC0-24 were well predicted, as shown in Table 12.

Table 13 – Summary of predicted and observed Cmax and AUC0-24 for 5 mg tadalafil administered to steady state in adults, with observed data from study LVAU

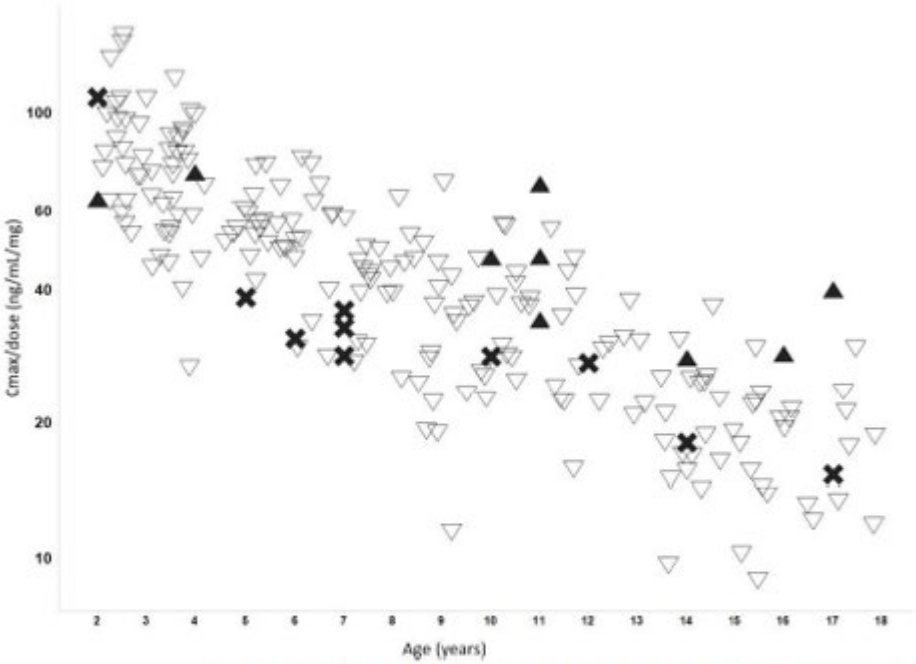
Parameter	Predicted [geometric mean (CV%)]	Observed [geometric mean (CV%)]	Predicted/Observed
$AUC_{0\text{-}24}$ (ng*h/mL)	2293 (44)	2741 (55)	0.84
C_{max} (ng/mL)	147 (33)	177 (41)	0.83

Abbreviations: $AUC_{0\text{-}24}$ = area under the concentration time curve from time 0 to 24 hours, C_{max} = maximum concentration, CV% = coefficient of variation .

Table 14 – Summary of predicted and observed Cmax, AUC0-∞, and Cmax and AUC ratios for 20mg tadalafil in the presence and absence of the strong CYP3A inhibiotr ketoconazole, with observed data from study LVEV

Parameter	Predicted [geometric mean (CV%)]	Observed [geometric mean (CV%)]	Predicted/Observed
$AUC_{0\text{-}\infty}$ (ng*h/mL)	9204 (45)	13006 (44)	0.71
Inhibited $AUC_{0\text{-}\infty}$ (ng*h/mL)	41357 (54)	53524 (49)	0.77
AUC ratio	4.5	4.1	1.09
C_{max} (ng/mL)	319 (30)	548 (24)	0.58
Inhibited C_{max} (ng/mL)	344 (30)	670 (30)	0.51
C_{max} ratio	1.1	1.2	0.88

Abbreviations: $AUC_{0\text{-}\infty}$ = area under the concentration time curve from time 0 to infinity, C_{max} = maximum concentration, CV% = coefficient of variation.



Abbreviations: C_{max} = maximum plasma concentration, PBPK = physiologically-based pharmacokinetic.
Observations are from study LVIG (2018), where filled triangles (▲) represent adjusted values for subjects on bosentan co-therapy, and × represent values from subjects not on bosentan. PBPK-predicted values are represented by open triangles (▽). Plot produced using TIBCO Spotfire Analyst 10.10.4

Figure 5 – PBPK-predicted and observed single dose tadalafil dose-normalised Cmax for children aged 2 to <18 years

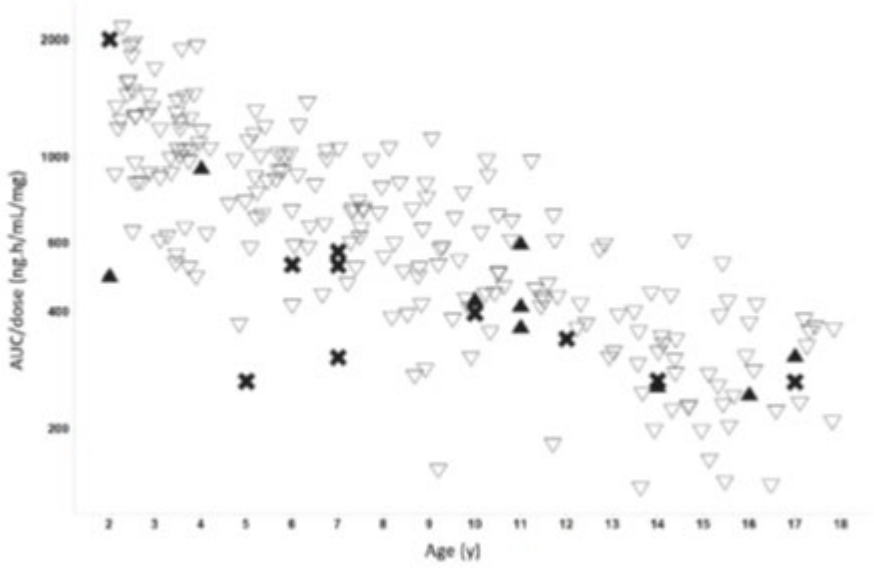


Figure 6 – PBPK-predicted and observed single dose tadalafil dose-normalised AUC0-24 for children aged 2 to <18 years

Following verification of the tadalafil PBPK model in adults and pediatric subjects aged 2 to <18, the tadalafil pediatric PBPK model was used to simulate single dose AUC0-24 in children from birth to <2

years, as presented in the left panel of Figure P02. For comparison, the right panel of Figure P02 shows all observed and predicted data for pediatric subjects.

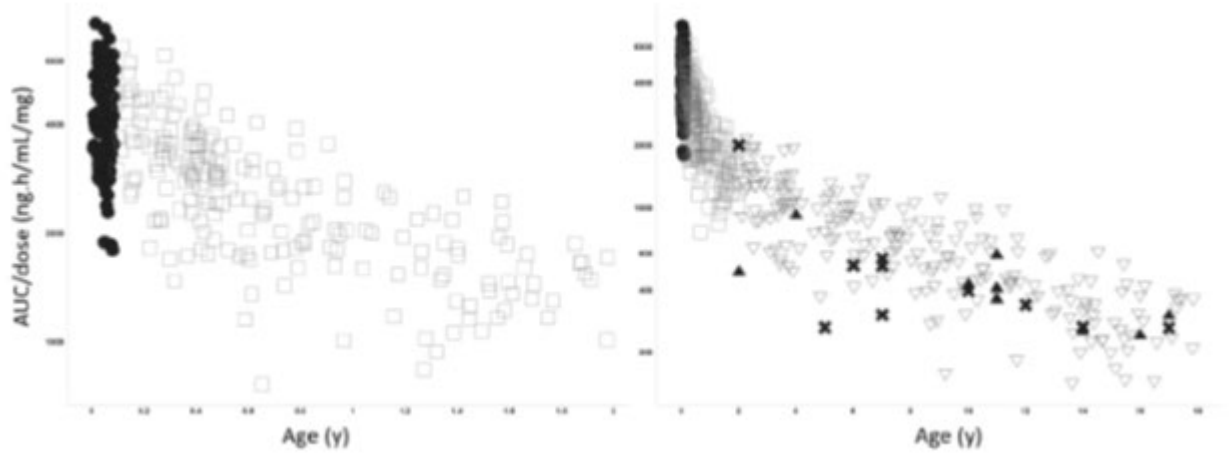


Figure 7 – PBPK-predicted single dose, dose-normalised AUC0-24 for tadalafil in children

In the birth to <1 month age group, increasing the CYP3A7 contribution to total CYP3A mediated HLM CLint reduced the PBPK-predicted mean, dose-normalized, single dose AUC0-24 by 47% to 2289 ng*h/mL and increased the projected starting dose to 4 mg. In addition, slowing of the maturation of the non-specific additional hepatic clearance pathway by replacing the 'fast' maturation profile with a 'slow' maturation profile increased the PBPK-predicted mean, dose normalized, single dose AUC0-24 by 7% to 4629 ng*h/mL, but had no effect on the projected tadalafil starting dose. The suggested clinical starting dose remained at 2 mg (0.7 mg/kg).

Table 15 – Suggested clinical starting doses of tadalafil for children from birth to <2 years old as predicted by physiologically-based pharmacokinetic modeling

Age Range	Median PBPK-Predicted Body Weight (kg)	PBPK-Predicted Mean Dose-normalized Single Dose AUC_{0-24} (ng*h/mL)	Suggested Clinical Dose (mg)[a]	Suggested Clinical Dose (mg/kg)[b]	Calculated Mean Single Dose AUC_{0-24} (ng*h/mL)[c]
Birth to <1 month	3.5	4308	2	0.7	10000
1 to <4 months	5.2	3801	3	0.5	10000
4 to <6 months	6.7	3007	3	0.5	10000
6 months to <1 year	8.9	2313	4	0.5	10000
1 to <2 years	11.7	1626	6	0.5	10000

Abbreviations: AUC_{0-24} = area under the concentration curve from 0 to 24 hours, PBPK = physiologically-based pharmacokinetic.

[a] Calculated as target AUC (10,000 ng/mL)/predicted single dose, dose normalized AUC_{0-24}. Values presented as calculated starting dose rounded to nearest 1 mg.

[b] Calculated as suggested clinical starting dose (mg)/median PBPK-predicted body weight (kg).

[c] Calculated as predicted single dose AUC_{0-24} * suggested clinical dose (mg).

Special populations

Impaired renal function

No new data on patients with impaired renal function has been generated since the granting of the PAH indication in adults.

Impaired hepatic function

No new data on patients with impaired hepatic function has been generated since the granting of the PAH indication in adults.

Weight

Weight was identified as a significant covariate on V/F, but not on CL/F of tadalafil. The relationship between post hoc estimates of CL/F and V/F and weight showed with every 10 kg decrease in body weight, V/F decreases by 13.7 L.

Pharmacokinetic interaction studies

No new data on pharmacokinetic interactions has been generated since the granting of the PAH indication in adults.

2.6.2.2. Pharmacodynamics

Mechanism of action

Tadalafil is a potent and selective inhibitor of PDE5, the enzyme responsible for the degradation of cGMP. Studies in vitro have shown that tadalafil is a selective inhibitor of PDE5. Phosphodiesterase 5 is found in the smooth muscle of the corpus cavernosum, prostate and bladder, as well as in vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is >10 000-fold more potent for PDE5 than for phosphodiesterase 1, phosphodiesterase 2, phosphodiesterase 4 and phosphodiesterase 7 enzymes, which are found in the heart, brain, blood vessels, liver, leucocytes, skeletal muscle and other organs. Tadalafil is >10 000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for phosphodiesterase 6, an enzyme found in the retina and is responsible for phototransduction. Tadalafil is also >9 000-fold more potent for PDE5 than for PDE8, PDE9 and PDE10, and 14-fold more potent for PDE5 than for PDE11. The tissue distribution and physiological effects of the inhibition of PDE8 through PDE11 have not been elucidated.

Pathophysiology of Pulmonary Arterial Hypertension and Phosphodiesterase 5 Inhibition as a Mechanism of Action for Pulmonary Arterial Hypertension Therapy

Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within in the pulmonary vascular smooth muscle. Phosphodiesterase 5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

Primary and Secondary pharmacology

Exposure-Efficacy

The parameter of 6MWD was used as the primary efficacy endpoint for efficacy evaluation in both LVHV (paediatric) and LVGY (adult) studies. In paediatric patients, the 6MWD was evaluated in a total of 35 patients in LVHV.

Comparison of the observed data between paediatric and adult patients

Figure P08 shows individual paediatric response over the course of Study LVHV, while Figure P09 shows the median response in paediatric patients, as well as the adult response in LVGY (placebo, 20

mg and 40 mg dose levels, only). The observed data are comparable between paediatric and adult patients with PAH.

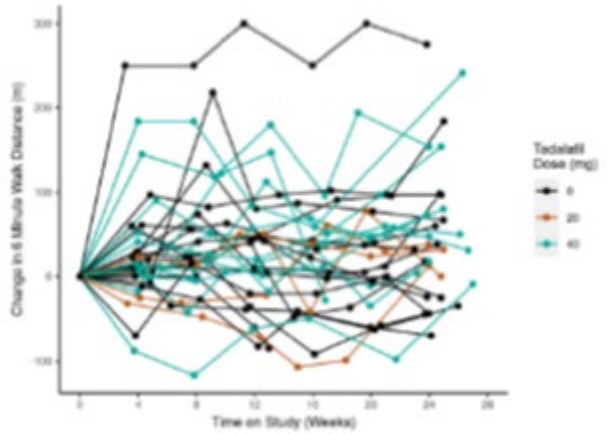
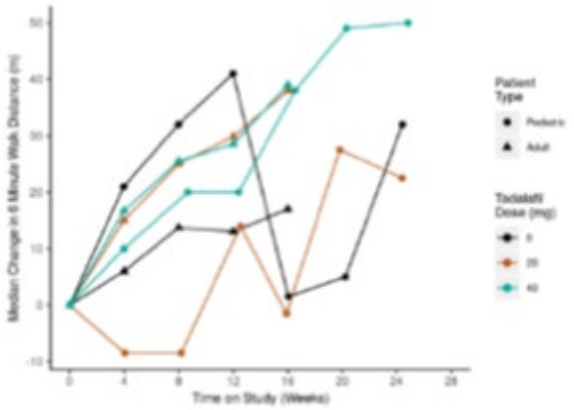


Figure 8 – Observed change from baseline in 6-minute walk distance (6MWD) over time in all patients in the LVHV paediatric dataset



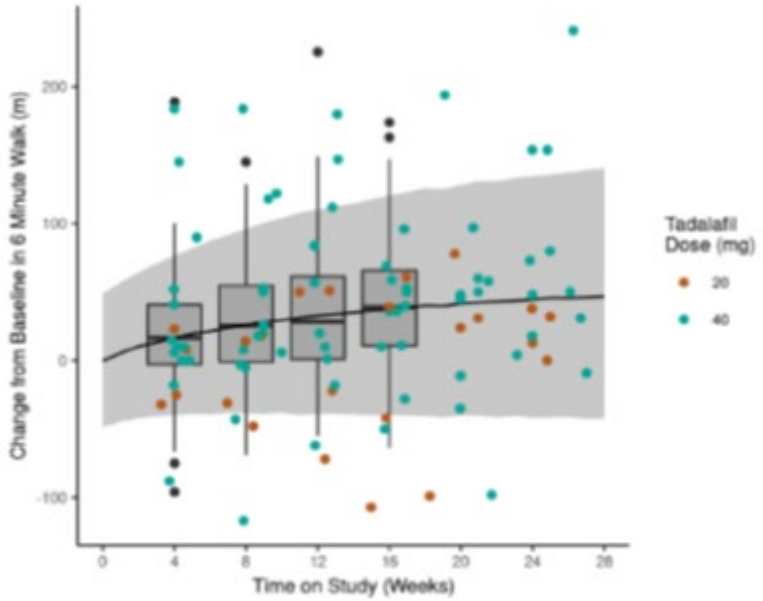
Adult data is limited to only those patients in LVGY who received placebo, 20 mg, or 40 mg tadalafil.

Figure 9 – Median observed change from baseline in 6-minute walk distance (6MWD) over time in adult (LVGY) and paediatric (LHVH) patients

Comparison between the observed paediatric data and model-estimated adult data

The observed data from paediatric Study LVHV (20 mg and 40 mg) was also compared to the results of adult Study LVGY (40 mg only) using a modelling approach. The time course and E-R relationship for 6MWD was previously characterised for the adult patients in the Phase 3 Study LVGY via exposure response modelling.

There was substantial overlap between the observed adult and paediatric data. The LVGY model developed based on adult data appeared to adequately capture the central tendency of the paediatric data, although the 90% prediction interval appeared to under-predict the degree of variability observed in the study. Altogether, the results suggest comparable 6MWD response between paediatric patients (at 20- and 40-mg dose) and adult patients (at 40-mg dose).



Paediatric response as a function of time in patients receiving tadalafil. Box plots represent the observed adult data at 40 mg in Study LVGY (extreme values represented as black dots). The brown and blue circles represent paediatric data. The adult study LVGY model-predicted response is also provided (black line is the median prediction, grey region represents the 90% prediction interval).

Figure 10 – Observed change from baseline in 6-minute walk distance (6MWD) over time in paediatric patients, with predicted responses from adult model

Modelling of combined paediatric and adult data

The parameters in the adult LVGY E-R model were re-estimated using the combined adult-paediatric dataset (Table P15). As shown in Table P15, the 95% confidence intervals for each parameter (as determined by the bootstrap evaluation) overlapped between models, suggesting overall similarity.

Table 16 - Population PK/PD Parameter Estimates in Original Adult Model and Re Estimated Parameters from Combined Adult-Paediatric Dataset

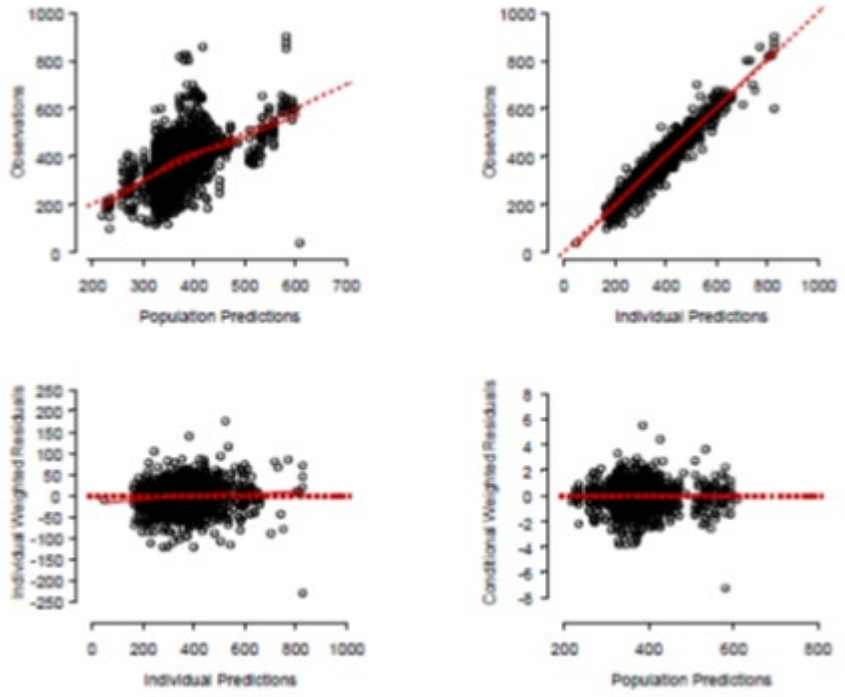
	Original LVGY Analysis		**Combined LVGY/LVHV Analysis**	
Parameter Description	**Population Estimate (%SEE) [95% CI]**	**Interindividual Variability (%SEE) [95% CI]**	**Population Estimate (%SEE) [95% CI]**	**Interindividual Variability (%SEE) [95% CI]**
Baseline 6-Minute Walk (meters)	321 (1.6) [311, 331]	0.0372 (9.6)a [0.0303, 0.0448]	325 (1.7) [314, 336]	0.0443 (9.6)a [0.0364, 0.0541]
Additive Shift for WHO Class I and II on Baseline 6-Minute Walk (m)	50.4 (13.8) [37.3, 64.2]		47.1 (17.5) [34.0, 65.4]	
Slope for Baseline 6-Minute Walk on Placebo Response (m)	186 (6.4) [162, 210]	NE	150 (7.3) [130, 172]	NE
Slope for Age on Placebo Response (m)	-150 (8.7) [-175, -122]		-123 (9.7) [-146, -99.1]	
Active Treatment Emax (m)	60.9 (17.2) [43.0, 88.2]	3870 (34.9)b [1870, 7720]	64.9 (16.6) [46.8, 91.6]	3230 (34.4)b [1540, 5970]
Power for AUC_{ss} on Emax	0.225 (45.3) [0.0540, 0.412]		0.217 (43.1) [0.0419, 0.385]	
Slope for Age on Emax (m/year)	-1.96 (25.1) [-3.29, -1.06]		-1.72 (24.4) [-2.91, -0.974]	
T50 for Active (weeks)	14.2 (33.8) [3.88, 27.6]	NE	12.9 (32.1) [4.37, 24.0]	NE
Additive Shift for PAH Related to Collagen Disorders on T50 (weeks)	14.0 (42.6) [4.71, 40.3]		17.5 (49.3) [5.58, 51.8]	
Additive Shift for Other PAH on T50 (weeks)	-3.12 (22.5) [-4.46, 6.19]		-2.15 (27.2) [-4.86, 4.84]	
Exponent for Baseline Walk on T50	1.50 (21.7) [0.415, 2.77]		1.45 (26.8) [0.206, 3.17]	

Additive Shift for Concomitant Calcium Channel Blockers on T50 (weeks)	-5.45 (34.5) [-10.8, 0.296]	-5.13 (33.7) [-10.4, 1.53]
Residual Error (SD in weeks) [95% CI]	29.5 (7.8) [27.1, 31.8]	31.6 (8.3) [29.0, 34.2]

Abbreviations: AUCss = AUC over one dosing interval at steady state; CI = confidence interval; Emax = maximum response to treatment; NE = not estimated; PAH = pulmonary arterial hypertension; PK/PD = pharmacokinetic/pharmacodynamic; SD = standard deviation; %SEE = percent standard error of the estimate; T50 = time at which 50% maximal response is achieved; WHO = World Health Organization.

a The estimate provided in the table is variance term η1.

b The estimate provided in the table is variance term η2.



