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Human Medicines Division

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

Adcirca

tadalafil

Procedure no.: EMA/H/C/001021/P46/022

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☒	Start of procedure	13/09/2021	13/09/2021
☒	CHMP Rapporteur Assessment Report	18/10/2021	18/10/2021
☒	CHMP members comments	29/10/2021	n/a
☒	Updated CHMP Rapporteur Assessment Report	04/11/2021	n/a
☒	CHMP adoption of conclusions	11/11/2021	11/11/2021

Table of contents

1. Introduction

On 26th August 2021, the MAH submitted a completed paediatric study (H6D-MC-LVHV) for tadalafil (Adcirca and Cialis), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

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

In accordance with Article 46 of the regulation (EC) No 1901/2006, Eli Lilly Nederland B.V. hereby submits to the EMA a final study report for the concerns the submission of the study H6D-MC-LVHV (LVHV).

Study LVHV is part of an EU Paediatric Investigation Plan (PIP) for tadalafil targeted to grant an indication for the treatment of pulmonary arterial hypertension (last PIP modification approved on 11 September 2020, EMEA-000452-PIP02-10-M06).

The MAH stated that study H6D-MC-LVHV (LVHV) titled "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" is part of a clinical development program. The extension application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by 20th December 2021. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

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

Study H6D-MC-LVHV was planned to administer orally once daily tadalafil or matching placebo. Tadalafil was expected to be given as the authorized tablets (for middle and heavy-weight cohort patients) or as a ready-to-use oral suspension (2.0 mg/mL tadalafil) developed for use in younger children (light-weight cohort patients).

Since no subjects were enrolled in the light weight cohort, the presentations of tadalafil used in the study were the same as the commercially approved product.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- 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".

2.3.2. Clinical study

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".

Description

Study H6D-MC-LVHV (LVHV) was a 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).

Methods

Study participants

- Key inclusion/exclusion criteria for this study:

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.

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.

Treatments

Tadalafil dose selection for the hereby submitted study LVHV was based on paediatric PK and safety data from the Phase 1b/2 study H6DMC-LVIG (please, see Cialis,Tadalafil Lilly, Adcirca, INN-tadalafil (europa.eu)) and the PK and safety data from the adult PAH development plan (pivotal study H6D-MC-LVGY [LVGY]). 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.

Subjects who met all of the eligibility criteria were randomised 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.

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).

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 to <18 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
    e. (confirmed 5 to 10 days later) for those subjects who were ≥6 years of age and
    f. were developmentally capable of performing the 6MWD test.
    g. 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.

- Additional Efficacy Measures

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.

- Safety Measures

Period 1 (Double-Blind Placebo-Controlled)

Safety during Period 1 was evaluated as secondary safety measure by using reported AEs (which included abnormalities detected by ECG or physical examination, as well as clinically significant laboratory abnormalities, body weight and height, vital signs, and eye examinations) and concomitant medications. If necessary, additional plasma tadalafil concentrations and protocol clinical laboratory data might be collected for subjects reporting an SAE.

Period 2 (Open-Label Extension)

Safety during Period 2 was evaluated as primary safety measure by monitoring any AEs, serious adverse events (SAEs), discontinuations due to AEs or death, change in body weight and height, eye examinations, concomitant medications, Tanner scale, and intellectual ability and cognitive functioning assessment.

Testicular integrity toxicity (such as sertoli cell function) was checked by monitoring changes in inhibin B biomarkers in male subjects from 9 years to <18 years of age. Inhibin B levels in subjects below the age of 9 years was collected in an exploratory manner. If necessary, additional plasma tadalafil concentrations and protocol clinical laboratory data was collected for subjects reporting an SAE.

Sample size

The original planned sample size was 134 subjects but was reduced to be 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 the extremely difficult enrolment experienced in the study and agreed with the EMA.

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.

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).

Subjects received study medication for 24 weeks in the double-blind period (Visits 2 to 9; Period 1), and then were eligible to be enrolled into an open-label 2-year extension period (Visits 10 to 17; Period 2) during which all subjects received tadalafil.

Statistical Methods

Given the small sample size, no formal comparisons were to be made between treatment groups. 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.

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.

- 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:

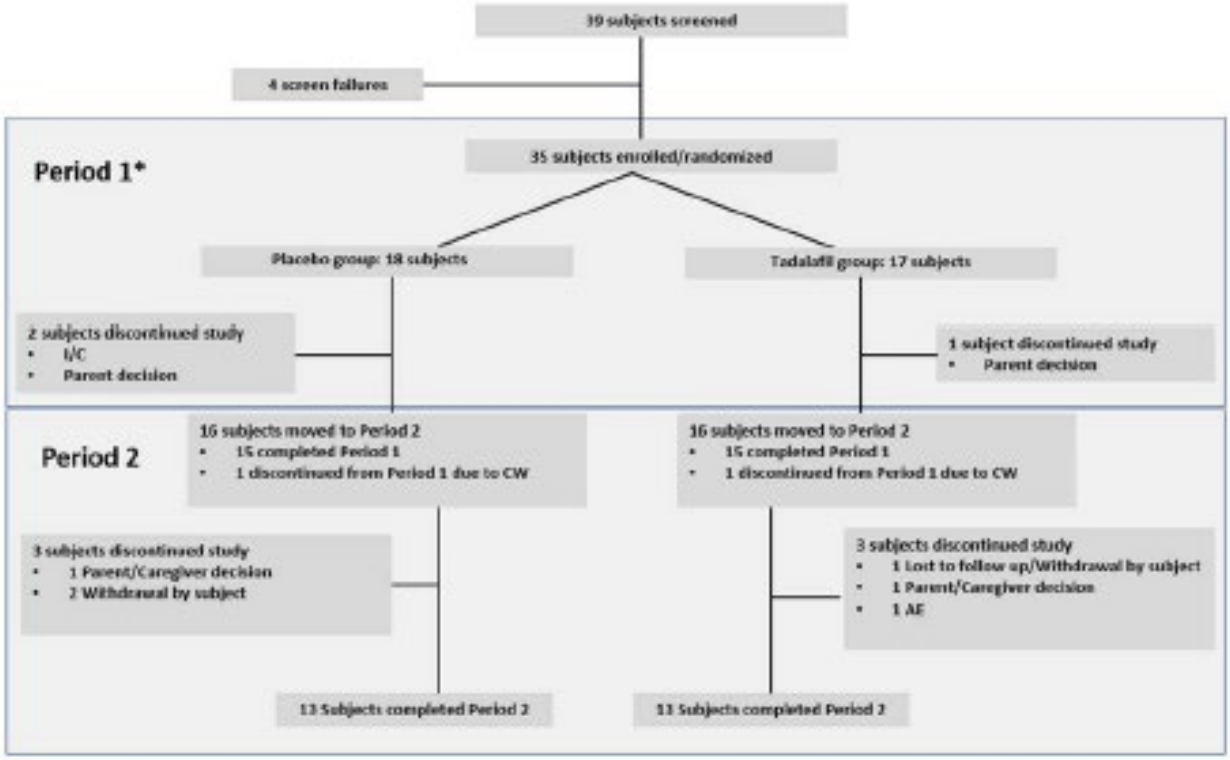
Proportions of subjects in each of the 7 response categories ("Very Much Better" to "Very Much Worse") of the CGI-I were summarized by visit. Changes from baseline (Day 1) to Weeks 16, 24, and endpoint in CHQ-PF28 scores were analysed with an analysis of covariance (ANCOVA) model that included terms 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 is shown in Figure 1.

Figure 1. Study participant disposition figure, Period 1 and Period 2



Abbreviations: AE = adverse event; CW = clinical worsening; I/C = inclusion criteria not met.
Source: Figure LVHV.4.1. (m5-3-5-4).

Recruitment

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.

Baseline data

Period 1 (Double-Blind Placebo-Controlled)

There were 16 male and 19 female 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 was enrolled younger than 6 years in the study. 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. No subjects were enrolled in light-weight (<25 kg) cohort.

The majority of subjects were white (n=26; 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), and 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.

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 majority of the subjects (n=32 [94.1%]) 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. Please, see Table 1.

Table 1. Concomitant Therapy - Endothelin Receptor Antagonist - Double-Blind Treatment Period, Primary Analysis Population

Preferred Term	Placebo (N=18)	Tadalafil (N=17)	Total (N=35)
Patients using >= 1 ERA medication	17 (94.4)	17 (100.0)	34 (97.1)
BOSENTAN	16 (88.9)	16 (94.1)	32 (91.4)
Duration of Use at Baseline (Days)			
Mean (SD)	310.2 (352.34)	649.8 (687.86)	480.0 (564.60)
Median	161.0	330.0	200.0
Min, Max	97, 1389	107, 2391	97, 2391
MACITENTAN	1 (5.6)	1 (5.9)	2 (5.7)
Duration of Use at Baseline (Days)			
Mean (SD)	103.0	103.0	103.0 (0.00)
Median	103.0	103.0	103.0
Min, Max	103, 103	103, 103	103, 103

Abbreviations: ERA = endothlin receptor antagonist; Max = maximum; Min = minimum; N = number of patients in the primary analysis population; n = number of patients per category; SD = standard deviation.