Lowess fit, a smoothed value given by a weighted linear least squares regression over the span of observations, for data presented (solid line) in addition to a line of unity (dashed line).
Abbreviations: ER = exposure-response.

Figure 11 – Goodness-of-fit plots for the re-estimated ER model (concluded)

Exposure-safety

No E-R analysis for safety was conducted.

2.6.3. Discussion on clinical pharmacology

No new clinical pharmacology studies were conducted to characterise PK in paediatrics or to support the paediatric PAH indication.

Absorption

The non-compartmental analysis of the absorption properties of tadalafil in paediatric patients aged 2 to <18 years showed similar tmax and bioavailability properties as the adult population. A 14% reduction on bioavailability was observed at the highest dose (40 mg) compared to 20 mg, which similarly impacted the adult population. It is unclear whether the dose effect on bioavailability could be associated to non-linear absorption or dissolution-limited processes. No specific information regarding the absorption and bioavailability in pediatric patients less than 2 years of age was available due to the lack of experimental evidence.

One clinical pharmacology Study, H6D-MC-LVIF (LVIF), was conducted to evaluate the PK of tadalafil as a suspension formulation and to determine the relative bioavailability compared to marketed tablets (20 mg Cialis) in healthy adult subjects to support the paediatric development program.

The results demonstrated that the suspension formulation is non bioequivalent to the tablet as the Cmax do not fall within the acceptance limits of 80.00%-125.00%. Since formulations are not bioequivalent, the CHMP was not in concordance with the MAH's claim that "*Based on comparative bioavailability data for the tablet and the suspension formulations, the oral suspension and film-coated tablets may be interchanged at a 20-mg dose*". The clinical relevance for efficacy of a different absorption rate and exposure during the first hours after administration of suspension without water and tablet with water (with 90% CI for AUC_{0-6} of 0.696-0.803 and for AUC_{0-12} of 0.789-0.894) was discussed by the MAH. It was acknowledged that differences in Cmax are not relevant, and a slower absorption may be associated to less risk of Cmax related side effects.

No new studies have been conducted in paediatrics to study the effect of food since the time of the adult PAH submission. Food does not affect the rate or extent of tadalafil absorption with tadalafil dosing up to and including 40 mg in adults, therefore, recommendations for adult patients can be extrapolated and tadalafil may be administered without regard to meals in paediatric patients (2 to <18 years old).

Elimination

Tadalafil systemic exposure is highly dependent on clearance via CYP3A4-mediated metabolism. Investigations by (Salem et al. 2014) have demonstrated that hepatic CYP3A4 increases from birth and reaches adult level by the age of approximately 2.5 years. Hence, biotransformation via CYP3A4-mediated pathways in adults and children > 2 years of age are expected to be similar.

Dose proportionality and time-dependency

No information was provided regarding the time-dependency effect in paediatrics aged 2 to <18 years. A justification of similar behaviour in paediatrics as observed in adults was provided, although no experimental information was available.

Pharmacokinetics in the target population

The clinical pharmacology properties of tadalafil have been characterized using a population-based analysis including PK and PD information in paediatric patients (≥2 to <18 years old) with pulmonary

arterial hypertension (PAH) and Duchenne muscular dystrophy (DMD) together with a physiologically based PK model (PBPK) to establish the dose recommendation in pediatric patients <2 years old with PAH.

In general, the dataset management, model building, and model assessment methodologies are considered appropriate. A pooled analysis combining 4 clinical trials (H6D-MC-LVHV, H6D-MC-LVIG, H6D-MC-LVGY and H6D-MC-LVJJ) in two disease indications is endorsed in order to characterize the time-course of tadalafil in the target population.

The structural population PK model is a one-compartment with linear absorption and disposition kinetics. Parameters were estimated with good precision based on the relative standard error and the final parameter estimates were similar as the parameters obtained in previous population PK models (H6D-MC-LVIG and H6D-MC-LVJJ). The large variability associated to the absorption rate constant is expected due to the large inter-individual variation on the absorption across paediatric patients and the lack of adequate information during the absorption phase. The inclusion of inter-individual variability on the relative bioavailability parameter could initially help the description of the individual data due to differences associated with the dose level.

The covariate analysis was conducted through the use of an SCM approach, which is endorsed by CHMP. However, the final covariates selected differ to the results with the SCM and the MAH explained that inadequate model performance justified their deletion.

The final population PK model seems able to characterize the overall tadalafil longitudinal PK data in the target population. A slight over-estimation of V/F could explain the under-prediction of the initial (highest) tadalafil concentrations (pc-VPC and GOF). Final parameter estimates were similar as for the base model and the bootstrap analysis confirmed the statistical relevance of the parameters. The inter-individual random effects of CL and F slightly diminished, but clearly increased (125% to 163%) for ka. The random effects were assumed to be symmetrically and independently distributed with a zero mean. However, random effects for Ka appears to have some bias in light weight patients and in patients aged 2 to 6 years, both groups of patients took the oral suspension formulation. In addition, the distribution of the absorption rate constant is also narrower for the suspension formulation. All this suggest that there could be differences in the absorption between the suspension and tablet formulations that could explain partially the large inter-individual random effects that have been attributed to Ka. However, the inclusion of formulation on ka was not statistically significant and did not allow to a reliable estimation of individual ka values in younger patients. On the other hand, no relevant trends were observed on individual ka values across different sub-groups of age or body weight, suggesting that the inter-individual random effects are not associated to those covariates. Despite the large inter-individual variability on ka, no mechanistic explanation could be associate to better characterize individual differences on the absorption rate constant.

Comparable exposures (AUC) were observed in adults and pediatric patients with or without concomitant administration of bosentan, which demonstrates the adequacy of the dosing regimen proposed.

A PBPK model was developed to predict the tadalafil exposure in paediatric patients < 2 years of age. To that end, adult data was initially considered to internally develop the PBPK model, which was considered adequate.

A graphical evaluation has been conducted representing the prediction intervals obtained from the PBPK model with the observed experimental data in paediatric patients below 18 years of age. This analysis should be considered with caution, since it is highly subjective and no numerical comparison of PK predicted and observed exposure metrics was provided. The PBPK model over-predicts the PK profile compared to the observed data in paediatric patients from 4 to 8 years of age. In paediatric

patients from 2 to less than 4 years of age the PBPK model is considered unreliable to characterize the data, since large differences in observed PK data are present and the PBPK model does not include 95% of the observed data within the prediction intervals, but only 50% of the observed data. In addition, results from Figure P05 are not considered informative, since no clear understanding of the prediction error of Cmax at each year was provided. At 2 years of age, seems that the PBPK model over-predicts the Cmax and does not capture the observed Cmax of subject patients with bosentan co-therapy, whereas at 4 years of age, the PBPK model tends to under-predict the Cmax values. On the other hand, Cmax levels of paediatric patients of 5 and 6 years of age are over-predicted compared to the observed Cmax value of patients without bosentan co-therapy. Therefore, the PBPK model seemed not suitable to predict the overall exposure in paediatric patients below 8 years of age and further refinement of the PBPK was required in order to inform for any dose schedule selection in paediatric patients below 8 years of age, and especially in the dose extrapolation below 2 years of age. The MAH updated the PBPK model to improve the overall performance on pediatric population for dose selection. Overall, the strategy included the improvement of the ka characterization in paediatric patients based on individual estimates from the popPK analysis, the adjustment of CYP3A4 maturation function to describe changes in CYP3A4 abundance across the different age cohorts and the improvement of Vss in children based on the information at steady-state. The strategy is endorsed and has improved model predictions at Day 1 in paediatric patients. However, at steady-state conditions, the PBPK model clearly over-predicts the Cmax and AUC for all paediatric patients (2-<4, 4-<8, 8-<12, and 12-<18 years). In addition, a trend towards higher over-prediction in younger paediatric sub-groups of patients is observed, suggesting that model refinements of the PBPK model are not suitable enough to characterize the exposure of tadalafil at steady-state conditions. It is agreed by CHMP that scarce experimental data and large inter-individual variability was present on tadalafil plasma-concentration data at steady-state conditions, which may affect an adequate model verification of the PBPK platform. Regarding the dose recommendation, the MAH has conducted a model-based approach evaluating different dosing regimens in pediatric patients from 6 months to less than 1 year of age and from 1 to less than 2 years of age. The target AUC0-24 and AUCss were established based on adult data. Given the inconsistency of the refined PBPK model at steady-state conditions, it is not possible to establish any dose recommendation of tadalafil based on model-predicted exposure levels across the different sub-groups of pediatric patients at steady-state. Moreover, the PBPK model tends to provide greater bias for younger sub-groups of patients (especially between 2-<4 years of age), suggesting that maturation CYP3A4 and Kp scalars are not adequately captured. In this sense, model extrapolation to younger patients receiving taldalafil (<2 years of age) is not considered appropriate. Higher dose levels were proposed for patients from 6-<1 and 1-<2 years of age: 8 mg QD and 10 mg QD, respectively. Although some deficiencies have been corrected, there are still important doubts about the predictive capacity of the PBPK model to be able to establish a dose recommendation in population groups where there is no experimental evidence.

Although from a methodological point of view the extrapolation exercise using a PBPK framework to support the dose recommendation in pediatric patients above 2 years of age may be endorsed, several concerns have been raised regarding the adequacy of the PBPK model to properly predict the tadalafil exposure in adults and pediatric patients below2 years old.

Due to the limitations of the model to establish a dose recommendation for patients under 2 years of age the indication has been restricted for patients aged above 2 years old.

Special populations

Clearance of tadalafil was shown to be similar between adults and children ≥2 years of age.

The use of similar dosing recommendations in paediatric patients (≥2 years of age) with impaired renal or hepatic function is endorsed.

Large differences in V/F were observed in extreme body weight patients, but no clinically relevant changes in Cmax is expected since different dose recommendation is provided in patients with low body weight.

Drug-drug interactions

No new data on pharmacokinetic interactions has been generated since the granting of the PAH indication in adults, which included detailed drug-drug interaction (DDI) data and recommendations.

The clinical evaluation of the effects of tadalafil as victim's or perpetrator's drug is scarce and similar for those DDI as observed in adult patients.

Since tadalafil is metabolized through CYP3A4 pathway, concomitant administration with strong CYP3A4 inhibitors should be avoided. The impact of CYP3A4 inducers (bosentan) on the pharmacokinetics of tadalafil in pediatric patients revealed 30-32% less exposure in patients with concomitant administration of bosentan.

The clearance of tadalafil is similar between children ≥ 2 years of age and adults. As such, recommendations regarding precautions for use and adjustment of doses in adults are applicable for children over 2 years of age.

Exposure-efficacy

The relationship between exposure and efficacy (6MWD) has been established in paediatric patients using a previously developed population PK/PD model in adults receiving 40 mg tadalafil. The results of the combined dataset analysis suggest that similar parameter estimates and adequate description of the observed data is present. The current PK/PD analysis revealed an increase in 6MWD over time, but no differences in the response was observed between 20 and 40 mg in paediatrics, which indicates that the dose recommendation allows to provide similar efficacy outcome. In addition, the efficacy was comparable with the results from the adult population, which confirmed that the similar exposure in paediatrics is expected to reach similar efficacy as well.

Exposure-safety

Exposure-safety was analysed in the LVHV, LVIG, and LVJJ studies. The analysis contains comparison of Adverse Events by quartile of estimated tadalafil AUCss. The results did not show increased number of AEs with increased exposure of tadalafil for any of the studies. No experimental safety data was available in paediatric patients under 2 years of age.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of tadalafil in paediatric patients have been characterized through a non-compartmental analysis and the development of a population PK model.

The characterization of the efficacy properties of tadalafil in paediatric patients from 2 to less than 18 years of age was conducted using a previously developed population PK/PD model in adults using 6MWD as the efficacy outcome. The results show similar behaviour over time between paediatric and adult patients and no relevant differences were observed between 20 and 40 mg dosing groups in paediatrics, which supports the adequacy of the dose recommendation.

Overall, the available clinical pharmacology data submitted supports the use of Adcirca in the approved indication,

2.6.5. Clinical efficacy

A single confirmatory efficacy and safety study H6D-MC-LVHV (LVHV) has been provided to support the use of Adcirca in paediatric patients with PAH.

Studies H6D-MC-LVIF, H6D-MC-LVIG, H6D-MC-LVJJ, and H6D-MC-LVGY, provided supportive clinical data (please refer to clinical pharmacology section for further details). The non-interventional Post-Authorization Safety Study (H6D-JE-TD01) also provided supportive effectiveness data regarding the use of tadalafil in paediatric patients.

The summary of the clinical studies supporting this application are shown in the tables below.

Table 17 - Overview of the main of tadalafil study included in the efficacy analysis: Study LVHV

Study ID (Protocol Number)		**Design**	**Study Posology**	**Study Primary Objective(s)**	**Subjs by arm entered/ compl.**	**Duration**	**Primary Endpoint**
H6D-MC-LVHV PIP study 4	This study was conducted at 15 study centers (screened subjects) in 9 countries: Brazil, Israel, Japan, Mexico, Turkey (Austria, Germany, France, and Poland from EU)	This was a phase 3, international, randomised, multicentre, 2-period (double-blind placebo-controlled [Period 1] and open-label extension [Period 2]), add-on (*i.e.*, in addition to the subject's current ERA) study to evaluate the efficacy, safety, and population PK of tadalafil in paediatric patients with PAH. Enrolled subjects were paediatric patients (≥6 months to <18 years) with WHO functional class II/III.	Patients were stratified into 3 weight cohorts: Heavy-weight Cohort (≥40 kg) Middle-weight Cohort (≥25 kg to <40 kg) Light-weight Cohort (<25 kg) The doses for each weight cohort targeted exposures comparable to 40 mg exposures of tadalafil in adults. <u>Period 1</u> Patients were randomized to receive either placebo or active drug in a 1:1 ratio. <u>Period 2</u> All patients received tadalafil once daily in an open-label fashion.	<u>Period 1 (double-blind [DB] period):</u> To evaluate the efficacy of tadalafil compared with placebo in improving 6MWD from baseline to Week 24 in paediatric patients with PAH who were already receiving treatment with ERAs. <u>Period 2 (open-label [OL]):</u> To evaluate the long-term safety of tadalafil while providing continued access to tadalafil for paediatric patients with PAH who were already receiving treatment with ERAs	<u>Period 1 DB):</u> 35 Paediatric patients with PAH. *Placebo* n=18 *Tadalafil* n= 17 <u>Period 2 (OL):</u> 32 Paediatric patients with PAH. *Tadalafil* n=32	<u>Screening period:</u> 4 weeks <u>Period 1 (DB):</u> 24 weeks <u>Period 2 (OL):</u> 2 years optional	<u>Period 1 (DB):</u> Improvement of 6MWD in meters, as assessed in a subset of subjects who were ≥6 to <18 years of age and were capable of performing a 6MWD test.

Table 18 - Overview of supportive studies Contributing to the efficacy or safety for the Paediatric PAH Indication

Study	**Primary Objective**	**Treatment Duration/Analysis Technique**	**Study Population/Number of Treated Participants**	**Dosing Regimen**	**Purpose**
Study LVIG[a]	***Period 1*** To characterise the PK of tadalafil in a paediatric population with PAH and establish an appropriate dose range for further clinical research.	***Period 1 (PK/Safety)*** Tadalafil QD for 10 weeks (5 consecutive weeks [approximately 35 days] for each	Patients with PAH aged 2.5 to 18 years, at the time of screening. *Planned:* 24 *Enrolled in Period 1*: 19 *Completers in Period 1:* 18 *Enrolled in Period 2:* 18	Tadalafil 2 mg - 40 mg daily administration as tablets or a 2 mg/mL oral suspension; dose ranges by weight cohort as follows: • Weight ≥40 kg	Safety and PK (non-compartmental analyses and Paediatric-adult PopPK model)

Study	Primary Objective	Treatment Duration/Analysis Technique	Study Population/Number of Treated Participants	Dosing Regimen	Purpose
	Period 2 To evaluate long-term safety of tadalafil and CW of PAH in paediatric patients.	dose [low and high]) in 2 sequential steps. ***Period 2 (OLE)*** Long-term safety of tadalafil up to 2 years.	*Completers in Period 2:* 14	Period 1: 10-40 mg QD Period 2: 15-40 mg QD • Weight ≥25 to <40 kg Period 1: 5-20 mg QD Period 2: 7.5-20 mg QD • Weight <25 kg Period 1: 2-20 mg QD Period 2: 7-20 mg QD	
LVHV data extrapolation study (sensitivity analysis for primary efficacy)	To increase precision in confirming the primary efficacy data from Study LVHV using a Bayesian approach that leverages data from the adult PAH study.	A Bayesian MMRM that extrapolated adult data from Study LVGY based upon the similarity of the paediatric data coming from Study LVHV (	Subset of randomised patients aged ≥6 to <18 years, developmentally capable of performing the 6MWD test. Patients meeting analysis criteria=34 LVGY: Pooled data from tadalafil 20- and 40-mg dose groups, which were most relevant to the doses in paediatric Study LVHV. Patients meeting analysis criteria=132	NA	Efficacy (PIP Study 8)
LVHV Primary Phase 2/3 Population PK Analysis (Paediatric-only model)	• To characterise the population PK of tadalafil in paediatric patients with PAH. • To identify patient factors that may influence tadalafil disposition in paediatric patients. • To derive post-hoc individual PK parameters in paediatric patients with PAH for E-R analysis.	Graphical visualisation and population PK modelling based upon the NONMEM program	Paediatric PK data from Studies LVHV, LVIG and LVJJ, and 1 patient from Study LVGY. 247 patients with 1152 observations	NA	PK and efficacy (dose recommendation), (PIP Study 7)
Exposure-Response Analyses	• To characterise the relationship between tadalafil exposure and 6MWD response for paediatric patients with PAH. • To compare exercise capacity measured as 6MWD in LVHV paediatric patients with PAH as compared to adults with PAH.	Data used to build the model: • Adult PK and 6MWD data from Study LVGY • Paediatric PK and 6MWD data from Study LVHV (	LVHV: Subset of randomised patients aged ≥6 to <18 years, developmentally capable of performing the 6MWD test, from placebo, tadalafil 20- and 40-mg. Patients meeting analysis criteria=35 LVGY: Pooled adult data from placebo, tadalafil 2.5-, 10-, 20- and 40-mg dose groups. Patients meeting analysis criteria=389	NA	Efficacy (dose recommendation), (PIP Study 7)
PBPK modelling	To support dosing in very young children with PAH by predicting recommended starting doses of tadalafil for paediatric patients aged <2 years.	A PBPK model for tadalafil was developed for adults. The model was adapted to predict PK in children. Following verification of the tadalafil PBPK model in adults and paediatric patients aged 2 to ≤18 years, the tadalafil paediatric PBPK model was used to simulate single dose $AUC_{(0-24)}$ in	NA	NA	Dose predictions for age <2 years, (PIP Study 7)

Study	Primary Objective	Treatment Duration/Analysis Technique	Study Population/Number of Treated Participants	Dosing Regimen	Purpose
		children from 6 months to <2 years old (Section			
Study TD01	To investigate the long-term safety and effectiveness of Adcirca in patients with PAH in real-world clinical practice.	• 2 years: Patients enrolled from 11 Dec 2009 to 31 Aug 2012 • 1 year: Patients enrolled from 01 Sep 2012 to 31 Aug 2013 • 3 months: Patients enrolled from 01 Sep 2013 to 28 Feb 2014	391 patients treated with tadalafil as part of study. Infants (<1 year) = 79 Preschool children (≥1 to ≤6 years) = 163 Children (≥7 to ≤14 years) = 110 Adolescents (≥15 to <18 years) = 39 Mean age±SD of paediatric patients=5.7±5.34 years.	Administration of tadalafil in paediatrics was conducted under real-world clinical practice, and the investigators determined the dosage of tadalafil. Starting dose (QD) • 40 mg: 5.9% • >20 to <40 mg: 1.5% • 20 mg: 21.0% • 10 to <20 mg: 23.0% • <10 mg: 48.6% Final dose (QD) • 40 mg per day: 17.4% • >20 to <40 mg: 5.6% • 20 mg: 16.9% • 10 to <20 mg: 25.3% • <10 mg: 34.8% No patients received more than 40 mg at the start or the end of administration.	Safety
Study LVJJ	To test the hypothesis that tadalafil once daily administered orally for 48 weeks lessened the decline in ambulatory ability as measured by the 6MWD compared to placebo in boys with DMD.	***Double-blind period:*** 48 weeks ***OLE (Period 1)*:** 48 weeks ***OLE (Period 2):*** 48 weeks Patients did not complete the OLE as the study was stopped.	Ambulatory boys with DMD, aged 7 to 14 years, on a stable dose of corticosteroids. • Randomised=331 • Placebo=116 • Tadalafil 0.3 mg/kg=102 • Tadalafil 0.6 mg/kg=113	Two tadalafil target doses • 0.3 mg/kg QD • 0.6 mg/kg QD	Safety and PK modelling for dose prediction
Study LVGY	To evaluate the safety and efficacy of the PDE5 inhibitor tadalafil in the treatment of adult patients with PAH.	Treatment period=16 weeks	Adult patients with PAH • Randomised=406 • Placebo=82 • Tadalafil=324 • Completed 16-week treatment=341	Tadalafil 2.5 mg, 10 mg, 20 mg or 40 mg QD	Safety, efficacy and PK/PD
Study LVIF	To determine the relative bioavailability of a tadalafil suspension (2 mg/mL) compared to marketed tadalafil tablets (Cialis®) when administered as single 20 mg oral doses to healthy subjects.	3 single doses on 3 separate occasions with a washout period of at least 7 days between consecutive dosing occasions.	Healthy adult subjects Randomised and received at least 1 dose: 18 Completed: 17	Tablet: 20 mg tadalafil Oral suspension: 20 mg and 40 mg tadalafil as a 2 mg/mL suspension (10 mL and 20 mL, respectively)	PK

2.6.5.1. Dose response studies

The dose recommendations are supported by clinical pharmacology (efficacy data extrapolation, PK modelling/simulation [PopPK, E-R, and PBPK analysis), efficacy and safety data from both paediatric and adult patients with PAH. For further discussion regarding dose selection in the paediatric population please refer to the clinical pharmacology section above.