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 alphabetically.
For each preferred term, a patient is counted only once even if the same preferred term is reported by a patient multiple times within the double-blind treatment period.
Duration of use is calculated as the randomization date - ERA start date + 1.

Source: Source: Table LVHV.14.13. (m5-3-5-4).

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 (71.9%) were in the heavy-weight group with the remainder 9 (28.1%) in the middle-weight group.

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

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

The majority of the subjects (n=30 [93.8%]) were taking bosentan as concomitant ERA.

Number analysed

Period 1 (Double-Blind Placebo-Controlled period)

All 35 randomised subjects who received at least 1 dose of study medication were included in the safety and efficacy analyses performed for Period 1, with the exception of the analysis of 6MWD. As 2 subjects of the 35 randomized subjects 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.

Period 2 (Open-Label Extension)

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

Efficacy results

- The primary efficacy variable:
    - 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).

- 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.

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.

- The additional efficacy variables:
    - WHO functional class during Period 1 (Double-Blind Placebo-Controlled)

From baseline to the Week 24 (Visit 9) of Period 1, 60.0% of subjects in the tadalafil group had no change in WHO functional class, 40.0% improved, and 0.0% worsened. In the placebo group, 80.0% of subjects had no change in WHO functional class, 20.0% improved, and 0.0% worsened.

    - WHO functional class during Period 2 (Open-Label Extension)

Majority of subjects had no change in WHO functional class (73.3% in the Tad-Tad group and 80% in the Pla-Tad group), along with improved WHO functional class (20% in both Tad-Tad group and Pla-Tad group). Please, see Table 2.

Table 2. Change in WHO Functional Classification from Baseline to Endpoint - Open-Label Treatment Period

Change in WHO Functional Class from Baseline to Endpoint (LOCF)
Open-Label Treatment Period
Patients Who Entered the Open-Label Treatment Period by Double-Blind Treatment Group

Treatment	N1	Number of Patients with WHO FC Change from Baseline to Endpoint[a]	No Change[b] n (%)	Improved[b] n (%)	Worsened[b] n (%)
Pla-Tad [c] (N =16)	15	3	12 (80.0)	3 (20.0)	0 (0.0)
Tad-Tad [c] (N =16)	15	4	11 (73.3)	3 (20.0)	1 (6.7)
Total (N =32)	30	7	23 (76.7)	6 (20.0)	1 (3.3)

Abbreviations: FC = functional class; LOCF = last observation carried forward; N = number of patients in the primary analysis population, who entered the open-label treatment period; n = number of patients per category; N1 = number of patients with non-missing data at baseline and at least one open label visit; WHO = world health organization.

The Primary Analysis Population includes all patients who received at least 1 dose of the study drug according to the randomised treatment.
[a] Baseline is Visit 9. Endpoint is defined as last available WHO FC value in Period 2.
[b] All percentages are calculated as n/N1*100.
[c] Treatment: Pla-Tad = Placebo in period 1 and Tadalafil in period 2; Tad-Tad = Tadalafil in period 1 and 2

Source: Table LVHV.5.3 (m5-3-5-4).

- Echocardiography during Period 1 (Double-Blind Placebo-Controlled)

From baseline to Week 24, it was observed a numerical improvement trend in the tadalafil treatment group in the following echocardiographic parameters:

- Tricuspid Annular Plane Systolic Excursion (TAPSE): treatment difference 0.43, 95% CI, 0.14 to 0.71;
- Left ventricular 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;
- Pericardial effusion: two subjects with reported pericardial effusion during 24 week treatment (1 subject each at Week 8 and at Week 16) from placebo group and none of the subjects reported pericardial effusion in tadalafil group.

Due to the small sample size, caution should be exercised in the interpretation of the model-adjusted means and associated CIs.

- N-terminal pro BNP concentrations (NT-Pro-BNP) during Period 1 (Double-Blind Placebo-Controlled)

During period 1, NT-Pro-BNP placebo-adjusted LS mean (SE) differences at Week 24 NT-Pro-BNP was -127.4, 95% CI, -247.05 to -7.80.

- Clinical Global Impression of Improvement (CGI-I) during Period 1 (Double-Blind Placebo-Controlled)

From baseline to Week 24, the overall improvement in symptoms of PAH were 64.3% in the tadalafil group and 46.7% in the placebo group, and worsening of PAH symptoms in CGI-I was not reported in either group.

- Child Health Questionnaire Parent Form 28 (CHQ-PF28) during Period 1 (Double-Blind Placebo-Controlled)

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).

- Magnetic Resonance Imaging (MRI) during Period 1 (Double-Blind Placebo-Controlled)

There were only 3 subjects (1 in placebo group, 2 in tadalafil group) who underwent MRI procedure during Period 1, hence a formal MRI data comparison was not performed due to small sample size.

- 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.

Pharmacokinetic/Pharmacodynamic Results

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

The number of subjects by cohort with measurable PK samples were as follows:

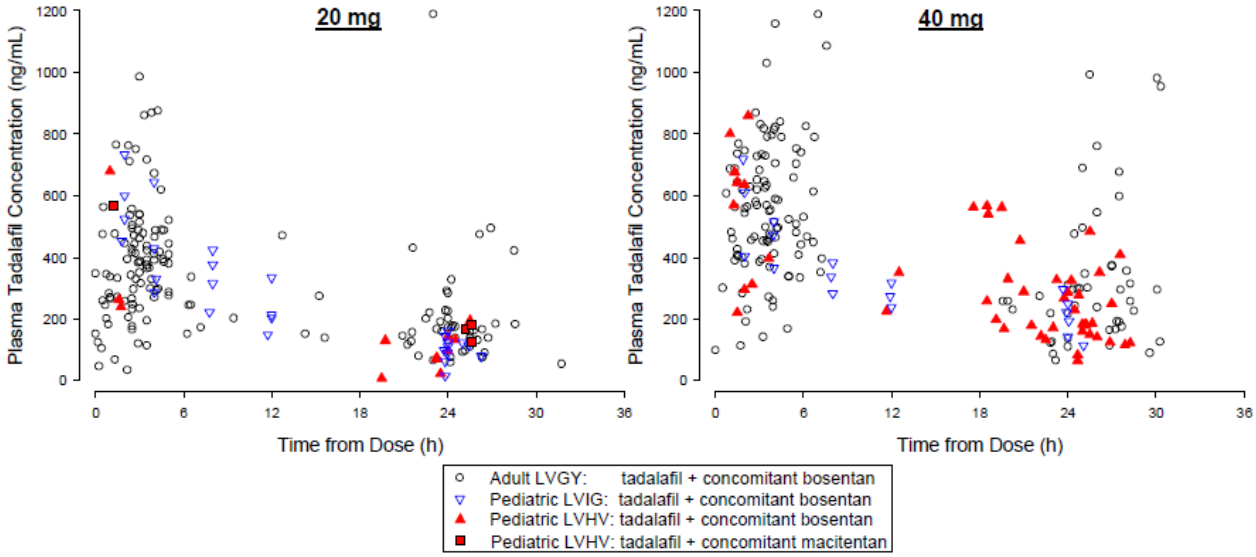
- Middle weight (≥25 kg to <40 kg), 20 mg (1 × 20 mg tablet), N = 4 subjects (16 total PK samples), and
- Heavy weight (≥40 kg), 40 mg (2 × 20 mg tablets), N = 13 subjects (48 total PK samples).

All subjects were on concomitant bosentan ERA treatment except 2 subjects who were on macitentan (only 1 of these 2 subjects was on tadalafil treatment during Period 1). The plasma tadalafil concentrations observed in this trial were comparable to those observed in the paediatric study LVIG for subjects receiving 20 mg or 40 mg tadalafil with concomitant bosentan. The 1 paediatric subject who received tadalafil and concomitant macitentan had tadalafil concentrations similar to other subjects who received tadalafil and concomitant bosentan. Figure 2 presents a graphical summary of the LVHV plasma concentrations of tadalafil differentiated by dose and ERA treatment for Period 1 compared with reference tadalafil concentrations from studies LVGY (adult) and LVIG (paediatric). As observed from this figure, the LVHV tadalafil concentrations were comparable to LVGY adult concentrations observed at the 20 mg and 40 mg doses and likewise similar to paediatric concentrations previously observed in study LVIG.