2.6.5.2. Main study

The main study submitted in support of this application was the pivotal clinical trial H6D-MC-LVHV (LVHV).

Study LVHV was a Phase 3, international, randomised (1:1), multicentre, 2-period (24 weeks double-blind placebo-controlled period [Period 1] and open-label 2-years extension period [Period 2]), add-on (*i.e.* in addition to the subject's current endothelin receptor antagonist [ERA]) study to evaluate the efficacy, safety, and population pharmacokinetics (PopPK) of tadalafil administered orally once daily in paediatric subjects from 6 months to less than 18 years of age with pulmonary arterial hypertension (PAH). The sample size was pre-specified as 34 subjects.

Screening and eligibility evaluation was performed during an approximately 28-day period prior to randomization and the administration of tadalafil. Period 1 was a 24-week study drug treatment phase. During this study period, patients continued receiving stable ERA therapy. Period 2 was an open-label extension (OLE) period that evaluated the long-term safety of tadalafil while providing continued access to tadalafil for paediatric patients completing Period 1. Patients entering Period 1 of the study were stratified into 1 of 3 weight cohorts based on their weight at the time of the screening visit (heavy-weight: ≥40 kg; middle-weight: ≥25 kg to <40 kg; or light-weight: <25 kg) and then be randomized (1:1) to tadalafil or placebo.

Study H6D-MC-LVHV (LVHV) - "A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension with an open-label long term extension"

Methods

- **Study Participants**

Key inclusion/exclusion criteria for Study LVHV:

Eligibility for enrolment was based on the results of screening for the following inclusion and exclusion criteria:

Inclusion criteria

- ≥6 months to <18 years of age (at screening).
- Currently had a diagnosis of PAH that was:
    - idiopathic, including hereditary,
    - related to connective tissue disease,
    - related to anorexigen use, or
    - associated with surgical repair of at least 6-month duration of congenital systemic to pulmonary shunt, for example,
        - atrial septal defect

        - ventricular septal defect, and
        - patent ductus arteriosus.

- Had a history of a diagnosis of PAH established by a resting mean pulmonary artery pressure (mPAP) ≥25 mm Hg, pulmonary artery wedge pressure ≤15 mm Hg, and a PVR ≥3 Wood units via RHC. In the event that a pulmonary artery wedge pressure could not be obtained during RHC, subjects with a left ventricular end diastolic pressure <15 mm Hg, normal left heart function, and absence of mitral stenosis on echocardiography could have been eligible for enrolment.

- Had a WHO functional class value of II or III at the time of screening.

- All subjects must have been receiving an ERA (such as bosentan or ambrisentan) and must have been on a maintenance dose with no change in dose (other than weight-based adjustments) for at least 12 weeks prior to screening and had a screening aspartate transaminase/alanine transaminase <3 times the ULN.

- If on conventional PAH medication, including, but not restricted to, anticoagulants, diuretics, digoxin, and oxygen therapy, the subject must have been on stable doses with no changes (other than weight-based adjustments) for at least 4 weeks before screening.

- Female patients of childbearing potential must test negative for pregnancy during screening. Female patients must agree to abstain from sexual activity or to use 2 different reliable methods of birth control as determined by the Investigator during the study.

- Written informed consent from parents (and written assent from appropriately aged patients).

Exclusion criteria

- Had 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.

- History of left-sided heart disease, including any of the following:
    - clinically significant (pulmonary artery occlusion pressure 15-18 mm Hg) aortic or mitral valve disease (i.e., aortic stenosis, aortic insufficiency, mitral stenosis, moderate or greater mitral regurgitation),
    - pericardial constriction,
    - restrictive or congestive cardiomyopathy,
    - left ventricular ejection fraction <40% by multigated radionucleotide angiogram, angiography, or echocardiography,
    - left ventricular shortening fraction <22% by echocardiography,

    - life-threatening cardiac arrhythmias, or
    - symptomatic coronary artery disease within 5 years of study entry.

- Unrepaired congenital heart disease.
- Had a history of angina pectoris or other condition that was treated with long- or short-acting nitrates within 12 weeks before administration of study medication.
- Had severe hepatic impairment, Child-Pugh Grade C.
- Diagnosed with a retinal disorder (e.g., hereditary retinal disorders, retinopathy of the preterm patient, and other retinal disorders).
- Had severe hypotension or uncontrolled hypertension as determined by the investigator.
- Concurrent PDE-5 inhibitor therapy (sildenafil or vardenafil) or had received PDE-5 inhibitor therapy within 12 weeks prior to the first study medication dosing (Day 1, Visit 2).
- Concurrent therapy with prostacyclin or its analogues within 12 weeks of screening.
- Commenced or discontinued a chronic conventional PAH medication including but not restricted to diuretics, anticoagulants, digoxin, and oxygen therapy within 4 weeks of screening.
- Current treatment with potent CYP3A4 inhibitors, such as antiretroviral therapy (protease inhibitor), systemic ketoconazole, or systemic itraconazole, or chronic use of potent CYP3A4 inducers, such as rifampicin.
- Diagnosis of Down syndrome.

- Locations of the Study LVHV:

This was a multicenter trial.

- **Treatments**

LVHV was a 2-period (double-blind placebo-controlled period [Period 1] and open-label extension period [Period 2]), add-on study where patients received the investigational product (tadalafil or placebo) in addition to the subject's current endothelin receptor antagonist (ERA).

Tadalafil

Tadalafil was administered to patients included in the tadalafil group during the Period 1 (double-blind period), as well as to all patients included in Period 2 (open-label extension) of the study.

Patients were stratified into 3 weight cohorts to receive tadalafil: heavy-weight cohort (≥40 kg), middle-weight cohort (≥25 kg to <40 kg) and light-weight cohort (<25 kg). Tadalafil dose of each weight cohort in this study was established and redefined based on Safety Monitoring Committee (SMC) and Sponsor review. The selected dose for each paediatric weight cohort reflected expected exposures comparable to the approved 40 mg dose of tadalafil in adults. For further information regarding tadalafil dose selection, please refer to the sections above.

Subjects who met all of the eligibility criteria were randomised (1:1) to receive orally once daily a fixed tadalafil dose based on their weight cohort (40 mg/day [2 x 20 mg tadalafil tablets] for the heavy-weight cohort, and 20 mg/day [1 x 20 mg tadalafil tablet] for the middle-weight cohort) or matching placebo tablet(s) orally once daily for 24 weeks in Period 1.

In Period 2, all subjects received tadalafil in an open-label fashion for up to 2 years. Subjects receiving tadalafil in Period 1 continued at the same dose in Period 2, unless the subject had changed the subject's weight cohort at the end of Period 1 (at Visit 9/early termination). Subjects receiving placebo in Period 1 received tadalafil in Period 2 at the corresponding tadalafil dose for the subject's weight cohort at entry into Period 2.

During Period 2, the dose of tadalafil might be adjusted if the subject's weight changed by at least 1 kg over or below the weight cohort thresholds of 25 kg and 40 kg. If this weight change occurs, the subject's dose of study medication might be adjusted so that they were receiving the appropriate weight cohort-related dose. During this study period, subjects continued to receive stable ERA therapy, which could be adjusted at the Investigator's discretion.

Placebo

Placebo was administered to patients included in the placebo group durind the Period 1 (double-blind period) of the study.

ERA

All patients received an endothelin receptor antagonist, such as bosentan or ambrisentan, during the whole study.

This study design requires patients to be receiving an ERA, and allows for the use of conventional PAH therapies. ERAs are required, as there are sufficient data available in the adult population to reasonably predict safety with ERA therapy (Study LVGY). A placebo-only treatment arm is not being proposed for this study, as assigning paediatric PAH patients to treatment with placebo alone may be viewed as unethical.

Treatment rescue

Conventional PAH medication, including but not restricted to, anticoagulants, diuretics, digoxin, and oxygen therapy were allowed during the study as rescue medication. If on conventional PAH medication, the patient must be on stable doses with no changes (other than weight-based adjustments) for at least 4 weeks before screening.

- **Objectives**

Primary objectives:

  - *Period 1 (Double-Blind Placebo-Controlled):*

- To evaluate the efficacy of tadalafil compared with placebo in improving 6-minute walk distance (6MWD) from baseline to Week 24, as assessed in a subset of subjects ≥6 to <18 years of age who were developmentally capable of performing a 6MWD test.

- *Period 2 (Open-Label Extension):*

  - To evaluate the long-term safety of tadalafil while providing continued access to tadalafil for paediatric patients with PAH who participated in Period 1.

Secondary objectives:

- *Period 1 (Double-Blind Placebo-Controlled):*

  - To assess the efficacy of tadalafil compared with placebo on time to clinical worsening (CW) and the incidence of CW.

  - To characterise the population PK of tadalafil in paediatric patients with PAH.

  - To assess the safety of tadalafil compared with placebo.

- *Period 2 (Open-Label Extension):*

  - To evaluate the incidence of CW and time to CW.

Additional objectives:

- *Period 1 (Double-Blind Placebo-Controlled):*

  - To assess the efficacy of tadalafil compared with placebo on changes in World Health Organization (WHO) functional classification.

  - To explore by cardiac magnetic resonance imaging (MRI), changes from Day 1 to Week 24 in the following cardiac MRI parameters:

    - left-ventricular [LV] ejection fraction

    - right-ventricular [RV] end diastolic volume

    - RV end systolic volume

    - RV ejection fraction

  - To evaluate by echocardiography, changes from Day 1 to Week 24 in the following echocardiographic parameters:

- tricuspid annular plane systolic excursion (TAPSE)

- eccentricity index (EI)

- pericardial effusion

- maximal tricuspid regurgitant velocity

- To evaluate change from Day 1 to Week 24 in N-terminal prohormone brain natriuretic peptide (NT-Pro-BNP) concentrations.

- To assess physician- and caregiver-reported health outcome, as measured by Clinical Global Impression of Improvement (CGI-I), and in a subset of subjects ≥5 years of age, Child Health Questionnaire Parent Form 28 (CHQ-PF28).

- *Period 2 (Open-Label Extension):*

  - There were no additional objectives.

- **Outcomes/endpoints**

Primary Efficacy Measure:

Period 1 (Double-Blind Placebo-Controlled)

- Improvement of 6MWD in meters, as assessed in a subset of subjects who were ≥6 years of age and were developmentally capable of performing a 6MWD test.

Secondary Efficacy and Pharmacokinetic Measures:

Period 1 (Double-Blind Placebo-Controlled)

- Clinical Worsening (CW)

Time to CW and the incidence of CW. Subjects who met any of the following 5 major criteria were considered to have met the definition of CW:

1. All-cause mortality

2. Lung or heart lung transplantation

3. Atrial septostomy or Potts shunt

4. Hospitalization for PAH progression

a. Hospitalization for PAH progression should not have been due to a potentially precipitating event such as pneumonia hemoptysis, etc; however, if after the hospitalization was completed, the subject was discharged and the subject remained worse, then the subject could be assessed for CW.

5. Worsening of PAH Subject had any of the following criteria:

a. New-onset syncope.

b. Addition of new PAH-specific concomitant therapy including, but not restricted to epoprostenol or treprostinil, sildenafil, vardenafil, or increase in dose of existing PAH specific concomitant therapy (for example, ERA).

c. Increase of 1 or more in WHO functional class (Attachment 8) in the protocol (except for subjects already in Class IV) only for subjects who were unable to perform the 6MWD test.

d. Worsening of WHO functional class and a decrease of 20% in the 6MWD test (confirmed 5 to 10 days later) for those subjects who were ≥6 years of age and were developmentally capable of performing the 6MWD test.

Criteria for CW (from Period 1) were adjudicated by an independent, blinded study-specific Clinical Endpoint Committee (CEC). This adjudication was used for data analysis, and was not used to guide subject treatment.

- Population PK characterisation

PK was assessed by measuring steady-state plasma tadalafil concentrations. During Period 1, plasma tadalafil concentrations were obtained at Weeks 2, 4, 16, and 24 (Visits 3, 4, 7, 9, respectively).

When pharmacodynamics and exposure–response were assessed, 6MWD was measured in paediatric subjects from 6 years of age and older, and who were capable of performing the test. During Period 1, it was assessed at Weeks 8, 12, 16, and 24.

Period 2 (Open-Label Extension)

- Incidence of and time to incidence of clinical worsening (CW) of PAH in the paediatric population with endpoint as overall incidence of at least 1 criterion of CW, and time to CW with endpoint as date of first dose to the date of CW event.

<u>Additional Efficacy Measures</u>

Period 1 (Double-Blind Placebo-Controlled)

- Changes in WHO functional classification

- Changes in cardiac MRI parameters:
    - LV ejection fraction
    - RV end diastolic volume
    - RV end systolic volume
    - RV ejection fraction
- Changes in echocardiography parameters:
    - TAPSE
    - EI
    - pericardial effusion
    - maximal tricuspid regurgitant velocity
- Changes in NT-Pro-BNP concentrations.
- Health Outcomes: CGI-I and CHQ-PF28 in subjects ≥5 years of age.

Period 2 (Open-Label Extension)

- Improvement of 6MWD distance in meters as measured in subjects who were ≥6 years of age and who were developmentally capable of performing a 6MWD test.
- Changes in WHO functional classification.

- **Sample size**

The primary efficacy measure was 6MWD and it was evaluated in this study during Period 1.

The original planned sample size was 134 subjects and an interim analysis of the 6MW data was also planned (approximately Q1 2017). However, the planned sample size was reduced to 34 subjects in conjunction with changing the primary efficacy measure (from time to CW to 6MWD) in a LVHV protocol amendment. This protocol amendment was approved on 13 Dec 2018 as a result of enrolment difficulties experienced in the study and agreed with the EMA.

Finally, at least 34 subjects were planned to be stratified by weight and randomised in a 1:1 ratio to tadalafil or placebo treatment in Period 1 of this study (n=17, tadalafil; n=17, placebo). To achieve a representative distribution of subject's ages, enrolment was monitored throughout the study to achieve ≥30% of all subjects <12 years of age.

It was considered that with 2 patients not having postbaseline 6MWD, a sample size of 32 randomized patients is assumed to be ≥6 to <18 years of age who are developmentally able to complete the 6MWD test. This sample size will provide 71% power to detect a placebo-adjusted mean difference in

change in 6MWD of 40 meters with a standard deviation of 60 meters and a two-sided significance level of 0.2.

Regarding the rules for discontinuation of patients, the Investigator or Sponsor could stop the study or stop the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

- **Randomisation and Blinding (masking)**

Screening and eligibility evaluations were performed during an approximately 28-day lead-in period (Visits 1 to 2) prior to randomising subjects to study medication.

Subjects were randomised (Day 1; Visit 2) to receive either placebo or tadalafil in a 1:1 ratio, based on weight cohort (heavy-weight, ≥40 kg; middle-weight, ≥25 kg to <40 kg; and light-weight, <25 kg), PAH aetiology (idiopathic-heritable, connective tissue/congenital heart disease, or other), and type of ERA (bosentan or other).

Assignment to treatment groups was determined by a computer-generated random sequence using an IXRS. The IXRS was used to assign bottles of tablets or liquid suspension containing double-blind study drug to each patient. An appropriate amount of investigational product was assigned to each patient to cover the study visit interval. Site personnel confirmed that they have located the correct bottles by entering a confirmation number found on the bottles into the IXRS prior to dispensing the investigational product to the patient.

- **Statistical methods**

Given the small, planned sample size (34 subjects), no formal comparisons were to be made between treatment groups. Hence, the overall treatment difference p-value and the visit-wise p-values was reported. With the exception of the primary analysis of 6MWD, 95% confidence intervals (CIs) were reported for the overall treatment difference and visit wise treatment differences.

Randomisation at Visit 2 (Day 1) was stratified by the following variables:

- weight cohort (heavy-weight: ≥40 kg; middle-weight: ≥25 kg to <40 kg; light-weight: <25 kg),
- ERA medication (bosentan or other),
- pulmonary arterial hypertension aetiology (idiopathic, connective tissue disease, anorexigen use, and associated to surgical repair).

These stratification factors, in addition to the baseline value of the analysis variable, were included as covariates in all the numerical models, unless otherwise specified.

- Efficacy:

Efficacy analyses, except 6MWD, were performed on the Primary Analysis Population. This population included all data from all randomised subjects who received at least 1 dose of the study medication according to the randomised treatment.

The analysis of six-minute walk distance analysis was performed on the 6MWD Analysis Population which included the subset of randomised subjects ≥6 to <18 years of age (at screening) who took at least 1 dose of study medication and were capable of performing a 6MWD test.

For each efficacy variable, the analysis included all randomised subjects with baseline and at least 1 postbaseline observation. Subjects with no postbaseline data for a particular efficacy endpoint were

excluded from the analysis of that endpoint. However, additional sensitivity analyses utilizing imputed values for missing post Day 1 data may be conducted for specific endpoints.

Analyses for Period 2 only included subjects who entered Period 2.

The comparison of change in 6MWD between tadalafil and placebo treatment groups was to be performed using a restricted maximum likelihood (REML)-based, mixed-model repeated measures (MMRM) approach. Factors in the MMRM model included visit, baseline (Day 1) 6MWD, weight cohort, PAH aetiology, type of ERA therapy, and treatment group. A treatment-by-visit interaction term was to be included. An interaction term for treatment-by-baseline value was to be evaluated and included in the model if the interaction term was significant at the 0.10 level ($p<0.10$).

Criteria for CW (from Period 1) were to be adjudicated by an independent, blinded study-specific Clinical Endpoint Committee (CEC). This adjudication was to be used for data analysis and was not to be used to guide subject treatment.

All efficacy measures will be summarized by descriptive statistics for each treatment group. For continuous variables, summary statistics will include the number of observations, mean, median, minimum and maximum values, and standard deviation or standard error. For categorical variables, counts and percentages will be tabulated for each category. The 25th percentile, median and 75th percentile will be presented for variables that are analyzed using ranktransformed data.

- Safety:

Safety analyses were conducted on the Primary Analysis Population.

Treatment-emergent AEs (TEAEs) are presented in listings and summaries by PT (preferred term; by descending incidence), by system order class (SOC) and PT, and also by maximum severity within SOC.

- Pharmacokinetic/Pharmacodynamic:

Plasma tadalafil concentration time data were explored graphically by dose and ERA treatment. Additional analyses were done using a population PK approach pooling tadalafil data across various studies including LVHV.

- Health Outcomes:

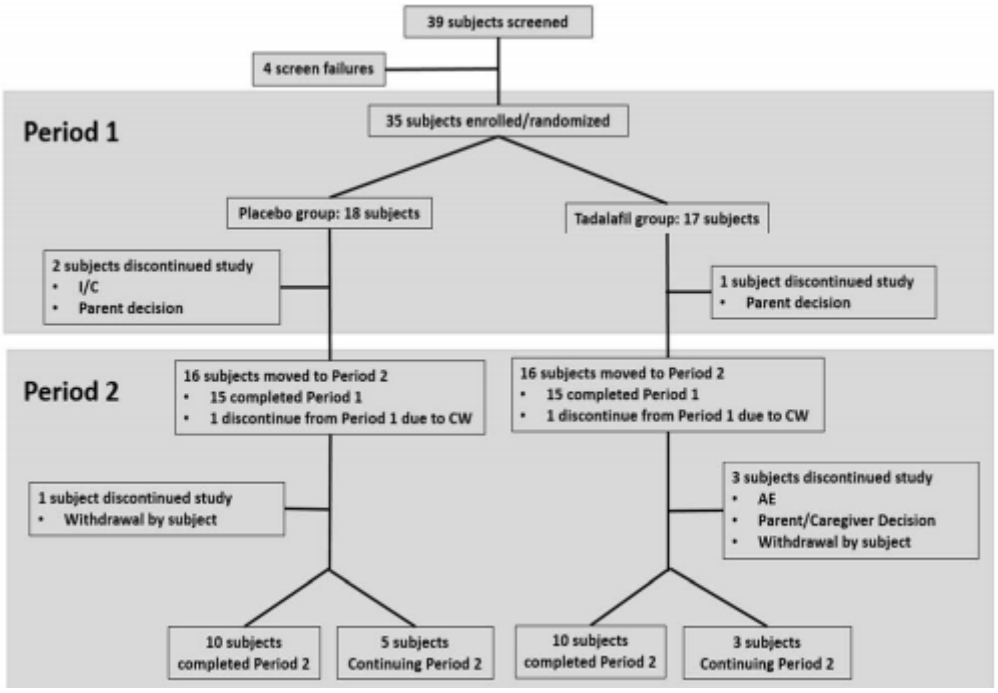
Proportions of subjects in each of the 7 response categories ("Very Much Better" to "Very Much Worse") of the CGI-I were summarized by visit. Changes from baseline (Day 1) to Weeks 16, 24, and endpoint in CHQ-PF28 scores were analysed with an analysis of covariance (ANCOVA) model that included terms for baseline (Day 1) score, weight cohort, PAH aetiology, type of ERA therapy, and treatment group.

Results

- **Participant flow**

Subject disposition in Period 1 and Period 2 of the Study LVHV is shown in Figure below.

Figure 12 - Subject disposition in study LVHV



Abbreviations: AE=adverse event; CW=clinical worsening; I/C=inclusion criteria not met.

- **Recruitment**

This study was conducted at 15 study centers, which enrolled participants in 9 countries (Brazil, Israel, Japan, Mexico, Turkey [Austria, Germany, France, and Poland from EU]).