Concentrations at 40 mg are generally higher than those observed at 20 mg, which is expected based upon the known PK profile of tadalafil. Note that for comparison purposes, data from only subjects who were on concomitant bosentan from the reference trials have been plotted.

Pharmacokinetic plasma concentration–time data from study LVHV were pooled with data from other protocols in a combined population analysis; details of the PK analyses are provided in a separate research report.

Figure 2. Plasma tadalafil concentrations versus time following 20 mg or 40 mg daily doses of tadalafil for Study LVHV with reference data from Studies LVGY (adult) and LVIG (paediatric)



Abbreviation: ERA = endothelin receptor antagonist.

Source: Figure LVHV.11.1. (m5-3-5-4).

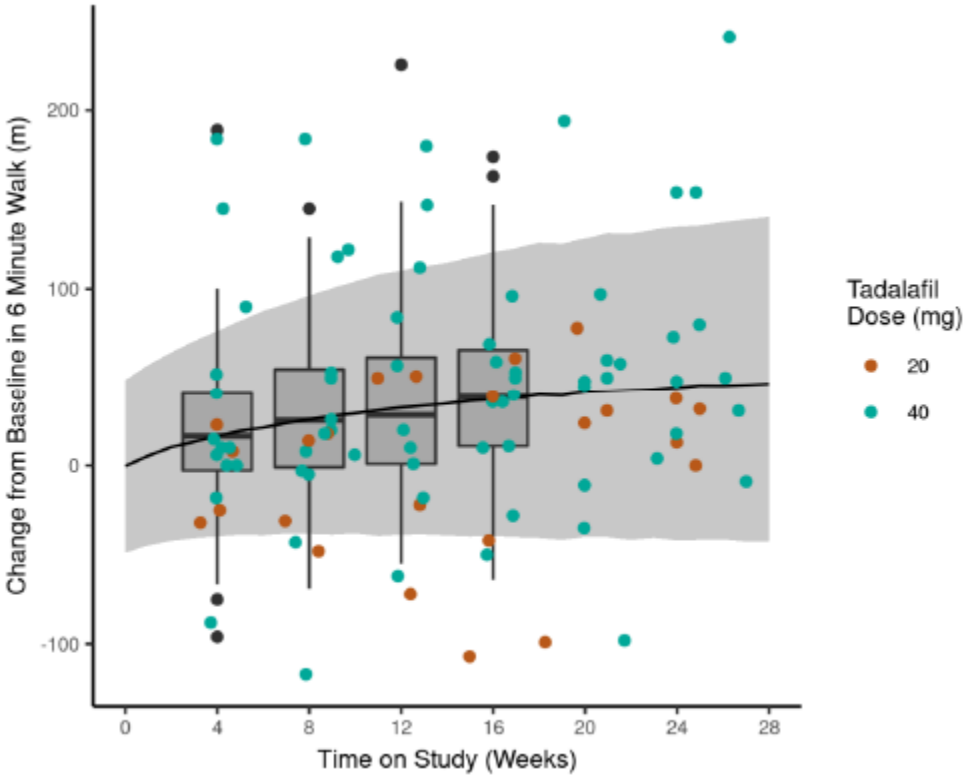
Due to lack of enrolment in younger children, PBPK modelling was conducted to support doses in paediatric patients aged <2 years. The results of the PBPK analysis are presented in a separate report and will be included and discussed further in the upcoming paediatric indication application.

During Period 1, pharmacodynamics was assessed by measuring 6MWD in paediatric subjects from 6 years of age and older, and who were capable of performing the test, at Weeks 8, 12, 16, and 24.

The 6MWD data from 20 mg and 40 mg were compared with the results of the adult study LVGY (40 mg only). The results of the adult study were displayed as observed data, whereas the LVGY exposure–response model was used to predict the data from LVHV (Figure 3).

There was substantial overlap between the observed adult and paediatric data. The LVGY exposure–response model appeared to adequately capture the central tendency of the paediatric data, although the 90% prediction interval appeared to underpredict the degree of variability observed in the trial. Altogether, the adult LVGY model appeared to adequately predict the data from study LVHV.

Figure 3. Observed change from baseline in 6-minute walk over time in paediatric patients, with predicted response from adult model



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 LVGY model-predicted response is also provided (black line is the median prediction; grey region represents the 90% prediction interval).

Source: Figure LVHV.5.3 (m5-3-5-4).

Safety results

- Extent of Exposure:

As of the date (18 March 2019) of last subject visit for the study LVHV double-blind placebo-controlled period (Period 1), 17 subjects received tadalafil and 18 subjects received placebo. The mean and median cumulative number of doses taken during Period 1 was 151.0 and 161.0 (range 43.0, 188.0) for tadalafil and 153.4 and 165.0 (range 27.0, 188.0) for placebo.

A total of 32 subjects received tadalafil once daily during Period 2, including subjects on placebo who began receiving tadalafil. The mean and median cumulative number of tadalafil doses taken during Period 2 were 597.9 and 679.5 (minimum range: 101.5 and maximum range: 746.5) in Tad-Tad group and 664.5 and 685.3 (minimum range: 476.0 and maximum range: 747.0). The mean and median number of exposure days to tadalafil for Period 2 was 638.8 and 721.0 days (range 164.0, 833.0 days).

- Deaths, Serious AEs, Discontinuation due to CW, and Overall AE Profile during Period 2 (Open-Label Extension):

The primary safety objective of study LVHV was to evaluate the long-term safety of tadalafil.

An overview of AEs reported in Period 2 is provided in Table 3.

There were no deaths reported in Period 2. A total of 5 subjects experienced SAEs (4 subjects in the Pla-Tad group [SAEs: anemia, gastroenteritis, hemoptysis and pneumonia] and 1 subject in the Tad-Tad group [SAEs: acute right ventricular failure]). None of the SAEs were considered to be related to tadalafil as judged by the investigator.

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.

Treatment-emergent adverse events (TEAEs) were reported in 23 subjects (11/16 [68.8%] subjects in the Pla-Tad group and 12/16 [75%] subjects in the Tad-Tad group). In Period 2, the most common TEAEs, occurring in ≥2 subjects in any group, were headache, dizziness, nasopharyngitis, and vomiting; each TEAE was 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 subjects (2/16 [12.5%] subjects in the Pla-Tad group and 3/16 [18.8%] subjects in the Tad-Tad group). Procedure-related event (anxiety) was reported in 1 subject in the Pla-Tad group. The most common of these AEs occurring in Period 2 were dizziness and headache (6.3% in the Tad-Tad group and the Pla-Tad group each).

Table 3. Summary of Adverse Events Open-Label Treatment Period

Adverse event[a]	[Pla-Tad][b] (N=16) n (%)	[Tad-Tad][b] (N=16) n (%)
Deaths[c]	0 (0.0)	0 (0.0)
Serious adverse events	4 (25.0)	1 (6.3)
Adverse events leading to discontinuation	0 (0.0)	1 (6.3)
Treatment-emergent adverse events[d]	11 (68.8)	12 (75.0)
Treatment-related adverse events	2 (12.5)	3 (18.8)
Procedure-related adverse events	1 (6.3)	0 (0.0)

Abbreviations: N = number of patients in the primary analysis population, who entered the open-label treatment period; n = number of patients per category.

All percentages are based upon the number of patients who entered the open-label treatment period.
a Patients may be counted in more than one 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 Deaths are also counted as serious adverse events and as adverse events leading to discontinuation.
d Treatment-emergent adverse events are defined as events that first occurred or worsened in severity after double blind period (Visit 9).

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.

Source: Table LVHV.5.6. (m5-3-5-4).

As regards of the adverse events of interest (AESIs) reported during Period 2, one subject in Pla-Tad group experienced spontaneous intermittent penile erections that was considered to be related to tadalafil as judged by the Investigator, one subject on Tad-Tad group experienced photopsia (not considered to be related to tadalafil as judged by the Investigator), and four subjects experienced uterine bleeding, two subjects in Pla-Tad group and 2 subject in Tad-Tad group. One of these subjects, was hospitalized for anemia and received a blood transfusion. One other subject experienced uterine bleeding event in Period 1 and Period 2, but only one event was considered to be related to tadalafil treatment as judged by the Investigator. The majority (80.0%) of uterine bleeding in this study were

considered not related to tadalafil treatment as judged by the Investigator. None of the subjects experienced priapism or hearing abnormalities. There were no pregnancies reported in the study.

- Physical Findings, and Other Observations Related to Safety during Period 2 (Open-Label Extension):

At the endpoint of Period 2, the mean change from baseline height was 9.82 cm (median: 10.5 cm) in the Pla-Tad group and 6.11 cm (median: 3 cm) in the Tad-Tad group. The mean change from baseline were 5.16 kg (median: 3.10 kg) and 5.73 kg (median: 4.95 kg) in the Tad-Tad and Pla-Tad groups, respectively. In change from baseline, there was difference of 3.71 cm in mean increase in height at the endpoint of Period 2 between the 2 treatment groups.