Period 1 (Double-Blind Placebo-Controlled)

A total of 39 subjects were screened for the study. Four subjects were screen failures and 35 subjects were randomly assigned to placebo (18 subjects) or tadalafil (17 subjects) treatment in Period 1 of this study and received at least 1 dose of study medication.

Period 2 (Open-Label Extension)

In Period 2, a total of 32 subjects (15 subjects each in the placebo and tadalafil groups that completed Period 1, and 1 subject from each group that discontinued Period 1 due to reported potential CW) were assigned to tadalafil and received at least 1 dose of the study medication.

Subjects who received placebo in Period 1 received tadalafil in Period 2 (referred to as Pla-Tad group) at the corresponding tadalafil dose for the subject's weight cohort at entry into Period 2. Subjects who received tadalafil in Period 1 continued at the same dose in Period 2 (referred as Tad-Tad group), unless the subject had changed the weight cohort at the end of Period 1.

Six subjects discontinued the study during Period 2 (1 due to an AE, 2 due to parent/caregiver decision, and 3 due to withdrawal by subject). The remaining 26 subjects completed Period 2 of the study.

- **Conduct of the study**

Following initiation of LVHV in July 2013, the MAH encountered issues with the study implementation

regarding the recruitment of paediatric patients with PAH. These included:

- disease rarity and complexity
- widespread off-label use of PAH therapies
- concerns from parents and investigators regarding the potential to be randomised to placebo, and
- multiple competing clinical trials with extremely low enrolment rate.

During the first 5 years of Study LVHV conduct, only 34 patients had been enrolled from 59 sites across 17 countries, despite substantive and specific actions to improve rates of recruitment. These enrolment challenges were also evident in Study LVIG.

In 2016, the MAH sought Scientific Advice to discuss the implementation issues with Study LVHV. The issues were further discussed in 2017 at European Medicines Agency (EMA)/Food and Drug Administration (FDA)/Health Canada multi-stakeholder workshop with input from key opinion leaders and patients. The outcome of the workshop was an acceptance that large placebo-controlled studies are unfeasible in this population. Following these regulatory interactions, the MAH reached an agreement with PDCO to (1) discontinue enrolment of Study LVHV at a smaller sample size (from original 134 to 34) and (2) utilise modelling and extrapolation to assess efficacy in the paediatric population.

The key modifications made to Study LVHV following its initiation were:

- reduction in the number of patients enrolled from 134 to 34 and
- change of primary endpoint from time to first clinical worsening (CW) to improvement in 6MWD from baseline to Week 24.

- **Baseline data**

Period 1 (Double-Blind Placebo-Controlled)

There were 16 male and 19 female randomized subjects in this study; the median age for the overall population was 14.2 years (ranged from 6.2 to 17.9 years) and 37.1% subjects were less than 12 years of age. No subject younger than 6 years was enrolled in the study. The majority of subjects (25/35; 71.4%) were in the heavy-weight cohort with the remainder (10/35; 28.6%) in the middle-weight cohort. No subjects were enrolled in the light-weight (<25 kg) cohort.

The majority of subjects were white (26/35; 74.3%), and 7 (20%) of total enrolled subjects were from sites in Europe.

For Period 1, the most common PAH aetiology was idiopathic PAH (n=26; 74.3%; with 11/18 [61.1%] subjects in the placebo group and 15/17 [88.2%] subjects in the tadalafil group). Remaining patients had a diagnosis of PAH associated with persisting or recurrent pulmonary hypertension after repair of a congenital systemic to pulmonary shunt (n=9; 25.7%; with 7/18 [38.9%] subjects in the placebo group and 2/17 [11.8%] subjects in tadalafil group). There were 80% of subjects in WHO functional Class II. Baseline clinical and disease characteristics for the Primary Analysis and 6MWD Populations included the same subjects and were therefore identical, as all subjects in the Primary Analysis Population were able to provide 6MWD data. The mean (SD) baseline 6MWD was 481.1 meters (132.77): 476.7 meters on the placebo group and 485.8 meters on the tadalafil group.

Table 19 - Patient Demographics and Baseline Clinical and Disease Characteristics - Double-Blind Treatment Period

	Placebo (N=18)	Tadalafil (N=17)	Total (N=35)
Age (years) [a]			
n	18	17	35
Mean (SD)	12.8 (3.39)	14.1 (3.49)	13.5 (3.45)
Median	13.4	15.8	14.2
Min, Max	7.3, 17.7	6.2, 17.9	6.2, 17.9
Age category - n (%)			
n	18 (100.0)	17 (100.0)	35 (100.0)
<6 years	0 (0.0)	0 (0.0)	0 (0.0)
≥6 and <12 years	8 (44.4)	5 (29.4)	13 (37.1)
≥12 years	10 (55.6)	12 (70.6)	22 (62.9)
***Weight category [b] - n (%)**			
n	18 (100.0)	17 (100.0)	35 (100.0)
Heavy weight	12 (66.7)	13 (76.5)	25 (71.4)
Middle weight	6 (33.3)	4 (23.5)	10 (28.6)
Light weight	0 (0.0)	0 (0.0)	0 (0.0)
Gender - n (%)			
n	18 (100.0)	17 (100.0)	35 (100.0)
Male	9 (50.0)	7 (41.2)	16 (45.7)
Female	9 (50.0)	10 (58.8)	19 (54.3)
PAH aetiology - n (%)			
n	18	17	35
Idiopathic	11 (61.1)	15 (88.2)	26 (74.3)
Related to collagen vascular disease	0 (0.0)	0 (0.0)	0 (0.0)
Related to anorexigen use	0 (0.0)	0 (0.0)	0 (0.0)
Associated to surgical repair of at least 6 month of a congenital systemic to pulmonary shunt	7 (38.9)	2 (11.8)	9 (25.7)
Duration of PAH (year)			
n	18	17	35
Mean (SD)	2.65 (3.219)	4.64 (5.536)	3.61 (4.541)
Median	0.78	1.81	1.40
Min, max	0.19, 10.44	0.29, 17.48	0.19, 17.48
Concomitant ERA Therapy - n (%)			
n	17	17	34
Bosentan	16 (94.1)	16 (94.1)	32 (94.1)
Other	1 (5.9)	1 (5.9)	2 (5.9)
Baseline WHO functional classification - n (%)			
n	18	17	35
Class I	0 (0.0)	0 (0.0)	0 (0.0)
Class II	14 (77.8)	14 (82.4)	28 (80.0)
Class III	4 (22.2)	3 (17.6)	7 (20.0)
Class IV	0 (0.0)	0 (0.0)	0 (0.0)
Baseline 6MWD (m) [a]			
n	18	17	35
Mean (SD)	476.7 (105.11)	485.8 (160.23)	481.1 (132.77)
Median	480.0	513.0	490.0
Min, max	246, 635	112, 815	112, 815

Abbreviations: 6MWD = 6-minute walk distance; ERA = endothelin receptor antagonist; max = maximum; min = minimum; N = number of patients in the primary analysis population; n = number of patients per category with nonmissing data; PAH = pulmonary arterial hypertension; SD = standard deviation; WHO = World Health Organization.

*Heavy-weight: ≥40 kg, middle-weight: ≥25 kg to <40 kg and light-weight: <25 kg.

The majority of the subjects (32/35; 91.4%) were taking bosentan as concomitant ERA, 2 patients were on macitentan as concomitant ERA (1 in each treatment group) and in a remaining patient the type of ERA was not specified (see table above).

Period 2 (Open-Label Extension)

There were 14 male and 18 female subjects who continued to Period 2; the median age for the overall population was 14.4 years (ranged from, 6.2 to 17.9 years). The majority of subjects (23/32; 71.9%) were in the heavy-weight group with the remaining (9/32; 28.1%) in the middle-weight group.

The majority of subjects were white (24/32; 75%), and 7/32 (21.9%) subjects were from Europe.

For Period 2, the most common PAH aetiology was idiopathic PAH (25/32; 78.1%) and PAH associated with persisting or recurrent pulmonary hypertension after repair of a congenital systemic to pulmonary shunt (7/32; 21.9%), and the majority of subjects had WHO functional Class II (25/32; 78.1%).

The majority of the subjects (30/32; 93.8%) were taking bosentan as concomitant ERA.

- **Numbers analysed**

Period 1 (Double-Blind Placebo-Controlled period)

All 35 randomised subjects who received at least 1 dose of study medication (17 subjects received tadalafil and 18 subjects received placebo) were included in the safety and efficacy analyses performed for Period 1, with the exception of the analysis of 6MWD. As 2 out of the 35 randomized subjects (1 subject in the placebo middle-weight cohort and 1 subject in the placebo heavy-weight) were not capable of performing a 6MWD test, only 33 subjects were analysed for the primary efficacy measure (6MWD).

The number of subjects by cohort with measurable PK samples (at Visits 3, 4, 7 and 9) were 4 subjects (16 total PK samples) from the middle weight cohort and 13 subjects (48 total PK samples) from the heavy weight cohort.

A total of 3 subjects (2 in the placebo group and 1 in the tadalafil group) discontinued from the study during period 1.

Period 2 (Open-Label Extension)

None of the 32 subjects who entered Period 2 were excluded from the safety and efficacy analyses.

- **Outcomes and estimation**

Primary efficacy variable (and corresponding sensitivity analyses):

6MWD during Period 1 (Double-Blind Placebo-Controlled period)

Since there were not at least 3 subjects per treatment at each PAH aetiology and ERA therapy level, neither factor was included in the model. Of the 35 randomised subjects, 33 were analysed for the primary efficacy measure (6MWD).

A numerical improvement in the tadalafil group (60.48 meters) compared to the placebo group (36.60 meters) was demonstrated at Week 24 corresponding to an LS placebo-adjusted mean (SE) difference of 23.88 (29.114) meters (80% CI, -14.25, 62.00).

Table 20 - 6-Minute-Walk Distance (Meters) - MMRM - Double Blind Treatment Period, 6-Minute Walk Analysis Population

Treatment	Time Point [a]	n	Mean	SD	Median	LS Mean Change [b]	SE	Treatment Difference (tadalafil vs Placebo) [b] LS Mean	SE	80% CI
Placebo (N=18)	Baseline	16	483.38	88.949	480.00					
	Week 4	16	516.63	131.760	503.00	33.20	16.902			
	Week 8	16	542.19	112.409	520.50	58.77	19.090			
	Week 12	16	516.69	136.222	511.50	33.27	19.903			
	Week 16	16	502.06	135.943	501.00	18.64	17.770			
	Week 20	15	520.87	133.065	497.00	22.32	21.274			
	Week 24	15	533.33	132.891	487.00	36.60	20.776			
tadalafil (N=17)	Baseline	17	485.76	160.231	513.00					
	Week 4	17	510.53	155.790	501.00	24.69	16.406	-8.51	23.541	(-39.35, 22.33)
	Week 8	17	508.35	164.836	504.00	22.52	18.528	-36.25	26.591	(-71.10, -1.39)
	Week 12	15	508.47	127.503	510.00	37.45	19.617	4.18	27.933	(-32.43, 40.79)
	Week 16	16	486.00	132.355	506.50	20.08	17.527	1.44	24.956	(-31.25, 34.13)
	Week 20	14	481.50	106.846	487.50	39.22	20.997	16.90	29.878	(-22.26, 56.06)
	Week 24	15	522.80	149.243	540.00	60.48	20.410	23.88	29.114	(-14.25, 62.00)

Abbreviations: 6MW = 6-minute walk; CI = confidence interval; ERA = endothelin receptor antagonist; LS Mean = least-squares mean; MMRM = mixed model repeated measures; N = number of patients in the 6-minute-walk population; n = number of patients with non-missing data at baseline and at least one post baseline visit; PAH = pulmonary arterial hypertension; SD = standard deviation; SE = standard error.

The Primary Analysis Population includes all patients who received at least 1 dose of the study drug according to the randomized treatment. 6MW Analysis Set includes the subset of the Primary Analysis Population who were > = 6 to < 18 years of age and were capable of performing a 6MW test.
[a] Baseline = Visit 2 (Day 1) value
[b] Change = value at visit - value at baseline.
The LS mean, standard error, 2-sided 80% confidence interval for comparison between tadalafil and placebo in change from baseline derived using mixed model repeated measures with terms for treatment group, visit, baseline 6MWD, and treatment-by-visit interaction. Note: An interaction term for Treatment*Baseline was not included in the model because it was not significant at the 0.10 level (p<0.10). ERA therapy and PAH aetiology were not included in the model since each didn't have at least 3 patients per treatment arm at each PAH aetiology or ERA therapy level.
Source: LVHV CSR Table LVHV.11.7

- 6MWD during Period 2 (Open-Label Extension)

In Period 2, the 6MWD mean change from baseline (Visit 9) increased by 7.73 metres at Year 1 and decreased by 4.58 metres at end of Period 2 (24 months) in the Pla-Tad group, and decreased by 21.50 metres at Year 1 and decreased by 32.58 metres at end of Period 2 (24 months) in the Tad-Tad group.

Six-Minute Walk Bayesian Mixed-Effects Model for Repeated Measures (Sensitivity Analysis)

This supportive (sensitivity) analysis to the primary analysis of Study LVHV using a Bayesian MMRM model that leveraged data from the adult study (LVGY) was conducted to increase precision in confirming the 6MWD efficacy endpoint. Factors included in the Bayesian MMRM model were similar to the primary analysis. Factors in the MMRM model included visit, baseline 6MWD, treatment group and treatment-by-visit. Bayesian posterior probability of active treatment arm being superior to placebo was calculated.

The adult study (Study LVGY) was used to build the adult component N (μA, ΣA) of the mixture prior distribution. In Study LVGY, a total of 405 patients were randomised equally to placebo, tadalafil 2.5 mg, 10 mg, 20 mg and 40 mg. A subset of 216 patients had bosentan as ERA therapy and were similar to the patient population in the paediatric study (Study LVHV). The highest 2 doses in the adult study were most relevant to the doses, which were studied in the paediatric study (Study LVHV). Approximately, 81% of the observed tadalafil area under the concentration versus time curve at steady state (AUCss) from Study LVGY predicted following 40 mg QD administration were within the fifth to 95th percentiles of those estimated following 20 mg. The pooled data from these doses provided an estimate of the mean and SE of the treatment difference versus placebo in 6MWD change from baseline across the time points. Hence, a subset of 132 patients were the focus of the analyses to form the adult component of the mixture prior distribution.

Diffused prior on the Bayesian MMRM model was used such that the resulting inference for these parameters would almost entirely be driven by the observed data in paediatric Study LVHV. This was analogous to the primary analysis. The mixture prior approach was also used where diffuse independent normal priors were used. This mixture prior approach dynamically and adaptively 'borrows' evidence from adult data from Study LVGY based upon the similarity of the paediatric data

coming from the ongoing Study LVHV using a prespecified weight of 0.8. This weight was determined using elicitation from medical experts. To understand the impact of the weight mixture, the model using the mixture prior distribution with a weight of 0.5 was examined.

Table E05 summarises changes from baseline in 6MWD at 24 weeks MMRM (primary analysis for the study) result and the Bayesian MMRM results with diffuse prior and mixture prior using weight of 0.5 and 0.8. The latter model resulted in the posterior mean difference of 27.13 m and 80% credible interval (4.94 to 42.73), which supports the positive trend suggested by the primary analysis in Study LVHV and indicates that tadalafil treatment improves the 6MWD compared to placebo at Week 24 in this paediatric patient population.

Table 21 - Summary of Changes from Baseline in 6MWD at 24 Weeks

	Tadalafil **LS Mean (SE)**	**Placebo** **LS Mean (SE)**	**Placebo-Adjusted LS Mean Difference (SE)**	**80% CI**	**Posterior probability for Placebo-adjusted mean difference >0**
6MWD (m) MMRM (Primary analysis)	60.48 (20.41)	36.60 (20.78)	23.88 (29.11)	(-14.25, 62.00)	-
6MWD (m) Bayesian MMRM with diffuse prior	60.06 (20.95)	35.32 (20.65)	24.74 (28.82)	(-11.00, 62.20)	
6MWD (m) Bayesian MMRM with mixture prior weigh 0.5	56.39 (15.81)	35.25 (16.02)	21.14 (13.83)	(1.87, 38.11)	
6MWD (m) Bayesian MMRM with mixture prior weigh 0.8	58.80 (15.35)	31.67 (15.14)	27.13 (11.09)	(4.94, 42.73)	0.975

Abbreviations: 6MWD = six-minute walk distance; CI = confidence interval; CrI = credible interval; LS = least square; MMRM = mixed-effects model for repeated measures; SE = standard error.

- The secondary efficacy variables:

  - Time to CW and Incidence of CW during Period 1 (Double-Blind Placebo-Controlled)

In Period 1, 2 subjects, 1 in each treatment group, reported to have potential CWs by Investigators. However, since both cases were not confirmed as qualified CWs by Clinical Endpoint Committee (CEC), these were not used for data analysis.

- One patient (heavy weight) in the placebo group was reported with worsening of PAH due to a WHO functional class increase and a 6MWD decrease. This case was not confirmed by the CEC because the site did not perform a confirmative 6MW test 5 to 10 days later as described in the protocol.
- One patient (heavy weight) in the tadalafil group reported a new-onset syncope as a CW event; while the CEC reviewed the case, the investigator revised the event to presyncope based upon the clinical information for this patient. Therefore, this was an invalid case based upon the CW definition in the protocol for a new-onset syncope.

Both subjects discontinued Period 1 study medication and moved into the Period 2 open-label portion of the study. It should be noted that both cases of CW were reported as AEs per protocol; however, neither subjects were considered withdrawn due to an AE.

- Time to CW and Incidence of CW during Period 2 (Open-Label Extension)

In Period 2, 5 subjects who had received tadalafil experienced CWs, 1 had new-onset syncope, 2 had increase in ERA dose, 1 had addition of new PAH-specific concomitant therapy, and 1 was hospitalised for PAH progression. Two CW subjects were in Pla-Tad (placebo in Period 1 and tadalafil in Period 2) group (12.5%) and 3 CW subjects in Tad-Tad (tadalafil in both Period 1 and 2) group (18.75%).

The number of participants with CW was inadequate to perform the statistical analysis for time to CW.

Additional efficacy variables for period 1:

The additional efficacy variables for Period 1 were analysis of WHO functional class, echocardiography, NT-pro-BNP concentrations, CGI-I and CHQ-PF28. These are briefly described in the following sections.

WHO Functional Class

Changes in WHO functional class from baseline to Week 24 for Period 1 is presented in Table E06. From baseline to Week 24 (Visit 9) of Period 1, the patients in the tadalafil group had a numerically higher and trending to the positive direction of WHO functional class improvement compared with the patients in the placebo group. Worsening of WHO functional class was not reported in either group.

Table 22 - Least Squares Mean Change for Secondary Endpoints from Baseline to Week 24

	Tadalafil	**Placebo**	**Placebo-Adjusted Differences; 95% CI**
WHO functional class (WHO FC Change from baseline)	40% improved 60% no change	20% improved 80% no change	NA
Echocardiography (LS Mean [SE]): -TAPSE -Left ventricular EI-systolic -Left ventricular EI-diastolic -TRV-max -Pericardial effusion	 0.33 (0.130) -0.29 (0.218) -0.08 (0.122) 1.68 (31.066) 0 patient in Period 1	 -0.10 (0.111) 0.11 (0.194) 0.08 (0.106) 17.01 (28.472) 2 patients in Period 1	 0.43 (0.136); 0.14, 0.71 -0.40 (0.225); -0.87, 0.07 -0.17 (0.124); -0.43, 0.09 -15.33 (29.443); -78.48,47.82 NA
NT-pro-BNP (LS Mean [SE])	-59.16 (59.639)	68.26 (49.412)	-127.4 (56.700); -247.05, -7.80
CGI-I (overall symptoms)	64.3% better[a]	46.7% better[a]	NA
CHQ-PF28 (summary score; LS Mean [SE])			

-Physical		9.28 (3.78)	
-Psychosocial	8.34 (4.52)	2.56 (1.06)	-0.94 (4.26); -9.75, 7.86
	0.86 (1.28)		-1.70 (1.19); -4.16, 0.76

Abbreviations: CGI-I = Clinical Global Impression of Improvement; CHQ-PF28 = Child Health Questionnaire Parent Form 28; CI = confidence interval; EI = eccentricity index; LS = least square; NA = not applicable; NT-pro-BNP = N-terminal prohormone brain natriuretic peptide; SE = standard error; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitant velocity; WHO = World Health Organization.

[a] "Better" includes responses of a ' minimally improved' , ' much improved' , or 'very much improved'.