One subject in the Pla-Tad group with normal baseline results had abnormal not clinically significant results for both eyes at the end of Period 2 (Visit 17). All subjects (n=11) who had received tadalafil during Period 1 had normal examinations in both eyes at baseline and end of Period 2 (Visit 17).

There were no AEs related to ECG findings observed in the study.

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.

There were no clinically significant trends observed from inhibin B biomarker concentrations (males only) and Tanner score (pubic hair and breast score for females; pubic hair and genital score for males).

- Deaths, Serious AEs, Discontinuation due to CW, and Overall AE Profile during Period 1 (Double-Blind Placebo-Controlled):

An overview of AEs reported in Period 1 is provided in Table 4.

There were no SAEs or deaths reported in Period 1.

There were 2 subjects (1 in each treatment group) who discontinued the study due to CW. However, as per the protocol, both cases were reported as AEs and both subjects who discontinued from Period 1 were moved into Period 2.

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). The most common TEAE, occurring in ≥2 subjects in tadalafil treated subjects, 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).

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 tadalafil group, 1 subject experienced increased hepatic enzymes and 1 subject experienced hypotension; both the events did not led to treatment discontinuation and the events were resolved while on tadalafil treatment without recurrence of the event.

Table 4. Overview of Adverse Events - Double-Blind Treatment Period
Primary Analysis Population

	Number (%) of Subjects		
Adverse Event[a]	Placebo N=18 n(%)	Tadalafil N=17 n(%)	Total N=35 n(%)
Deaths[b]	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[c]	8 (44.4)	15 (88.2)	23 (65.7)
Treatment-related adverse events	1 (5.6)	8 (47.1)	9 (25.7)
Procedure-related adverse events	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: N = number of subjects in the analysis population; n = number of subjects per category.

The Primary Analysis Population included all subjects 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 Subjects were counted in more than one category, but only once per category per subject.
b Deaths are counted as serious adverse events and as adverse events leading to discontinuation.
c Treatment-emergent adverse events are defined as events that first occurred or worsened in severity after baseline(Visit 2).

Source: Table LVHV.12.3. (m5-3-5-4).

The most common SOCs were infections and infestations (47.1%, tadalafil; 22.2%, placebo) and nervous system disorders (41.2%, tadalafil; 11.1%, placebo).

All of the AEs in the tadalafil group were mild or moderate in severity. A total of 15 subjects reported the maximum severity grade as mild (52.9% in the tadalafil group and 33.3% in the placebo group), 7 as moderate (35.3% in the tadalafil group and 5.6% in the placebo group), and 1 as severe (5.6% in the placebo group).

Regarding the adverse events of interest (AESIs) reported during Period 1, one subject in tadalafil group experienced spontaneous intermittent penile erections, and one subject experienced uterine bleeding in the tadalafil group. None of the subjects experienced priapism, hearing or visual abnormalities. There were no pregnancies reported in the study.

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

Clinical laboratory evaluations were conducted only during Period 1. 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.

- Vital Signs, Physical Findings, and Other Observations Related to Safety during Period 1 (Double-Blind Placebo-Controlled):

At the endpoint of Period 1, the mean increase in height was o 2.43 cm (median: 2 cm) in the placebo group and 1.68 cm (median: 1 cm) in the tadalafil group. The mean and median change in weight was ≤1 kg in both treatment groups at the endpoint of Period 1.

Mean decreases from baseline in supine SBP 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 SBP ranging from 0.35 and 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 DBP 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.

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.

2.3.3. Discussion on clinical aspects

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

This Article 46 procedure of Regulation (EC) No1901/2006, concerns the submission of the study H6D-MC-LVHV (LVHV) titled "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", which is part of a clinical development program. Actually, study LVHV is part of an EU Paediatric Investigation Plan (PIP) for tadalafil targeted to grant an indication in the paediatric population for the treatment of pulmonary arterial hypertension (EMA Decision number P/0376/2020; EMEA-000452-PIP02-10-M06) for oral use as film-coated tablets and oral suspension.

Study LVHV 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). Eligible patients were from 6 months to less than 18 years of age with PAH classified as WHO functional Class II or III and were stratified into 3 weight cohorts (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 concomitant ERA (bosentan or other). The study design is considered acceptable for a phase 3, add-on study performed in paediatric subjects from 6 years of age and older with PAH.