- **Echocardiography:** The LS mean (SE) changes from baseline to Week 24 for each echocardiography parameter between tadalafil and placebo are shown in Table E06. A positive trend of potential efficacy in echocardiographic parameters (such as TAPSE, LV eccentricity index (EI)-systolic and LV EI-diastolic) was seen. Two patients with reported pericardial effusion during 24-week treatment (1 patient each at Week 8 and at Week 16) from placebo group and none of the patients reported pericardial effusion in tadalafil group.
- **N-Terminal Prohormone Brain Natriuretic Peptide:** Least squares mean (SE) changes from baseline in NT-pro-BNP measurements and placebo-adjusted LS mean (SE) differences at Week 24 in the primary analysis population in Table E06. The LS mean (SE) change in NT-pro-BNP concentrations were significantly better for tadalafil than for placebo (placebo-adjusted LS mean [SE] differences).
- **Clinical Global Impression of Improvement:** Patient outcome assessments using the CGI-I are presented in Table E06. From baseline to Week 24, the overall improvement in symptoms of PAH were numerically higher in the tadalafil group compared with the placebo group and worsening of PAH symptoms in CGI-I was not reported in either group.
- **Child Health Questionnaire Parent Form 28:** Analyses of parameters assessed by the CHQ-PF28 are presented in Table E06. Least squares mean (SE) changes from baseline for global health scale in CHQ-PF28 measurements at Week 24 in the analysis population, aged $\geqslant$5. The summary scores and subtest domains did not show any differences in LS mean changes from baseline to Week 24.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23 - Summary of efficacy for trial H6D-MC-LVHV

Title: A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension	
Study identifier	H6D-MC-LVHV (NCT01824290)

<table>
<tr><td colspan="4"><u>Title:</u> A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension</td></tr>
<tr><td>Study identifier</td><td colspan="3">H6D-MC-LVHV (NCT01824290)</td></tr>
<tr><td>Design</td><td colspan="3">Phase 3, international, randomised, multicentre, 2-period (24 weeks double-blind placebo-controlled period [Period 1] and open-label 2-years extension period [Period 2]), add-on (i.e., in addition to the subject's current endothelin receptor antagonist [ERA]) study to evaluate the efficacy, safety, and population pharmacokinetics (PK) of tadalafil administered orally once daily in paediatric subjects from 6 months to less than 18 years of age with pulmonary arterial hypertension (PAH).</td></tr>
<tr><td></td><td colspan="2">Duration of main phase :
Duration of Run-in phase:
Duration of Extension phase:</td><td>24-week (6-month), double-blind (DB) period
4-week screening period
2-year, open-label (OL) period</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority (DB period)</td></tr>
<tr><td></td><td colspan="2">DB period</td><td>Tadalafil (n=17) or placebo (n=18), for 24 weeks Patients were planned to be stratified into 3 weight cohorts:
Heavy-weight Cohort (≥40 kg)
Tadalafil n=13,
Placebo (n=12)
Middle-weight Cohort (≥25 kg to <40 kg)
Tadalafil n=4,
Placebo (n=6)
Light-weight Cohort (<25 kg)
Tadalafil n=0,
Placebo (n=0)</td></tr>
<tr><td></td><td colspan="2">OL period</td><td>Tadalafil (n= 32 children) for 727 days (median), open label.</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>Change in 6MWD</td><td>Change in 6 minute walk distance</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>TTCW</td><td>Time to clinical worsening</td></tr>
<tr><td>Database lock</td><td colspan="3">03 May 2021</td></tr>
<tr><td colspan="4"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Intent to treat24 weeks</td></tr>
<tr><td>Descriptive statistics and estimate variability</td><td colspan="3"><table><tr><th></th><th>Placebo LS Mean (SE)</th><th>Tadalafil LS Mean (SE)</th><th>Placebo-Adjusted LS Mean Difference (SE)</th><th>80% CI</th></tr><tr><td>6MWD (m) MMRM (Primary analysis)</td><td>36.60 (20.78)</td><td>60.48 (20.41)</td><td>23.88 (29.11)</td><td>(-14.25, 62.00)</td></tr></table>
No statistical analysis was tempted due to insufficient sample size (n= 17 children on tadalafil and 18 on placebo).</td></tr>
<tr><td>Analysis description</td><td colspan="3">Secondary analysis</td></tr>
</table>

Title: A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension	
Study identifier	H6D-MC-LVHV (NCT01824290)
Analysis population and time point description	Intent to treat, 24 weeks
Descriptive statistics and estimate variability	Time to CW during Period 1 (Double-Blind Placebo-Controlled). In Period 1, two subjects, 1 in each treatment group, reported to have potential CWs by Investigators. However, since both cases were not confirmed as qualified CWs by Clinical Endpoint Committee (CEC), these were not used for data analysis.

2.6.5.3. Supportive study

The main supportive study (for effectiveness) is the Japanese post-marketing study (H6D-JE-TD01). Among the 391 paediatric patients included (23.3% of the total population), 79 patients were less than 1 year of age, 163 patients were 1 to 6 years, 110 patients were 7 to 14 years, and 39 patients were 15 to 18 years. Mean age ± standard deviation (SD) was 5.7 ± 5.34 years, and 51.7% of the patients were boys. Changes in WHO classification showed a tendency toward improvement at 3 months, 1 year, 2 years after the start of administration, and final observation in paediatrics was improvement in 8.6% (30/348 patients), 16.5% (40/243 patients), 19.7% (26/132 patients), and 16.3% (57/349 patients), respectively. The incidence of deterioration in WHO functional class at 3 months, 1 year and 2 years was 0.6% (2/348 patients), 0.8% (2/243 patients), 1.5% (2/132 patients), and 2.3% (8/349 patients), respectively. These data support the use of tadalafil in the paediatric population.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

A single confirmatory efficacy and safety study H6D-MC-LVHV (LVHV) has been provided to support the use of Adcirca in paediatric patients with PAH. As mentioned above, other studies were also submitted in order to provide supportive clinical data.

The CHMP considered that the study design and efficacy and safety outcomes/endpoints are acceptable for a phase 3, add-on study performed in paediatric subjects with PAH.

The primary objective of study LVHV Period 1 was to evaluate the efficacy of tadalafil compared with placebo in improving 6-minute walk distance (6MWD) from baseline to Week 24, as assessed in a subset of subjects ≥6 to <18 years of age who were developmentally capable of performing a 6MWD test. The 6MWD test is a functional tool who has been validated across several disorders. It should be noted that in children it has been shown to have significant variability in relation to several aspects such as parental training for 6MWT, patient willingness to outperform another attending child or concomitant medication which may increase or decrease the feeling of fatigue.

Selected dose for each paediatric weight cohort reflected expected exposures comparable to the approved 40 mg dose of tadalafil in adults, based on paediatric PK and safety data from study H6DMC-LVIG (LVIG) and the PK and safety data from the adult PAH development plan (pivotal study H6D-MC-LVGY [LVGY]), as reviewed by the Safety Monitoring Committee (SMC) and Sponsor.

As presented in the results section above, following initiation of LVHV study the MAH encountered significant study implementation challenges with respect to recruitment of paediatric patients with PAH for which SA was sought.

The difficulties in recruitment in study LVHV significantly altered the study design and conduct. Major changes were introduced regarding the number of patients enrolled (from 134 to 34) and change of primary endpoint from time to first clinical worsening (CW) to improvement in 6MWD from baseline to Week 24. CHMP recognises the difficulties associated with using CW as primary endpoint and acknowledged the need for change in the primary endpoint.

Efficacy data and additional analyses

In the initial applied indication, the MAH claimed in the wording of the indication that "Efficacy in patients ≥ 6 years in terms of improvement of exercise capacity has been shown in IPAH and PAH associated with surgical repair of at least 6-month duration of simple congenital systemic to pulmonary shunt". However, the number of patients with PAH associated with surgical repair is very scarce (only 2/17 subjects in tadalafil group, study LVHV). The MAH was requested to provide further efficacy or effectiveness data in this subgroup, either from other clinical trials or from observational studies or registries but was unable to provide further data. As a result, "PAH associated with surgical repair" aetiology was deleted from the proposed wording of the paediatric indication.

There were some numerical imbalances among baseline treatment arms (Table E03), but the imbalance appears to be conservative in the sense that tadalafil arm included older patients with longer disease duration.

The majority of subjects (n=25 [71.4%]) were in the heavy-weight cohort with the remainder (n=10 [28.6%]) in the middle-weight cohort. Due to a smaller sample size (35 subjects) than originally planned (134 subjects) in the study, balance of the stratification factors weight cohorts, PAH aetiology and type of concomitant ERA were not achieved among the treatment groups. It should be highlighted that there were a lack of enrolled patients in the light-weight (<25 kg) cohort of study LVHV and a lack of clinical data in children < 2 years which limits the ability to establish conclusions on the effect of Adcirca in younger patients.

Regarding the efficacy measures, the change in 6MWD from baseline to the end of period 1 (Week 24) in the tadalafil treatment group (60.48 meters) showed numerically higher increase in Least-Square (LS) mean 6MWD at Week 24 than placebo group (36.60 meters), with a placebo-adjusted LS mean treatment difference of 23.88 meters (80% CI, -14.25, 62.00). Although statistical significance testing was not performed between the tadalafil and placebo treatment groups due to the low sample size, a positive trend can be ascertained in terms of the primary efficacy endpoint. Nevertheless, when the change in 6MWD was also evaluated during the Period 2 (from Period 2 baseline to the end of Period 2 [Month 24; Visit 17]) as additional efficacy variable, the mean 6MWD decreased by 4.58 meters in the Pla-Tad group and 32.58 meters in Tad-Tad group. Mentioned differences on the improvement in exercise capacity may be due to the difficulties to interpret extension efficacy data where there is no control group. Given the known pharmacological effect of tadalafil on retinal function (i.e.: blue-tinted vision), the MAH was requested to provide information on whether blinding was truly met or not, i.e. whether investigators were asked to comment on their perception of which arm patients were allocated to in the period 1 of the trial. The MAH clarified that unblinding did not occur until the reporting database was validated and locked for final statistical analysis on 15 May 2019. Investigators were not asked to provide their perception on patient allocation to study arms during the study, and therefore it is not possible to fully ascertain that the investigators were not able to distinguish between placebo or active treatment based on patient symptomatology (such as colour perception). The impact on study results is, therefore, unknown.

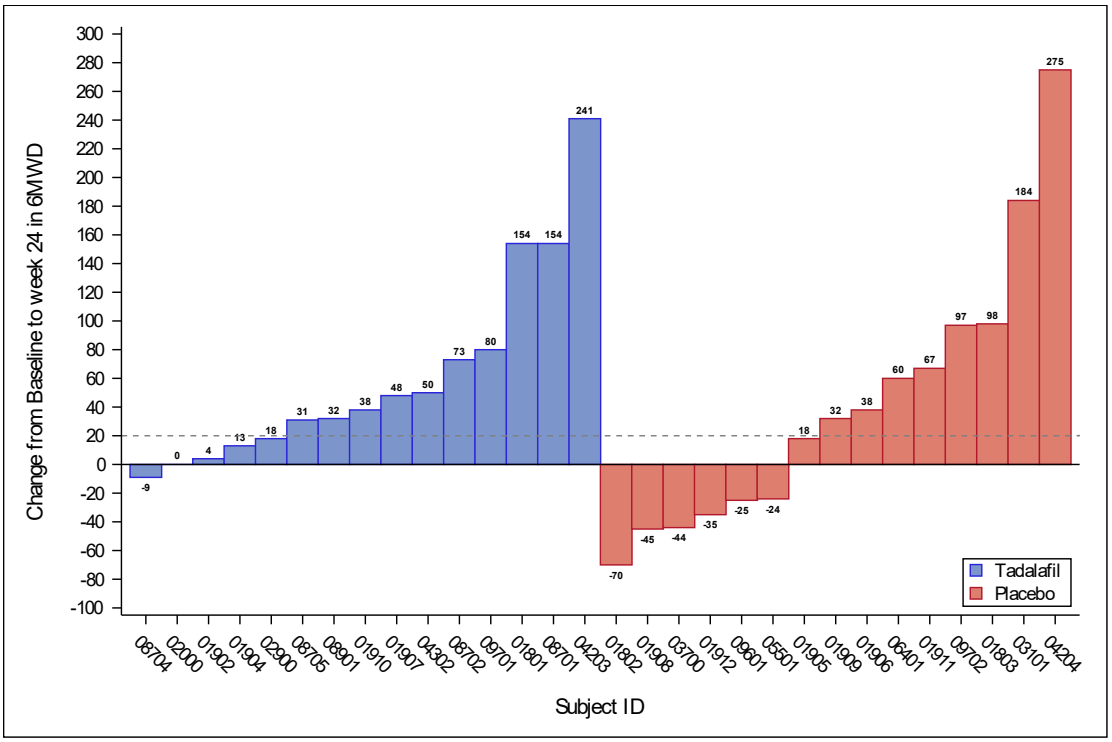
Regarding the mixed model used for the analysis of 6MWD, the MAH was requested to clarify why at week 24, the observed mean change in 6MWD compared to baseline was higher in the patients randomised to placebo compared to tadalafil (49.95m versus 37.04m) which implies a mean

difference of 12,91m to the detriment of tadalafil. However, the overall conclusion is that there is a model-based difference of 23.88m in favour of tadalafil. The MAH only explained that the LS mean changes came from the model but not why they are completely different from the changes calculated with the crude means. Therefore, the appropriateness of the mixed model is still questioned. The MAH was also requested to clarify whether the model is appropriate or that the LS mean difference found was driven by assumptions rather than the crude measurements, e.g. non-normality of the data or outliers (mean and median values tend to differ) implicit MAR imputation (more missingness in tadalafil). The MAH clarified that the small difference observed between crude mean change (20.07m) and LS mean change (23.88m) is due to the model adjustment for various covariates and factors in MMRM (treatment group, visit, baseline 6MWD, and treatment-by-visit interaction). The consistency between the crude estimate of the treatment effect and the model adjustment estimate suggested that the results from the MMRM model are consistent, appropriate, and valid.

Regarding safety, it is agreed that the data provided by the MAH do not point toward a different safety profile for children <2 years old. The applicant provided after request the post-marketing data provided by the MAH (7000 children 0-17 year exposed to Adcirca), divided in the same manner as the age groups for AEs, and therefore, the number of AEs relative the exposure could be evaluated and did not show any safety concern. The MAH committed to ensure that data on both exposure and AEs will be presented divided in age groups in the PSURs.

Three Bayesian MMRM sensitivity analyses were conducted: Bayesian MMRM analysis with diffuse prior and mixture prior using weight of 0.5 and 0.8. The analysis with mixture prior weight 0.8 resulted in the posterior mean difference of 27.13 m and 80% credible interval (4.94 to 42.73), which supports the positive trend suggested by the primary analysis in Study LVHV. Overall, the methods are endorsed as sensitivity analysis and no statistical conclusions should be made to justify the results since they are very limited, mainly due to the small sample size. Regardless, the favourable trend observed in 6MWD (point estimate of 23.88 meters in the main analysis and between 21.14m to 27.13 m in the Bayesian MMRM analyses) in study LVHV is considered to be of clinical relevance and is consistent with the 26 metres improvement observed in adults with tadalafil 40 mg (placebo-adjusted median increase in 6MWD). In order to further explore the clinical relevance of these results, the MAH was requested to conduct an ad-hoc analysis of responders, defined as an improvement by at least 20 metres at week 24 compared with baseline values. The trend for responders is in favour of tadalafil (10 vs 8; OR = 1.75; 95%CI: 0.40 to 7.66), where responders are defined as subjects with 6MWD improvement of at least 20 metres from baseline at Week 24. However, the analysis is limited by the small sample size. The magnitude of response was not different between treatment and placebo responders. In an ultra-rare disorder, it is considered to be more relevant to know which were the causes of individual behaviour for the different endpoints during period 1. As such, the MAH was requested to provide a by-subject waterfall figure to help clarifying these findings. By-subject waterfall plot for 6MWD shows that only one patient on tadalafil and six patients on placebo experienced a worsening in 6MWD from baseline to week 24. Therefore, the tadalafil improvement in 6MWD versus placebo is a mix of improvement in all but one patient in the tadalafil group, coupled with a worsening in 6MWD in almost half of patients in the placebo group.

Figure 13 - By-subject waterfall plot for 6MWD (percentage change from baseline to Week 24, Study LVHV). Double-blind treatment period. 6MW Analysis population



Abbreviation: 6MWD= 6-minute walk distance.

Clinical worsening cases were only recorded in five subjects who received tadalafil during the Period 2 of the study LVHV (1 new-onset syncope, 2 increase in ERA dose, 1 addition of new PAH-specific concomitant therapy, and 1 hospitalization for PAH progression). Any interpretation of these results both in Period and in Period 2 periods deems to be hampered by the low number of subjects included in the study. Therefore, study LVHV was considered as supportive of the efficacy of tadalafil in children. Approval of the indication in children was mainly based on an extrapolation exercise of the efficacy from adults showing similar exposure using PK/PD data analyses (see clinical pharmacology section).

The positive trend of potential efficacy of tadalafil versus placebo observed in the 6MWD as primary efficacy endpoint, seems to be supported by the majority of the additional efficacy measurements. All subtest domains and summary score on physical and psychological dimensions in CHQ-PF28 did not show a difference between tadalafil and placebo treatment group, with the exception of Global Health (treatment difference 7.26, 95% CI, -9.25 to 23.77).

The main supportive study (for effectiveness) is the Japanese post-marketing study (H6D-JE-TD01). The results obtained from this study further support the efficacy and safety data seen from the main trial.

In children younger than age 6 years, efficacy has been extrapolated based upon exposure-matching to the adult efficacious dose range. This is mainly due to limited availability of pharmacodynamic measures and lack of a suitable and approved clinical endpoint.

The MAH reviewed the disease course, response, and the PK/PD-relationships. It was agreed that the disease course in children less than 6 years is very similar to adults and, therefore, it can be expected a similar response based upon PK/PD relationships and exposure-matching. Extrapolation from adults based on exposure matching can be accepted.

Additionally, the applicant provided long-term effectiveness and safety data available from the Japanese PMS TD01 that included 50 children aged < 6 months and 70 children aged 6 months to 2 years old , 105 children aged ≥2 to less than 6 years and 166 children aged ≥ 6 years, for a total of 391 children . The observation period extended up to a maximum of 2 years. The number of children in study TD01 is considered quite relevant for this submission. The data available in children between 6 months and 2 years of age from study TD01 show similar changes in WHO FC compared to older children. It is reassuring that no children between 6 months and 6 years experienced worsening in WHO FC. In addition, survival rate in children aged 6 months to < 2 years was quite high: 97.6% (95%CI: 83.9 to 99.7) at one year and 93.1% (95%CI: 73.8 to 98.3) at 2 years. There were other positive trends regarding a numerical decrease from baseline in PAP, PVRI and TRPG, and an increase in cardiac index from baseline at all time points. Safety profile in children aged 6 months to 6 years was similar to that reported in the overall paediatric population of study TD01 (n = 391) (refer also to safety section of this report).

The applicant was also asked to send a text proposal for describing study TD01 in section 5.1 of the SmPC, but considering study limitations (single cohort, not randomisation by age or treatment group, presence of confounding factors like concomitant medications or other drugs for PAH, limited number of paediatric patients with pulmonary haemodynamic values and 6MW data only collected for paediatric patients capable of performing the 6MW test), the company did not propose to include study TD01 in section 5.1 of the SmPC, which is agreed.

It should be highlighted that most of the data in support of the use of Adcirca in the younger children i.e. under 2 years old comes from study TD01. However, this study presents some clear limitations (single cohort, no randomisation, presence of confounding factors like concomitant medications or other drugs for PAH, limited number of paediatric patients with pulmonary haemodynamic values and 6MW data only collected for paediatric patients capable of performing the 6MW test). No additional efficacy or effectiveness data in these subgroups for paediatric PAH patients was available. There was also no concordance between the doses used in study TD01 and the proposed doses to be administered in the younger patients.

Further refinement of the PBPK model was needed to provide a proposed dosing regimen where the exposure in paediatric patients match the adult exposures for which efficacy and safety has been established. The CHMP considered that despite the improvements introduced in the model insufficient clarifications were provided and important doubts still remained about the predictive capacity of the PBPK model to be able to establish a dose recommendation in population groups where there is no experimental evidence. Considering all the uncertainties above, it was not possible for CHMP to establish an efficacious and safe posology in children aged 6 months to < 2 years without the availability of some clinical PK data in this age subset. In addition, the lack of a PK study to assess the food effect was considered a major issue for establishing the posology in younger children. All these outstanding issues prevented from including children < 2 years in the indication. However, the CHMP considered that the available efficacy data allows to support the use of Adcirca in the treatment of PAH for children aged 2 years and older.

2.6.7. Conclusions on the clinical efficacy

A total of 51 paediatric patients aged from 2.5 to 17 years with PAH were treated with tadalafil in clinical trials (H6D-MC-LVHV, H6D-MC-LVIG). A total of 391 Japanese paediatric patients with PAH, from new-born to < 18 years, were treated with tadalafil in an observational post-marketing study (H6D-JE-TD01).

The main efficacy data of tadalafil in children with PAH was obtained from study LVHV which included 35 patients aged 6.2 to 17.9 years (median age of 14.2 years), coupled with a extrapolation exercise from adults (Bayesian MMRM sensitivity analysis).

In study LVHV, a total of 17 patients were treated once daily with ADCIRCA 20 mg (middle-weight cohort, ≥ 25 kg to < 40 kg) or 40 mg (heavy-weight cohort, ≥ 40 kg), and 18 patients were treated with placebo, for 24 weeks.

Regarding the efficacy measures, the change in 6MWD from baseline to the end of period 1 (Week 24) in the tadalafil treatment group (60.48 meters) showed numerically higher increase in Least-Square (LS) mean 6MWD at Week 24 than placebo group (36.60 meters), with a placebo-adjusted LS mean treatment difference of 23.88 meters (80% CI, -14.25, 62.00). Although statistical significance testing was not performed between the tadalafil and placebo treatment groups due to the low sample size, a positive trend can be ascertained in terms of the primary efficacy endpoint.

The positive trend of potential efficacy of tadalafil versus placebo observed in the 6MWD as primary efficacy endpoint, seems to be supported by the majority of the additional efficacy measurements.

In children younger than age 6 years, efficacy has been extrapolated based upon exposure-matching to the adult efficacious dose range. It is agreed by CHMP that the disease course in children less than 6 years is very similar to adults and, therefore, it can be expected a similar response based upon PK/PD relationships and exposure-matching. Extrapolation from adults based on exposure matching can therefore be accepted.

However, for children under 2 years old most of the data in support of the use of Adcirca in the younger children comes from study TD01 which has several limitations. Considering all the uncertainties highlighted in the discussion above, it was not possible for CHMP to establish an efficacious and safe posology in children aged 6 months to < 2 years without the availability of some clinical PK data in this age subset. In addition, the lack of a PK study to assess the food effect was considered a major issue for establishing the posology in younger children. All these outstanding issues prevented from including children < 2 years in the indication. However, the CHMP considered that the available efficacy data allows to support the use of Adcirca in the treatment of PAH for children aged 2 years and older.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The primary safety analysis presented in this application is based upon Period 1 of **Study LVHV**, a randomised, Phase 3, 2-period, add-on (i.e., in addition to the patient's current endothelin receptor antagonist [ERA]) study.

Supportive safety data from 3 additional studies are also presented.

- **Study LVHV** – Period 2 – open-label extension (OLE).
- **Study LVIG** – a clinical pharmacology multiple ascending dose study that assessed the pharmacokinetic (PK) and safety in a paediatric population with PAH.
- **Study TD01** – a post-marketing observational study that enrolled adult and paediatric patients with PAH who received tadalafil. The maximum duration of the observational period was 2 years.

- **Study LVJJ** – a Phase 3, global, multicentre, randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil in male paediatric patients with DMD.

Table 24 - Overview of Tadalafil Studies Included in the Safety Analyses

Study	LVHV	LVIG	TD01	LVJJ
Primary Objective	**Period 1**: To evaluate the efficacy of tadalafil compared with placebo in improving 6-minute walk distance (6MWD) from baseline to Week 24, as assessed in a subset of patients ≥6 to <18 years of age who were developmentally capable of performing a 6-minute walk (6MW) test. **Period 2**: To evaluate the long-term safety of tadalafil while providing continued access to tadalafil for paediatric patients with PAH who participated in Period 1.	**Period 1:** To characterise the PK of tadalafil in a paediatric population with PAH and establish an appropriate dose range for further clinical research. **Period 2**: To evaluate long-term safety of tadalafil, clinical worsening, and cardiopulmonary hemodynamic changes from baseline (Period 1) to the end of the 3-month treatment period in Period 2 assessed using echocardiography.	To evaluate the long-term safety and effectiveness of tadalafil in patients with PAH in Japanese patients.	To evaluate the efficacy and safety of tadalafil 0.3 mg/kg and 0.6 mg/kg orally once daily in boys with DMD who were already receiving treatment with corticosteroids.
Study Design	Phase 3, multicentre, randomised, 2-period (double-blind placebo-controlled [Period 1] and OLE [Period 2]), add-on study (in addition to the patient's	Phase 1b/2, multicentre, international, open-label, clinical pharmacology MAD study Enrolled patients from 2.5 years to <18 years of age, either naïve to PAH-specific therapy or receiving ERA.	Postmarketing observational study in Japan Enrolled patients from a wide age range (newborn to 94 years of age), (but for this analysis, only patients <18 years of age are	Phase 3, global, multicentre, randomised, double-blind, placebo-controlled, parallel, 3-arm study Enrolled boys from 7 to14 years of age

	ERA) Enrolled paediatric patients from ≥6 months to <18 years of age with WHO functional class II/ III.		included)	
Treatment Dose	Patients were stratified into 3 weight cohorts: heavy-weight (≥40 kg) middle-weight (≥25 kg to <40 kg) light-weight (<25 kg; no patients were enrolled in this cohort). The 20 or 40 mg dose for each weight cohort targeted exposures comparable to 40 mg exposures of tadalafil in adults. In Period 2, all patients received tadalafil once daily in an open-label fashion.	The doses selected 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. 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. In Period 2, the dose may have been increased (by the investigator), but did not exceed the maximum dose established for the weight cohort in Period 1.	Administration of tadalafil was conducted under real-world clinical practice. The investigators determined the dosage of tadalafil.	Patients were randomised to receive a tadalafil maximum dose of 20 mg or 40 mg in the 0.3-mg/kg/day and the 0.6 mg/kg/day dose groups, respectively, given as a combination of 2.5-, 5-, 10-, and 20-mg tablets administered orally once daily.
Number of Paediatric participants	**Period 1**: 35 (18 patients treated with placebo and 17 patients treated with tadalafil) **Period 2**: 32 patients	19 patients treated with tadalafil	391 patients treated with tadalafil	**Double-Blind period:** 330 (116 patients treated with placebo, 214 patients treated with tadalafil) The study was terminated post the double-blind period as the study did not achieve its primary

				endpoint.
Treatment Duration	**Period 1 (Double-blind period)**: 24-week (6-month) **Period 2 (OLE)**: 2-year (optional and open-label)	**Period 1 (PK/Safety/Tolerability)**: 10 weeks (QD) [~35days] for each dose [low and high]) in 2 sequential steps. **Period 2 (OLE)**: 2 years	The maximum duration of the observational period was 2 years.	**Screening**: 14 days **Double-Blind period**: 48 weeks **OLE (Period 1)**: 48 weeks

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Demographic and Other Characteristics of Study Population

Demographic and baseline patient characteristics for randomised patients are summarised below.

Study LVHV

Period 1

There were 16 male and 19 female patients in this study; the median age for the overall population was 14.2 years (ranged from 6.2 to 17.9 years) and 37.1% patients were less than 12 years of age. No patient was enrolled younger than 6 years in the study (in other words, there were no light-weight cohort patients enrolled).

The majority of patients were white (26 [74.3%]) and 7 (20%) of total enrolled patients were from sites in Europe (Germany, France, Poland) and Turkey.

PAH aetiologies were predominantly idiopathic PAH (74.3%: 61.1% on the placebo group and 88.2% on the tadalafil group) and PAH associated with persisting or recurrent pulmonary hypertension (PH) after repair of a congenital systemic to pulmonary shunt (25.7%; 38.9% on the placebo group and 11.8% on tadalafil group). The majority of patients were in WHO functional class II (80%).

The majority of patients (25 [71.4%]) were in the heavy-weight cohort with the remainder (10 [28.6%]) in the middle-weight cohort.

Baseline clinical and disease characteristics for the Primary Analysis and 6MW Populations included the same patients and were therefore identical, as all patients in the primary analysis population were able to provide 6MW data. The majority of patients (94.1%) were taking bosentan as concomitant ERA.

Period 2

There were 14 male and 18 female patients who continued to Period 2; the median age for the overall population was 14.4 years (ranged from 6.2 to 17.9 years). The majority of patients were white 24 (75%) and 7 (21.9%) were from Europe. The majority of patients (23 [71.9%]) were in the heavy-weight group with the remainder (9 [28.1%]) in the middle-weight group. Pulmonary arterial hypertension aetiologies were predominantly idiopathic PAH (n=25; 78.1%) and PAH associated with persisting or recurrent PH after repair of a congenital systemic to pulmonary shunt (n=7; 21.9%); the majority of patients had WHO functional class II (n=25; 78.1%).

Study LVIG

Nineteen paediatric patients with PAH, 6 male and 13 female, aged 2.5 to 17 years at the time of enrolment participated in Period 1. One patient in the middle-weight cohort was 17 years, 11.5 months at the time of enrolment. Twelve of the 19 patients (63%) were enrolled from Europe (France, United Kingdom, Poland, and Spain).

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

Dose and duration of exposure

In Period 1 of Study LVHV, tadalafil QD dose was 40 mg for the heavy-weight cohort and 20 mg for the middle-weight cohort. In total, 17 patients received tadalafil and 18 patients received placebo during Period 1. The mean and median cumulative number of doses taken during Period 1 was 151.0 and 161.0 (range 43.0 to 188.0) for tadalafil and 153.4 and 165.0 (range 27.0 to 188.0) for placebo. The mean days of exposure for Period 1 was 170.4 (SD =16.00) for tadalafil and 158.4 (SD = 39.49) for placebo.

In Period 2, all patients (32) received tadalafil QD dose of 20 mg in middle-weight cohort and 40 mg in heavy-weight cohort. The mean and median cumulative number of tadalafil doses taken during Period 2 in Tad-Tad group were 597.9 and 679.5 (range 101.5 to 746.5) and in Pla-Tad group were 664.5 and 685.3 (range 476.0 to 747.0). The mean days of exposure for Period 2 was 656.0 (SD =187.19) for Tad-Tad group and 708.6 (SD = 78.97) for Pla-Tad group. Overall, 26 patients completed the 24-month follow-up.

In Study LVIG, the mean days of exposure to tadalafil were similar across weight cohorts for Period 1 (70.67, 66.14 and 69.67 days for the light-, medium- and heavy-weight cohorts, respectively). Overall mean days of exposure to tadalafil were similar across weight cohorts (761.17, 673.29 and 659.00 days for the light-, middle- and heavy-weight cohorts, respectively).

In Study LVJJ of the 331 randomized patients, 330 received a dose of study medication. The overall mean age was 9.6 years and the majority of patients were white (79.2%). Mean duration of exposure was 333.3 days in the placebo group, 335.9 days in the tadalafil 0.3 mg/kg group, and 330.2 days in the tadalafil 0.6 mg/kg group. In the open-label analysis set, mean exposure duration during the OLE period was 244.1 days in the tadalafil 0.3 mg/kg group and 233.5 days in the tadalafil 0.6 mg/kg group. The patients were also receiving corticosteroids throughout the study and 96.4% received $\geqslant$ 1 concomitant medication in addition to corticosteroids.

In the observational Study TD01, the maximum exposure was 2 years.

2.6.8.2. Adverse events

1) Study LVHV

a) Period 1 (Double-Blind Treatment)

Table 25 - Overview of Adverse Events - Double-Blind Treatment Period Primary Analysis Population

Adverse Events[a]	Placebo N=18 n(%)	Tadalafil N=17 n(%)	Total N=35 n(%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to discontinuation	1 (5.6)	1 (5.9)	2 (5.7)
Treatment-emergent adverse events[b]	8 (44.4)	15 (88.2)	23 (65.7)
Treatment-related adverse events[c]	1 (5.6)	8 (47.1)	9 (25.7)
Procedure-related adverse events	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE = adverse events; MedDRA: Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population;

n = number of patients per category; SAE = serious adverse events.

The Primary Analysis Population included all patients who received at least 1 dose of the study medication according to the randomised treatment. All percentages are based on the Primary Analysis Population.

a Patients were counted in more than 1 category, but only once per category per patient.

b Treatment-emergent adverse events are defined as events that first occurred or worsened in severity after baseline (Visit 2).

c Treatment-related adverse events are defined as events that are determined by the investigator to be possibly related to a study drug. Some AEs indicated as treatment-related may not be treatment emergent (in cases where an equally or more severe event with the same preferred term is present at baseline). MedDRA Version 21.1.

- ***Treatment-Emergent Adverse Events (TEAEs)***

There were 23 subjects who reported at least 1 TEAE, (8/18) (44.4%) subjects in the placebo group and 15/17 (88.2%) subjects in the tadalafil group reported at least 1 TEAE during Period 1. The most common TEAEs, occurring in ≥2 patients in tadalafil-treated patients, were headache (29.4%, tadalafil; 11.1%, placebo), upper respiratory tract infection (17.6%, tadalafil; 5.6%, placebo), influenza (17.6%, tadalafil; 0.0%, placebo), arthralgia (11.8%, tadalafil; 5.6%, placebo), and epistaxis (11.8%, tadalafil; 5.6%, placebo). All of the AEs in the tadalafil group were mild or moderate in severity.

- ***Treatment-Related Adverse Events***

Table 26 - Treatment-Related Adverse Events, <u>Double-Blind Treatment Period,</u> Primary Analysis Population

Preferred Term	Placebo (N=18) n	(%)	Tadalafil (N=17) n	(%)	Total (N=35) n	(%)
Patients with > = 1 Treatment-Related AE	1	(5.6)	8	(47.1)	9	(25.7)
Headache	1	(5.6)	4	(23.5)	5	(14.3)
Back pain	0	(0.0)	1	(5.9)	1	(2.9)
Flushing	0	(0.0)	1	(5.9)	1	(2.9)
Hepatic enzyme increased	0	(0.0)	1	(5.9)	1	(2.9)
Hypotension	0	(0.0)	1	(5.9)	1	(2.9)
Menorrhagia*b	0	(0.0)	1	(10.0)	1	(5.3)
Rash	0	(0.0)	1	(5.9)	1	(2.9)
Somnolence	0	(0.0)	1	(5.9)	1	(2.9)
Spontaneous penile erection*a	0	(0.0)	1	(14.3)	1	(6.3)

Abbreviations: AE = adverse event; N = number of patients in the analysis population; n = number of patients with at least one treatment-related adverse event per category.

The Primary Analysis Population includes all patients who received at least 1 dose of the study drug according to the randomized treatment. All percentages are based on the Primary Analysis Population.
Preferred terms are ordered by decreasing frequency in the tadalafil group.
[a] Denominator adjusted because gender-specific event for males: N=9 (Placebo), N=7 (Tadalafil), N=16 (Total).
[b] Denominator adjusted because gender-specific event for females: N=9 (Placebo), N=10 (Tadalafil), N=19 (Total).
Note: Treatment-related adverse events are defined as events that are determined by the investigator to be possibly related to astudy drug. Some AEs indicated as treatment-related may not be treatment emergent (in cases where an equally or more severe event with the same preferred term is present at baseline).

b) ***<u>Period 2 (Open-Label Treatment Period)</u>***

Table 27 - Overview of Adverse Events Open-Label Treatment Period

Adverse Events[a]	[Pla-Tad][b]	[Tad-Tad][b]	Total

	N=16 n(%)	N=16 n(%)	N=32 n(%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	4 (25.0)	1 (6.3)	5 (15.6)
Adverse events leading to discontinuation	0 (0.0)	1 (6.3)	1 (3.1)
Treatment-emergent adverse events[c]	11 (68.8)	12 (75.0)	23 (71.9)
Treatment-related adverse events[d]	2 (12.5)	3 (18.8)	5 (15.6)
Procedure-related adverse events	1 (6.3)	0 (0.0)	1 (3.1)

Abbreviations: AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the primary analysis population, who entered the open-label treatment period; n = number of patients per category; SAE = serious adverse events.

All percentages are based upon the number of patients who entered the open-label treatment period.

a Patients may be counted in more than 1 category, but only once per category per patient.

b Treatment: Pla-Tad = Placebo in Period 1 and tadalafil in Period 2; Tad-Tad = Tadalafil in Period 1 and 2.

c Treatment-emergent adverse events are defined as events that first occurred or worsened in severity after double-blind period (Visit 9).

d Treatment-related adverse events are defined as events that are determined by the investigator to be possibly related to a study drug. Some AEs indicated as treatment-related may not be treatment emergent (in cases where an equally or more severe event with the same preferred term is present at baseline).

Note: Adverse events are presented from beginning of Period 2 (open-label treatment period) to end of Period 2, using Visits 1 to 9 as the baseline period for determining treatment-emergent.

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- ***Treatment-Emergent Adverse Events***

  The most common TEAEs occurring in ≥2 patients in any group, were headache (18.8%, Tad-Tad group; 12.5%, Pla-Tad group), dizziness (18.8%, Tad-Tad group; 6.3%, Pla-Tad group), nasopharyngitis (18.8%, Tad-Tad group; 6.3%, Pla-Tad group), vomiting (18.8%, Tad-Tad group; 0.0%, Pla-Tad group), abdominal pain upper (12.5%, Tad-Tad group; 0.0%, Pla-Tad group), arthralgia (12.5%, Tad-Tad group; 0.0%, Pla-Tad group), pharyngitis (12.5%, Tad-Tad group; 0.0%, Pla-Tad group), upper respiratory tract infection (12.5%, Tad-Tad group; 0.0%, Pla-Tad group), acute sinusitis (0.0%, Tad-Tad group; 12.5%, Pla-Tad group), anaemia (0.0%, Tad-Tad group; 12.5%, Pla-Tad group), and rhinitis (0.0%, Tad-Tad group; 12.5%, Pla-Tad group).

- ***Treatment-Related Adverse Events***

  Procedure-related event (anxiety) was reported in 1 subject in the Pla-Tad group.

Table 28 - Treatment-related AEs, period 2 of study LVHV

Preferred Term	Pla-Tad [a] (N=16) n	(%)	Tad-Tad [a] (N=16) n	(%)	Total (N=32) n	(%)
atients with > = 1 Treatment-Related AE	2	(12.5)	3	(18.8)	5	(15.6)
Dizziness	1	(6.3)	1	(6.3)	2	(6.3)
Excessive masturbation	0	(0.0)	1	(6.3)	1	(3.1)
Exercise tolerance decreased	0	(0.0)	1	(6.3)	1	(3.1)
Headache	1	(6.3)	1	(6.3)	2	(6.3)
Menorrhagia*c	0	(0.0)	1	(10.0)	1	(5.6)
Pain in extremity	0	(0.0)	1	(6.3)	1	(3.1)
Spontaneous penile erection*b	1	(12.5)	0	(0.0)	1	(7.1)

2) Study LVIG

Table 29 - Overview of Adverse Events by Weight Cohort: Safety Population

	Weight Cohort						Total (N = 19)	
	Light (<25 kg) (N = 6)		Middle (25 to <40 kg) (N = 7)		Heavy (≥40 kg) (N = 6)			
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Overall[a]								
AEs	76	6 (100.00)	77	7 (100.00)	83	6 (100.00)	236	19 (100.00)
TEAEs	64	6 (100.00)	65	7 (100.00)	72	6 (100.00)	201	19 (100.00)
Deaths	0	0 (0.00)	1	1 (14.29)	1	1 (16.67)	2	2 (10.53)
SAEs	4	1 (16.67)	9	4 (57.14)	5	3 (50.00)	18	8 (42.11)
AEs leading to study drug discontinuation	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)
AEs related to study drug	10	3 (50.00)	7	1 (14.29)	1	1 (16.67)	18	5 (26.32)
AEs related to study procedure	0	0 (0.00)	2	1 (14.29)	1	1 (16.67)	3	2 (10.53)
Period 1								
AEs	28	5 (83.33)	37	6 (85.71)	25	5 (83.33)	90	16 (84.21)
TEAEs	16	5 (83.33)	25	6 (85.71)	14	5 (83.33)	55	16 (84.21)
Deaths	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)
SAEs	0	0 (0.00)	1	1 (14.29)	1	1 (16.67)	2	2 (10.53)
AEs leading to study drug discontinuation	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)
AEs related to study drug	6	2 (33.33)	6	1 (14.29)	1	1 (16.67)	13	4 (21.05)
AEs related to study procedure	0	0 (0.00)	2	1 (14.29)	1	1 (16.67)	3	2

								(10.53)
Period 2								
AEs	62	6 (100.00)	56	6 (100.00)	73	6 (100.00)	191	18 (100.00)
TEAEs	38	5 (83.33)	38	6 (100.00)	56	6 (100.00)	132	17 (94.44)
Deaths	0	0 (0.00)	1	1 (16.67)	1	1 (16.67)	2	2 (11.11)
SAEs	4	1 (16.67)	8	3 (50.00)	4	3 (50.00)	16	7 (38.89)
AEs leading to study drug discontinuation	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)
AEs related to study drug	5	3 (50.00)	4	1 (16.67)	0	0 (0.00)	9	4 (22.22)
AEs related to study procedure	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)

Abbreviations: AE = adverse event; N = number of patients in each cohort; n = number of patients with non-missing values for the indicated variable or response in each cohort for each period; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Percentages are based on the number of patients in each cohort. Patients are counted once in each category; events are counted once for each unique SOC, preferred term, onset date, and patient. Period 1 TEAE is defined as period 1 AE that first occurred or worsened (increased in severity) after first dose of study drug in Period 1. Period 2 TEAE is defined as Period 2 AE that first occurred or worsened (increased in severity) after first dose of study drug in Period 2.

[a] Overall TEAE includes AE during the course of study that first occurred or worsened (increased in severity) after first dose of study drug in Period 1.

- ***Treatment-Emergent Adverse Events***

  During period 1he most frequent TEAE was pyrexia. During Period 2, the most frequent TEAEs (occurring in >2 patients) were headache, vomiting, nasopharyngitis, gastroenteritis, angina pectoris, and PAH.

- ***Treatment-Related Adverse Events***

  Headache was the most commonly reported TEAE considered by the investigator to be possibly related to tadalafil. During period 1 pain in extremity, swelling of eyelid, swelling face, urticaria, constipation, faeces soft, abdominal pain, pruritus, rash, and vasodilation were reported as TEAEs considered related by the investigator. Abdominal pain, rash, and decreased appetite were reported during Period 2.

3) <u>Study LVJJ</u>

In the double-blind period, there were no significant differences between the tadalafil 0.3 mg/kg group and placebo or between the tadalafil 0.6 mg/kg group and placebo in the proportion of patients who reported ≥1 SAE, TEAE, study disease-related AE, procedure-related AE, adjunctive treatment-related AE (i.e., corticosteroid therapy), or who discontinued due to AE. There was a significant difference between the tadalafil 0.6 mg/kg group and placebo in the proportion of patients who experienced ≥1 AE considered possibly related to study drug by the investigator (59.8% versus 41.4%; p=.006). In the OLE, the proportion of patients reporting ≥1 TEAE was 56.0% in the tadalafil 0.3 mg/kg group and 61.2% in the tadalafil 0.6 mg/kg group. Adverse events considered to be related to study drug by the investigator were reported in 11.3% of patients in the tadalafil 0.3 mg/kg group and 13.3% of patients in the tadalafil 0.6 mg/kg group. Approximately, one-fourth of patients reported AEs considered by the investigator to be related to study disease (26.7% of patients in each group) and 6.7% had AEs assessed by the investigator as being related to corticosteroid therapy (3.3% tadalafil 0.3 mg/kg; 9.7% tadalafil 0.6 mg/kg).

The overall safety profile in Study LVJJ was generally consistent with the known safety profile of tadalafil and the paediatric DMD study population receiving corticosteroids

2.6.8.3. Serious adverse event/deaths/other significant events

- ***Deaths (Study LVHV, LVIG and LVJJ)***

No deaths were reported in the Study LVHV (Period 1 or Period 2). In Study LVIG, there were 2 deaths, both in Period 2. Neither death was related to tadalafil as judged by the investigator (in the first case the cause of death was reported as postoperative cardiac arrest after a Potts shunt procedure and the second patient died due to cardiac failure). No deaths were reported in Study LVJJ.

- ***Serious Adverse Events***

1) Study LVHV

a) Period 1 (Double-Blind Treatment)

There were no SAEs in Period 1 of LVHV.

b) Period 2 (Open-Label Treatment Period)

A total of 5 patients experienced ≥1 SAE (4 patients in the Pla-Tad group and 1 patient in the Tad-Tad group). None of them were considered to be related to tadalafil as judged by the investigator.

Table 30 - Serious Adverse Events - Open-Label Treatment Period

Preferred Term	Pla-Tad [a] (N=16) n (%)	Tad-Tad [a] (N=16) n (%)	Total (N=32) n (%)
Patients with >= 1 SAE	4 (25.0)	1 (6.3)	5 (15.6)
Acute right ventricular failure	0 (0.0)	1 (6.3)	1 (3.1)
Anaemia	1 (6.3)	0 (0.0)	1 (3.1)
Gastroenteritis	1 (6.3)	0 (0.0)	1 (3.1)
Haemoptysis	1 (6.3)	0 (0.0)	1 (3.1)
Pneumonia	1 (6.3)	0 (0.0)	1 (3.1)

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Abbreviations: N = number of patients in the primary analysis population, who entered the open-label treatment period; n = number of
patients with at least one serious adverse event per category; SAE = serious adverse event.

All percentages are based on the number of patients who entered the open-label treatment period. Preferred terms are ordered by decreasing frequency in the Tad-Tad group.
[a] Treatment: Pla-Tad = Placebo in period 1 and Tadalafil in period 2; Tad-Tad = Tadalafil in period 1 and 2
[b] Denominator adjusted because gender-specific event for males: N=8 (Pla-Tad), N=6 (Tad-Tad), N=14(Total).
[c] Denominator adjusted because gender-specific event for females: N=8 (Pla-Tad), N=10 (Tad-Tad), N=18 (Total).
MedDRA Version 24.0

2) Study LVIG

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.

3) Study LVJJ

During the double-blind treatment period, fifteen patients (4.5%) reported ≥1 SAE. The proportion of patients reporting ≥1 SAE was not significantly different between either of the tadalafil treatment groups and placebo. The most common SAEs reported in the study were fall (n=3), femur fracture

(n=2), and tendinous contracture (n=2). During the OLE, 6 patients in the tadalafil 0.3 mg/kg group reported a total of 7 SAEs and 9 patients in the tadalafil 0.6 mg/kg group reported a total of 12 SAEs. Across both tadalafil treatment groups, fall and femur fracture were the only individual SAEs reported by more than 1 patient during the OLE (2 patients each).

- ***Adverse Events of Special Interest***

The AESIs included in this submission (hypotension, priapism, hearing abnormality, visual abnormality and uterine haemorrhage) were selected based upon PDE5 inhibitors class risks, on known risks for tadalafil use in adults (including the potential and important risks included in the EU Risk Management Plan [RMP]) and on additional topics of interest to the PDCO regarding PAH (described in the PIP).

In Study LVHV (Periods 1 and 2), 6 patients reported AESIs.

During Period 1, there was 1 moderate hypotension that did not lead to treatment discontinuation and resolved, while tadalafil treatment continued. This event was considered a treatment-related AE by the investigator. Seven other AEs possibly related to hypotension (dizziness, presyncope, syncope, loss of consciousness) were reported in 7 patients. However, of all of these AEs, 5 were considered to be related to PAH or CW by the study investigator. In the OLE period (Period 2), 2 of the dizziness events were considered treatment-related but no hypotension or decrease in BP were reported. The review of these 7 cases did not conclude these were hypotension-related events. No hypotension events occurred in Period 2.

Uterine bleeding was described in 4 patients (6 events) receiving tadalafil. One patient in the tadalafil group from Period 1 experienced uterine bleeding and 4 patients experienced 5 events of uterine bleeding in Period 2; 2 patients in Pla-Tad group and 2 patients in Tad-Tad group. Three events were mild, 2 events were moderate and 1 event was serious needing a blood transfusion (this case was considered a treatment-related AE). All cases of uterine bleeding resolved while patients remained on study medication.

In Period 2, one case of mild visual abnormality was reported 80 days after the onset of dosing; the event resolved the same day. The event was not considered to be related to tadalafil as judged by the investigator.

There were no patients with priapism. Two patients experienced spontaneous intermittent penile erections (1 on tadalafil group during Period 1 and 1 on Pla-Tad group during Period 2) that resolved spontaneously. No hearing abnormalities were reported in the study.

In Study LVIG (Period 1 and 2), there was 1 mild orthostatic hypotension not considered treatment-related AE that recovered on the same day. Other AEs possibly related to hypotension (dizziness, presyncope, syncope and loss of consciousness) were reported in 5 patients, all considered to be related to PAH. None of them were classified as treatment-related AEs. The review of these 5 cases did not conclude these were hypotension-related events.

In addition, there was 1 mild uterine bleeding not considered treatment-related AE that recovered without treatment and 1 moderate visual abnormality not considered treatment-related AE that recovered in the same day. No hearing abnormalities or priaprism were reported.

2.6.8.4. Laboratory findings

1) Study LVHV

-Clinical Laboratory Evaluations during Period 1 (Double-Blind Placebo-Controlled):

Safety laboratory tests (including chemistry, hematology, coagulation and urinalysis) were performed during Period 1 of the study only. There were no clinically relevant mean changes from baseline to end of study (Period 1) in laboratory parameters in both placebo and tadalafil treatment groups.

No patients in the tadalafil and placebo group met the criteria of having an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) more than 3-fold the upper limit of normal (ULN) and having a total bilirubin more than 1.5-fold the ULN postbaseline.

A total of 9 patients (3 on tadalafil and 6 on placebo), and 3 patients (2 on tadalafil and 1 on placebo) had shifts from normal to abnormal range in urine protein and blood occult, respectively. One patient on placebo had glucose present in urine at the end of the study.

- Vital Signs, Physical Findings, and Other Observations Related to Safety

The following key findings for Period 1 and Period 2 were observed:

- The mean and median change in weight was ≤1 kg in both treatment groups at the endpoint of Period 1. The mean increase in height at the endpoint of Period 1 was approximately 0.75 cm difference between the 2 treatment groups.
- During Period 2, mean (median) weight increases from baseline (last non-missing value before or at Visit 2) to endpoint (Visit 17) in all patients were 5.73 (4.95) kg and 5.16 (3.10) kg in the Pla-Tad and Tad-Tad groups, respectively. In change from baseline, there was a difference of 3.71 cm in mean increase in height at the endpoint of Period 2 between the 2 treatment groups. The difference could be partially due to difference in age-related growth curve expectations and gender differences between the groups, i.e., more male patients in the Pla-Tad group (n=8, 50%) compared to Tad-Tad group (n=6, 37.5%).
- Mean decreases from baseline in supine systolic blood pressure of ≤3.00 mm Hg and median changes from 0 to -3.00 mm Hg were observed in the placebo group. In the tadalafil group, mean increases in supine systolic blood pressure ranging from 0.35 to 7.07 mm Hg and median increases no larger than 5.00 mm Hg were observed throughout Period 1.
- Mean and median increases or decreases from baseline in supine diastolic blood pressure no larger in magnitude than 3.00 mm Hg were observed in the placebo group. In the tadalafil group, mean increases no larger than 1.20 mm Hg and median changes ranging from 0 to 1.00 mm Hg were observed.
- The mean and median increases in supine HR no larger than 4 bpm were observed in the placebo group whereas mean increases or decreases no larger in magnitude than approximately 6 bpm were observed in the tadalafil group.
- During Period 1, all 15 subjects in the placebo group had normal right and left eye results at Week 24, including 2 subjects who had an abnormal not clinically significant (NCS) result at baseline.
- Out of 13 subjects in the tadalafil group, 12 had normal results at baseline and at Week 24, and the remaining 1 subject with normal baseline had an abnormal NCS result in both the right and left eyes at Week 24, and had a normal examination at Year 2 (Visit 17).
- There were no AEs related to ECG findings observed in the study.
- There were no clinically significant trends observed from inhibin B, Tanner score, and IQ testing evaluations based on the available data.

- No clinical information of relevance was provided as regards of intellectual ability and cognitive function assessments since the submitted summary statistics were based on only 1 to 4 subjects aged ≥6 years 0 months to 16 years 11 months.

2) Study LVIG

There were neither patterns nor trends in clinical laboratory evaluations, vital sign measurements or electrocardiogram readings indicating adverse effects related to tadalafil treatment in the Study LVIG. Inhibin B was monitored in male patients only. A baseline sample was collected on Day 1 of Period 1 and at Years 1 and 2 of Period 2. Inhibin B values increased over time compared to baseline values in male patients both <9 and ≥9 years of age indicating normal testicular function.

2.6.8.5. Safety in special populations

Intrinsic factors such as different age groups (in adults), gender and renal impairment are described in the Summary of Product Characteristics (SmPC).

Ethnical differences were evaluated comparing Japanese and non-Japanese data from adult PAH Study LVIG. Japanese subset showed similar trends in efficacy and safety to the whole population. There is no scientific evidence to support that Japanese paediatric patients are different enough that safety data are not informative to clinicians.

The Study LVIG divided patients by different weight subgroups, but the groups did not differ in safety profile.

Table 31 - Treatment-Emergent Adverse Events by Preferred Term and Weight Cohort: Events Occurring in ≥ 2 Patients (Overall): 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 (%)**
Number (%) of Patients with a TEAE	6 (100.00)	7 (100.00)	6 (100.00)	19 (100.00)
Headache	2 (33.33)	2 (28.57)	2 (33.33)	6 (31.58)
Nasopharyngitis	2 (33.33)	1 (14.29)	2 (33.33)	5 (26.32)
Pyrexia	2 (33.33)	2 (28.57)	1 (16.67)	5 (26.32)
Vomiting	2 (33.33)	2 (28.57)	1 (16.67)	5 (26.32)
Gastroenteritis	3 (50.00)	0	1 (16.67)	4 (21.05)
Pulmonary arterial hypertension	1 (16.67)	1 (14.29)	2 (33.33)	4 (21.05)
Angina pectoris	1 (16.67)	0	2 (33.33)	3 (15.79)
Bronchitis	2 (33.33)	1 (14.29)	0	3 (15.79)
Nausea	1 (16.67)	1 (14.29)	1 (16.67)	3 (15.79)
Oropharyngeal pain	0	3 (42.86)	0	3 (15.79)
Pain in extremity	0	2 (28.57)	1 (16.67)	3 (15.79)
Rhinorrhoea	2 (33.33)	0	1 (16.67)	3 (15.79)
Abdominal pain	1 (16.67)	1 (14.29)	0	2 (10.53)
Anxiety	0	1 (14.29)	1 (16.67)	2 (10.53)
Cough	0	1 (14.29)	1 (16.67)	2 (10.53)
Decreased appetite	1 (16.67)	1 (14.29)	0	2 (10.53)
Diarrhoea	1 (16.67)	0	1 (16.67)	2 (10.53)
Ear infection	1 (16.67)	1 (14.29)	0	2 (10.53)
Ear pain	0	0	2 (33.33)	2 (10.53)
Ecchymosis	2 (33.33)	0	0	2 (10.53)
Epistaxis	1 (16.67)	1 (14.29)	0	2 (10.53)
Gastroesophageal reflux disease	1 (16.67)	1 (14.29)	0	2 (10.53)
Iron deficiency anaemia	0	1 (14.29)	1 (16.67)	2 (10.53)
Rash	1(16.67)	1 (14.29)	0	2 (10.53)
Respiratory tract infection	0	0	2 (33.33)	2 (10.53)
Syncope	1(16.67)	1 (14.29)	0	2 (10.53)
Upper respiratory tract infection	1 (16.67)	0	1 (16.67)	2 (10.53)
Urticaria	0	2 (28.57)	0	2 (10.53)
Viral infection	0	1 (14.29)	1 (16.67)	2 (10.53)

No new data regarding renal impairment or hepatic impairment was presented.

2.6.8.6. Safety related to drug-drug interactions and other interactions

With the exception of Studies LVHV and LVIG, all drug interaction studies have been conducted in adults for the original marketing application.

Based on the adult drug-drug interaction studies, nitrates are contraindicated in patients taking tadalafil due to risk of hypotension. In patients, who are taking alpha blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients. The combination of tadalafil and doxazosin is not recommended. There are no known interactions of tadalafil with other medications.

2.6.8.7. Discontinuation due to adverse events

Study LVH

a) Period 1(Double-Blind Treatment) (Primary safety analysis)

There were no discontinuations due to AEs in Period 1 of LVHV. Two patients were initially discontinued in Period 1 of Study LVHV due to events of clinical worsening (CW) reported by principal investigator (as per protocol); however, the events were later adjudicated by the Clinical Endpoint Committee (CEC) as they were not considered CW, and the patients continued in Period 2.

b) Period 2 (Open-Label Treatment Period)

One subject discontinued due to an AE (headache) in the Tad-Tad group. This 17.5-year-old white female received the first dose of tadalafil (40 mg) in Period 2. The subject had idiopathic PAH and received concomitant bosentan. On day 275 of Period 2, the patient experienced dizziness, decreased exercise tolerance, headache; all of moderate severity. All events were reported as resolved on Day 72 after onset of the events.

2) Study LVIG

There were no patient discontinuations due to AEs in any weight cohort in any Period.

3) Study LVJJ:

In Study LVJJ, during the double-blind Period, 5 patients (1.5%) discontinued because of an AE: 2 patients in the placebo group, 2 patients in the tadalafil 0.3 mg/kg group (adverse events of epistaxis and myocarditis), and 1 patient in the tadalafil 0.6 mg/kg group (adverse event of urticaria). One patient discontinued from the OLE because of a TEAE of dysesthesia that was mild in severity.

2.6.8.8. Post marketing experience

As of 30 September 2020, approximately 84.6 million patients worldwide have been exposed to tadalafil. Adcirca data is based upon age and gender distribution data from the MarketScan database.

Reviews of this off-label use in paediatrics have been provided in previous PSURs and no new signals were identified.

Cumulatively throughout 15 October 2020, Lilly's safety database captured 1147 AEs from 423 paediatric postmarketing reports (<18 years old). Of these 423 cases, 225 (53.2%) were female, 188 (44.4%) were male and the gender was unknown in 10 cases (2.4%).

The majority of reported cases were between 2- and 18-years old.

Table 32 - Estimated Age and Gender Distributions of Cumulative Postmarketing Patient Exposure for Adcirca

Age Group	n	%
0 days to <28 days (Newborn Infants)	1	0.2 %
28 days to <24 months (Infants & Toddlers)	49	11.6 %
2 years to <12 years (Children)	206	48.7 %
12 years to <18 years (Adolescents)	167	39.5 %

Abbreviation: n = number of cases

Of these cases, 253 (59.8%) were spontaneous reports, 154 (36.4%) from noninterventional postmarketing studies (136 AEs and SAEs from Study TD01), 9 (2.1%) from literature and 7 (1.7%) from regulatory authority. Regarding seriousness, 150 cases were reported as SAEs (35.5%) and 273 were reported as nonserious (64.5%). In total, 29 cases (6.9%) had fatal outcome.

The most frequently reported SAEs were PH, pneumonia, PAH, syncope, hypotension and cardiac failure, most of them are related to PAH's symptoms. Of the 29 cases with fatal outcome, 16 were from Study TD01 (described below). Of the remaining 13 cases, 7 cases were reported by health care providers (HCPs), 2 were from literature and 4 were reported by consumers. Of the 7 cases reported by HCPs, in 3 the event was considered not related to tadalafil, in 3 the relatedness assessment was not provided and in 1 case the nurse considered the event possibly related to tadalafil. The 2 cases from literature suspected of tadalafil relatedness (1 suicide case and 1 PAH case with clinical worsening).

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

The data presented show a consistent safety profile with the already known safety profile of tadalafil in adult patients with PAH. Data from LVHV and LVIG, conducted as a part of the PIP, do not raise any major safety concern and neither appears to emerge from the post-marketing data provided, which can be considered supportive to data from clinical trials.

There is a limited sample size included in clinical trials (51 PAH patients treated with tadalafil). Although, it is accepted that due the rarity of the disease, the safety database may be quite limited, some limitations regarding the provided sample size were considered relevant:

There is a lack of controlled data from patients <6 years and only data from 17 patients aged >6 years are controlled. The observational Study TD01 is the only study that provides safety data in patients <2 years old, while safety data for patients ≥2 years and <6 years also comes from study TD01 and the open label of Phase 1b/2 LVIG Study. Although data initially provided did not suggest a worse safety profile in the lower age-subset of patients, robustness of such data were limited.

To achieve a more detailed and comparative view of the safety profile of tadalafil by age subgroup, the MAH was requested to provide a summary of all safety data available in children <6 years and <2 years, to discuss about potential safety issues and to comment on the need to ensure the collection of post-marketing data in these age subsets.

In this regard, the MAH has provided the analysis of safety data by age subgroups from studies TD01 and LVIG, as well as from post-marketing reports (including literature).

The overall number of children aged <2 years (n=120; all from study TD01), and ≥2 to <6 years (n=109; of them 105 from study TD01 and 4 from study LVIG) are considered quite relevant for this submission given the rarity of the disease. In this population, the safety profile of tadalafil appears manageable and similar irrespective of children-age. Reported adverse events were not unexpected for PAH patients. Supportive safety data from pharmacovigilance (as of September 2021; 7000 peadiatric patients exposed) and literature do not suggest a different trend.

Nonetheless, inherent limitations to Study TD01 (observational nature, uncontrolled design, confounding factors) and to Study LVIG (uncontrolled design and limited subgroup's sample size) should not be overlooked and, therefore, it is acknowledged that a robust conclusion on safety results cannot be drawn.

On the other hand, it is acknowledged that recruitment challenges may affect the collection of post-marketing data by means of a new clinical trial in these lower-age patients. Despite of this fact, the MAH will continue to review all paediatric events through routine pharmacovigilance activities.

In summary, CHMP considers that, despite of known limitations, including the rarity of the disease, all the evidence provided suggest that safety is similar in all age groups. and that the safety profile in younger children is acceptable. No further measures are considered to be needed in this younger population in terms of safety.

Main long-term data come from the 32 patients who entered the 24-month long-term OLE period (Period 2 of Study LVHV) of which 26 patients completed it. Additional data from the 18 patients from Period 2 of Study LVIG (2 years) were available, in conjunction with supportive Japanese patients from observational study (H6D-JE-TD01) which also provides data up to 2 years. No new long-term safety concerns were observed either.

2.6.10. Conclusions on the clinical safety

The primary safety analysis is based on the doubled blind period of Study LVHV (n=17 tadalafil treated patients), which can be considered as the 'pivotal' trial within this submission. From its results, it can be concluded that tadalafil was well-tolerated in paediatric population > 6 years. Overall, the AEs in this trial were similar to those observed in the pivotal trials in adult PAH patients and are consistent with the safety profile of tadalafil and AEs expected in this patient population. There were no deaths or SAEs and there were no discontinuations due to AEs. The most frequently reported AE were headache.

Data presented from PAH paediatric patients show a consistent safety profile with the already known safety profile of tadalafil in adults with PAH. Data from LVHV and LVIG (51 patients treated with tadalafil), conducted as a part of the PIP, do not raise any major safety concern and neither appears to emerge from the post-marketing data provided, which can be considered as supportive to data from clinical trials.

Supportive safety data in PAH (32 patients from the OLE period of Study LVHV, 19 from Study LVIG and 391 from the observational study TD01) are generally consistent with the data observed from LVHV study. Data from Study LVJJ in DMD paediatric patients treated with tadalafil can be also considered as supportive evidence.

Although, it is accepted that due the rarity of the disease, the safety database may be quite limited, some limitations regarding the provided sample size should be highlighted. Specially, that there is a lack of controlled data from patients < 6 years and only data from 17 patients aged > 6 years are controlled. The observational Study TD01 is the only study that provides safety data in patients <2 years old, while safety data for patients ≥2 years and <6 years also comes from study TD01 and the open label of Phase 1b/2 LVIG Study.

Nevertheless, the overall number of children aged < 2 years (n=120; all from study TD01), and ≥2 to <6 years (n= 109; of them 105 from study TD01 and 4 from study LVIG) are considered quite relevant for this submission given the rarity of the disease. In this population, safety profile of tadalafil appears manageable and similar irrespective of children-age. Reported adverse events were not unexpected for PAH patients. Supportive safety data from pharmacovigilance (7000 paediatric patients exposed) and literature do not suggest a different trend. Regarding the post-marketing data (7000 children 0-17 year exposed to Adcirca), the MAH was requested to divide exposure in the same manner as the age groups for AEs, to be able to evaluate the amount of AEs relative to the exposure. The MAH provided this information and also committed to present data on both exposure and AEs divided in age groups in the PSURs.

Nonetheless, inherent limitations to Study TD01 (observational nature, uncontrolled design, confounding factors) and to Study LVIG (uncontrolled design and limited subgroup's sample size) should be not be overlooked and, therefore, it is acknowledged that a robust conclusion about safety results cannot be drawn.

On the other hand, it is acknowledged that recruitment challenges may affect the collection of post-marketing data by means of a new clinical trial in these lower-age patients. Despite of this fact, the MAH will continue to review all paediatric events through routine pharmacovigilance activities.

Thus, even taking into account the limitations with the safety database including the rarity of the disease, all the evidence provided suggest that safety is similar in all age groups. Overall, the data provided allows to conclude that the safety profile in younger children is acceptable. No further measures are considered to be needed in this younger population in terms of safety. Long-term safety data, which includes data up to 2 years, do not show a relevant difference with safety in the short term.

Overall, the totality of the clinical safety data currently available, suggests that tadalafil has an acceptable safety profile in the paediatric population. The AE profile, including the types and incidence of adverse events, were similar to the adult studies presented in the original marketing application.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of Safety Concerns	
Important identified risks[a]	None
Important potential risks[b]	None
Missing information[c]	None

[a] Hypotension/increased hypotensive effect and priapism are no longer considered important identified risks.

[b] Nonarteritic anterior ischaemic optic neuropathy and sudden hearing loss are no longer considered important potential risks in this RMP.

[c] Characterisation of adverse events in elderly patients (≥65 years of age) for once-a-day ED and BPH indications is no longer considered missing information in this RMP. See Module SVII for additional information.

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 9.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Marketing Authorisation Holder (MAH) *submited an application for Adcirca (tadalafil) for the following proposed new indication for paediatric pulmonary arterial hypertension (PAH) specifically:*

"Treatment of paediatric patients aged 6 months to 17 years old with PAH classified as WHO functional class II and III. Efficacy in patients ≥ 6 years in terms of improvement of exercise capacity has been shown in IPAH and PAH associated with surgical repair of at least 6-month duration of simple congenital systemic to pulmonary shunt."

Pulmonary arterial hypertension (PAH) is a rare, progressive, highly debilitating disease characterised by vascular obstruction and the variable presence of vasoconstriction, leading to increased pulmonary vascular resistance (PVR) and right-sided heart failure. If left untreated, PAH ultimately leads to right ventricular failure and death.

Paediatric PAH is a rare and complex condition associated with diverse cardiac, pulmonary, and systemic diseases, with significant morbidity and mortality. It shares some similarities with adult PAH, but there are important known differences in vascular function, foetal origins of disease, growth and development, genetics, natural history, underlying disease, responses of the right ventricle, responsiveness to PAH-specific therapies, and gaps in knowledge, particularly in the youngest age groups.

Because of the limitations in conducting paediatric studies, therapeutic strategies used for adult PAH have not been studied sufficiently in children to allow the definition of potential toxicities or optimal dosing..

3.1.2. Available therapies and unmet medical need

Therapies that are currently approved for the treatment of PAH in adults, in various geographies around the world, include prostacyclin and its analogues (epoprostenol, treprostinil, iloprost and beraprost), endothelin receptor antagonists (ERAs; bosentan, macitentan and ambrisentan), PDE5 inhibitors (sildenafil and tadalafil), soluble guanylate cyclase stimulator (riociguat) and selective prostacyclin receptor agonist (selexipag). Of them, sildenafil and bosentan are approved in children.

3.1.3. Main clinical studies

Study LVHV, the single pivotal trial in this application, was a phase 3, international, randomised, multicentre, 2-period (24 weeks double-blind placebo-controlled period [Period 1] and open-label extension (OLE) of up to 2 years [Period 2], add-on (i.e. in addition to the subject's current endothelin receptor antagonist [ERA]) study to evaluate the efficacy, safety, and population pharmacokinetics (PK) of tadalafil administered orally once daily (QD), as the authorized tablets (20 mg) or as a ready-to-use suspension (2.0 mg/mL), to at least 34 paediatric patients with pulmonary arterial hypertension (PAH)..

3.2. Favourable effects

The efficacy data of tadalafil in children with PAH is mainly based on study LVHV (n=35), coupled with an extrapolation exercise from adults (Bayesian MMRM sensitivity analysis).

The primary objective of period 1 was to evaluate the efficacy of tadalafil compared with placebo in improving 6MWD from baseline to Week 24, as assessed in patients ≥ 6 to < 18 years of age who were developmentally capable of performing a 6MW test. The change in 6MWD from baseline to the end of period 1 (Week 24) in the tadalafil treatment group (60.48 meters) showed numerically higher increase in Least-Square (LS) mean 6MWD at Week 24 than placebo group (36.60 meters), with a placebo-adjusted LS mean treatment difference of 23.88 meters (80% CI, -14.25, 62.00).

Additionally, in paediatric patients with PAH aged ≥ 2 to < 18 years, an exposure-response (ER) model was used to predict 6MWD based upon paediatric exposure following 20 or 40 mg daily doses estimated using a Population PK model and an established adult ER model (H6D-MC-LVGY). The model demonstrated similarity of response between model-predicted and the actual observed 6MWD in paediatric patients aged 6 to < 18 years from Study H6D-MC-LVHV.

Three Bayesian MMRM sensitivity analyses were conducted: Bayesian MMRM analysis with diffuse prior and mixture prior using weight of 0.5 and 0.8. The analysis with mixture prior weight 0.8 resulted in the posterior mean difference of 27.13 m and 80% credible interval (4.94 to 42.73), which supports the positive trend suggested by the primary analysis in Study LVHV.

Clinical worsening cases were only recorded in five subjects who received tadalafil during the Period 2 of the study LVHV (1 new-onset syncope, 2 increase in ERA dose, 1 addition of new PAH-specific concomitant therapy, and 1 hospitalization for PAH progression).

The positive trend of potential efficacy of tadalafil versus placebo observed in the 6MWD as primary

efficacy endpoint, seems to be supported by the majority of the additional efficacy measurements, such as NT-Pro-BNP (treatment difference -127.4, 95% CI, -247.05 to -7.80), WHO functional class for Period 1 (improved in tadalafil 40.0%, placebo 20.0%; no worsening from either group), echocardiographic parameters (TAPSE: treatment difference 0.43, 95% CI, 0.14 to 0.71; left ventricular eccentricity index [EI]-systolic: treatment difference -0.40, 95% CI, -0.87 to 0.07; left ventricular EI-diastolic: treatment difference -0.17, 95% CI, -0.43 to 0.09; 3 subjects with reported pericardial effusion for placebo group, absent for these subjects at baseline in tadalafil, during Period 1), CGI-I (improved in tadalafil 64.3%, placebo 46.7%). All subtest domains and summary score on physical and psychological dimensions in CHQ-PF28 did not show a difference between tadalafil and placebo treatment group, with the exception of Global Health (treatment difference 7.26, 95% CI, -9.25 to 23.77).

The main supportive study (for effectiveness) is the Japanese post-marketing study (H6D-JE-TD01). Among the 391 paediatric patients included (23.3% of the total population), 79 patients were less than 1 year of age, 163 patients were 1 to 6 years, 110 patients were 7 to 14 years, and 39 patients were 15 to 18 years. Mean age ± standard deviation (SD) was 5.7 ± 5.34 years, and 51.7% of the patients were boys. Changes in WHO classification showed a tendency toward improvement at 3 months, 1 year, 2 years after the start of administration, and final observation in paediatrics was 8.6% (30/348 patients), 16.5% (40/243 patients), 19.7% (26/132 patients), and 16.3% (57/349 patients), respectively. The incidence of deterioration in WHO functional class at 3 months, 1 year and 2 years was 0.6% (2/348 patients), 0.8% (2/243 patients), 1.5% (2/132 patients), and 2.3% (8/349 patients), respectively.

3.3. Uncertainties and limitations about favourable effects

There were important doubts about the predictive capacity of the PBPK model to be able to establish a dose recommendation in population groups where there is no experimental evidence. It is unlikely that an accurate posology in children aged 6 months to < 2 years could be recommended without generating some clinical PK data in this age subset. In addition, the lack of a PK study to assess the food effect was considered a major inconvenience for establishing the posology in younger children and the company did not commit to conduct the drug-food interaction study with the oral solution suggested by the CHMP.

Sample size of the single pivotal trial was rather small. A total of thirty-five patients, 16 male and 19 female, aged 6 to 17 years were randomly (1:1) assigned to placebo (n=18) or tadalafil (n=17) treatment in Period 1 of this study and received at least 1 dose of study medication. The majority of the subjects (n= 32; 94.1%) were taking bosentan as concomitant ERA. PAH aetiologies were idiopathic PAH (n=26; 74.3%). In the initially applied indication, the MAH claimed that "Efficacy in patients ≥ 6 years in terms of improvement of exercise capacity has been shown in IPAH and PAH associated with surgical repair of at least 6-month duration of simple congenital systemic to pulmonary shunt". However, the number of patients with PAH associated with surgical repair is very scarce (only 2/17 subjects in tadalafil group, study LVHV). The MAH was unable to provide further efficacy or effectiveness data in this subgroup, either from other clinical trials or from observational studies or registries, and therefore this disease aetiology was deleted from the proposed indication.

The majority of subjects (n=25 [71.4%]) were in the heavy-weight cohort with the remainder (n=10 [28.6%]) in the middle-weight cohort. Due to a smaller sample size (35 subjects) than originally planned (134 subjects) in the study, the balance of the stratification factors weight cohorts, PAH aetiology and type of concomitant ERA were not achieved among the treatment groups. The lack of enrolled patients in the light-weight (<25 kg) and patients < 2 years cohort could negatively impact on

the limits of a claimed therapeutic indication for the treatment of pulmonary arterial hypertension in the paediatric population.

The Company reviewed the disease course, response, and the PK/PD-relationships. It was agreed that the disease course in children less than 6 years is very similar to adults and, therefore, it can be expected a similar response based upon PK/PD relationships and exposure-matching. Extrapolation from adults based on exposure matching was accepted.

Although statistical significance testing was not performed between the tadalafil and placebo treatment groups due to the low sample size, a positive trend can be ascertained in terms of the primary efficacy endpoint. Nevertheless, when the change in 6MWD was also evaluated during the Period 2 (from Period 2 baseline to the end of Period 2 [Month 24; Visit 17]) as additional efficacy variable, the mean 6MWD decreased by 4.58 meters in the Pla-Tad group and 32.58 meters in Tad-Tad group. Mentioned differences on the improvement in exercise capacity may be due to the difficulties to interpret extension efficacy data where there is no control group.

3.4. Unfavourable effects

Regarding safety results, there were no deaths in neither period. There were no SAEs or discontinuations due to AEs during Period 1, but 5 SAEs (acute right ventricular failure, anemia, gastroenteritis, hemoptysis, and pneumonia) were reported during Period 2. None of the SAEs were considered to be related to study medication or study procedures. One subject was discontinued due to AE (headache) during Period 2. Therefore, no concern or clear pattern emerges based upon these events.

The overall incidence of AEs was higher in tadalafil group compared with placebo. During Period 1, there were 23 subjects who reported at least 1 treatment-emergent adverse event (TEAE) (8/18 [44.4%] subjects in the placebo group and 15/17 [88.2%] subjects in the tadalafil group). The most common TEAE, occurring in ≥2 subjects in any group, were headache (29.4%, tadalafil; 11.1%, placebo) and upper respiratory tract infection (17.6%, tadalafil; 5.6%, placebo). All of the AEs in the tadalafil group were mild or moderate in severity. Treatment-related AEs were reported in 9 subjects (1/18 [5.6%] subject in the placebo group and 8/17 [47.1%] subjects in the tadalafil group). The most common of these AEs, occurring in ≥2 subjects in tadalafil group, was headache (23.5%, tadalafil; 5.6%, placebo). In the tadalafil group, only 1 subject experienced hypotension and only 1 subject experienced 1 AE of hepatic enzyme elevation, but did not meet the criteria of having an AST and ALT more than 3-fold the ULN.

For Period 2 (OLE), there were 23 of the 32 subjects (71.9%) who reported at least 1 TEAE, being the most common (≥2 subjects), headache, dizziness, nasopharyngitis and vomiting; each reported by 18.8% of the treated subjects. The majority of TEAEs were mild or moderate in severity. Treatment-related AEs were reported in 5 of the 32 subjects (15.6%). The most common of these AEs occurring in Period 2 were dizziness and headache (6.3% of the subjects each).

The risk of AEs of special interest (AESIs) does not seem to be increased in this population. One patient in Period 1 experienced an AESI of hypotension (treatment-related AE) that did not lead to treatment discontinuation and resolved. There were no AEs of priapism. A total of 2 subjects (1 in each period; 2 AE) experienced spontaneous intermittent penile erection that resolved spontaneously. There was 1 event of a visual abnormality (photopsia) during Period 2 that was not considered to be related to tadalafil by the Investigator. There were 4 subjects (all on tadalafil; 6 AEs) with uterine bleeding during the study. Only one of them was associated with an SAE of anemia and required a blood transfusion and all were resolved without treatment discontinuation. None of the subjects

experienced hearing abnormalities during the study.

Main long-term data come from the 32 patients who entered the 24-month long-term OLE period (Period 2 of Study LVHV) of which 26 patients completed it. Additional data from the 18 patients from Period 2 of Study LVIG (2 years) were available, in conjunction with supportive Japanese patients from observational study (H6D-JE-TD01) which also provides data up to 2 years. No new long-term safety concerns were observed either. Supportive safety data from study LVIG, postmarketing and literature data concurs with the data observed from LVHV study.

3.5. Uncertainties and limitations about unfavourable effects

There is limited sample size included in clinical trials (51 PAH patients treated with tadalafil). Although, it is accepted that due the rarity of the disease, the safety database may be quite limited, some limitations regarding the provided sample size should be pointed out:

There is a lack of controlled data from patients <6 years and only data from 17 patients aged >6 years are controlled. The observational Study TD01 is the only study that provides safety data in patients <2 years old, while safety data for patients ≥2 years and <6 years also comes from study TD01 and the open label of Phase 1b/2 LVIG Study.

Inherent limitations to Study TD01 (observational nature, uncontrolled design, confounding factors) and to Study LVIG (uncontrolled design and limited subgroup's sample size) should be not be overlooked and, therefore, it is acknowledged that a robust conclusion on safety results cannot be drawn.

A possible collection of post-marketing data by means of a new clinical trial in these lower-age patients is not view as feasible by the MAH due to known recruitment challenges. Despite of this fact, the MAH will continue to review all paediatric events through routine pharmacovigilance activities.

3.6. Effects Table

The following table provides an assessment of the key favourable and unfavourable effects, strength of evidence and limitations and uncertainties regarding the data presented in the registration study.

Table 33 - Effects Table for Tadalafil in the Treatment of Paediatric Pulmonary Arterial Hypertension

Effect	Short Description	Tadalafil	PBO	Tadalafil-PBO Difference 80%/95% CI	Strength/Uncertainties/ Limitations of Evidence
Favourable Effects - Study LVHV Period 1					
6MWD (m) - primary analysis	LS mean change from baseline to Week 24 (SE)	60.48 (20.41)	36.60 (20.78)	23.88 (29.11) -14.25, 62.00	**Strengths:** • Consistency between the 6MWD primary analysis, Bayesian sensitivity analyses and PBPK modelling. • Numerical improvements on WHO functional assessments, NT-pro-BNP and echocardiographic parameters. • Consistent effect of the positive trend across secondary efficacy assessments. **Uncertainties/Limitations:** • Small sample size supporting the efficacy evidence. • No direct efficacy data for those aged <6 years.
NT-pro-BNP	LS mean change from baseline to Week 24 (SE)	-59.16 (59.639)	68.26 (49.412)	-127.4 (56.700) -247.05, -7.80	
WHO-functional class (FC)	Patients with WHO FC change from baseline, %	Improved: 40 No change: 60	20 80	20 -20 NA	
Echocardiography					
TAPSE	LS mean change from baseline to Week 24 (SE)	0.33 (0.130)	-0.10 (0.111)	0.43 (0.136) 0.14 to 0.71	
Left ventricular EI-systolic		-0.29 (0.218)	0.11 (0.194)	-0.40 (0.225) -0.87 to 0.07	
Left ventricular EI-diastolic		-0.08 (0.122)	0.08 (0.106)	-0.17 (0.124) -0.43 to 0.09	
TRV-max		1.68 (31.066)	17.01 (28.47)	-15.33 (29.443) -78.48 to 47.82	
Pericardial effusion		0 patient in Period 1	2 patients in Period 1	-2 cases	
CGI-I (overall symptoms)	% improvement at endpoint[a]	64.3	46.7	NA NA	
	% worsening from Day 1	0	0	0 NA	

Effect	Short Description	Tadalafil	Placebo	Strength/Uncertainties/ Limitations of evidence
Unfavourable Effects				

Hypotensive effect	Clinical trial, n (%)	Study LVHV Period 1: 1 (5.9%) OLE: 0 (0) Study LVIG Period 1: 1 (5.26%) OLE: 0 (0)	0 (0) NA NA NA	**Strengths:** • Safety profile of tadalafil is consistent across the paediatric clinical program (Study LVHV, open-label Study LVIG), with adult PAH data and with the disease state being studied. • No new safety signals were identified. • Hypotensive effect is considered a key risk due to the potential for the event to be sudden and severe. Events were nonserious, with one exception Study TD01. **Uncertainties/ Limitations:** • Small sample size supporting the safety evidence in the paediatric PAH clinical studies. • Lack of exposures in the youngest age group (<2 years) in the paediatric PAH clinical studies.

Abbreviations: 6MWD = 6-minute walk distance; CGI-I = Clinical Global Impression of Improvement; CI = confidence interval; EI = eccentricity index; FC = functional class; LS = least-square; LVHV = Study H6D-MC-LVHV; LVIG = Study H6D-MC-LVIG; NA = not applicable; n = number of patients per category; NA = not applicable; NT-pro-BNP = N-terminal prohormone brain natriuretic peptide; OLE = open-label extension; PAH = pulmonary arterial hypertension; PASS = Postauthorisation Safety Study; PBO = placebo; PBPK = physiologically based pharmacokinetic; SE = standard error; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitant velocity; TD01 = Study H6D-JE-TD01; WHO = World Health Organization.

*Study TD01 is a postmarketing surveillance (PMS) noninterventional PASS.

[a] Includes responses of a 'minimally improved', 'much improved' or 'very much improved'.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy data of tadalafil in children with PAH is mainly based on study LVHV (n=35), coupled with an extrapolation exercise from adults (Bayesian MMRM sensitivity analysis).

In study LHVH there was an improvement in exercise capacity (6MWD) (point estimate of 23.88 meters in the main analysis and between 21.14m to 27.13 m in the Bayesian MMRM analyses). The 6MWD endpoint has been shown in the adult PAH population to correlate with long term clinical outcome and is generally used to follow exercise tolerance in paediatric PAH patients of appropriate age, being a reliable test in children ≥ 7 years. Interventional clinical trials in adults with PAH have commonly used the 6MWD test to demonstrate efficacy for drug approval [Ollivier, et al. J Am Heart Assoc. 2019;8:e011306].

In absolute terms, the increase in 6MWD was consistent with the one reported in adults. The main analysis of 6MWD was also supported by three Bayesian MMRM sensitivity analyses and favourable trends observed in other secondary endpoints. 6MWD in study LVHV may be considered of clinical relevance and is consistent with the 26 metres improvement observed in adults with tadalafil 40 mg (placebo-adjusted median increase in 6MWD).

The risks observed in the paediatric population were similar to those found in adults, with headache and hypotension occurring commonly. These events are usually mild to moderate and manageable in standard practice.

3.7.2. Balance of benefits and risks

The efficacy data of tadalafil in children with PAH is mainly based on exploratory data from study LVHV (n=35) in children ≥ 6 years, coupled with a extrapolation exercise from adults (Bayesian MMRM sensitivity analysis) and a PK/PD modelling (children 2-6 years) and simulation (children between 6 months and 2 years). This is mainly due to limited availability of pharmacodynamic measures and lack of a suitable and approved clinical endpoint, but also due to the lack of insufficient recruitment in PK and efficacy trials.

The benefits observed in exercise capacity in study LVHV in children were consistent with those found in adults. An ad hoc analysis of responders in 6MWD of study LVHV was also numerically in favour of tadalafil vs. placebo. The risks observed in the paediatric population were also similar to those found in adults. Therefore, the balance between benefits and risks observed in children can be regarded as similarly positive as in adults.

However, the pivotal study LVHV has several limitations, mainly related to the small sample size, and is exploratory in nature. No inferences of statistical superiority versus placebo can be made. Furthermore, the number of children is insufficient to allow for any conclusion in some of the patients' subsets mentioned in the proposed indication (i.e. PAH due to surgical repair) or children <25 kg body weight or <2 years old, for whom no clinical data of efficacy have been generated.

The MAH has provided effectiveness data in children < 6 years from observational study TD01 in Japan (n=391 paediatric patients), which are supportive, but the dose used in study TD01 is higher than the one recommended in the SmPC: the median dose in children aged <1 year in study TD01 was 5 mg (and not 4 mg as proposed), while in children between 1 and 2 years, the median dose was 7 mg (and not 6 mg as proposed). Despite having accepted the possibility of extrapolation from adults, further refinement of the PBPK model was requested in patients 2-8 years of age was needed, coupled with a proposed dosing regimen where the exposure in paediatric patients match the adult exposures for which efficacy and safety has been established.

Even after the refinement of the PBPK model, there were still important doubts about the predictive capacity of the PBPK model to be able to establish a dose recommendation in population groups where there is no experimental evidence. Based on a "refinement" of the PBPK model the applicant proposed a new posology for children below 2 years that was twice the dose proposed initially. The CHMP concluded that it is unlikely that a recommendation for an accurate posology in children aged 6 months to < 2 years could be made without the availability of some clinical PK data in this age subset. In addition, the lack of a PK study to assess the food effect is considered a major inconvenient for establishing the posology in younger children and the company is not able to conduct the drug-food interaction study with the oral solution suggested by the CHMP. All these outstanding issues prevented from including children < 2 years in the indication. However, the B/R was considered positive for children aged 2 years and older.

During the procedure, the MAH proposed to include "positive trend towards improvement in terms of exercise capacity" in the wording of the indication and not to delete "PAH associated with surgical repair". Both statements were considered inappropriate. Regarding the mention of positive trends in 6MWD in the paediatric indication, it may be interpreted as the CHMP as approving an indication based on trends only, and such statement is misleading. In addition, no extrapolation from adults to children can be made for PAH due to surgical repair, as this aetiology is not approved for adults. The said PAH aetiology was finally removed from the requested indication.

The paediatric indication finally accepted was "Treatment of paediatric patients aged 2 years and above with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III".

It was mainly based in the extrapolation exercise from adults accepted in the CHMP guidelines (EMA reflection paper EMA/189724/2018 and related guidelines), coupled with PK data and PK/PD modelling. It included only children aged 2 years and above (as no accurate dose could be defined for children between 6 months and less than 2 years) and no mention was made to improve exercise capacity or disease aetiology due to the reasons discussed above.

3.7.3. Additional considerations on the benefit-risk balance

N/A.

3.8. Conclusions

The overall benefit/risk balance of Adcirca is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Adcirca is not similar to Opsumit, Adempas and Trepulmix within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Adcirca favourable in the following indication:

Treatment of paediatric patients aged 2 years and above with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Adcirca subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.