The primary objective of study H6D-MC-LVHV (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. Key secondary objectives of Period 2 were to assess the time to clinical worsening (CW) and the incidence of CW, to characterise the population PK of tadalafil in paediatric patients with PAH and to assess the safety of tadalafil compared with placebo. Additional efficacy measurements of tadalafil compared with placebo included changes on WHO functional classification, cardiac MRI parameters, haemodynamics by using echocardiography, NT-Pro-BNP concentrations, and physician/caregiver-reported health outcomes (CGI-I and CHQ-PF28 in subjects ≥5 years of age). The primary objective of study LVHV Period 2 was to evaluate the long-term safety of tadalafil while providing continued access to tadalafil for paediatric patients with PAH who participated in Period 1. The secondary objective was to evaluate the incidence of CW, and time to CW. Changes on 6MWD and WHO functional classification were also evaluated during the Period 2 as additional efficacy measurements. Proposed efficacy and safety endpoints are appears to be relevant to develop a medicinal product for the treatment of PAH in paediatric subjects from 6 years of age and older.

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 the 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.

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%; with 11/18 [61.1%] subjects in the placebo group and 15/17 [88.2%] subjects in the tadalafil group) and 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. 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. Therefore, it should be kept on mind that the lack of enrolled patients in the light-weight (<25 kg) cohort or enrolled patients with forms of associated pulmonary arterial hypertension (APAH) due to congenital heart disease, different to PAH associated with systemic to pulmonary shunts (such as Eisenmenger syndrome, PAH with small defects and PAH after corrective cardiac surgery subpopulations), could negatively impact on the limits of a claimed therapeutic indication for the treatment of pulmonary arterial hypertension in the paediatric population.

There were thirty-two subjects, 14 male and 18 female, who continued to Period 2. The most commonly received concomitant ERA was bosentan (n= 30; 93.8% of the subjects). For Period 2, PAH aetiologies were idiopathic PAH (n=25; 78.1%) and PAH associated with persisting or recurrent pulmonary hypertension after repair of a congenital systemic to pulmonary shunt (n=7; 21.9%), and the majority of subjects had WHO functional Class II (n=25; 78.1%). The majority of subjects, 23 (71.9%) were in the heavy-weight group with the remainder 9 (28.1%) in the middle-weight group.

As there was no subject from the light-weight cohort, tadalafil was only administered as 20 mg tablets during study LVHV. The administered doses were 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.

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.

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.

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 plasma tadalafil concentrations observed in study LVHV appears to be comparable to those observed in the paediatric study LVIG for subjects receiving 20 or 40 mg tadalafil with concomitant bosentan. The plasma tadalafil concentrations observed in this study were comparable to those observed in the adult study LVGY for its subgroup of patients already on bosentan therapy who were administered 20 or 40 mg tadalafil and within the exposure range of the approved 40 mg dose. Moreover, the adult LVGY exposure–response model appeared to adequately predict the 6MWD data from study LVHV.

As regards of the study LVHV safety results, there were no deaths in Periods 1 and 2. There were no SAEs or discontinuations due to AEs during Period 1, but 5 SAEs (acute right ventricular failure, anaemia, gastroenteritis, haemoptysis, 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.

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 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 $\geqslant$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). Only 1 subject in the tadalafil group experienced 1 AE of hepatic enzyme elevation was reported with ALT level 80 IU/L (reference range 6 to 43 IU/L), but did not meet the criteria of having an AST and ALT more than 3-

fold the ULN when assessed the chemistry test results related to hepatic functions (ALT, AST, and total bilirubin).

For Period 2, there were 23 subjects who reported at least 1 TEAE, being the most common (≥2 subjects) in any group, headache, dizziness, nasopharyngitis and vomiting; each TEAE was 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 subjects (2/16 [12.5%] subjects in the Pla-Tad group and 3/16 [18.8%] subjects in the Tad-Tad group) during Period 2. Procedure-related event (anxiety) was reported in 1 subject in the Pla-Tad group. The most common of these AEs occurring in Period 2 were dizziness and headache (6.3% in the Tad-Tad group and the Pla-Tad group each).

There were 8 AEs of special interest (AESIs) that occurred in tadalafil treated subjects. A total of 2 subjects (1 in each period; 2 AE) experienced spontaneous intermittent penile erection during the study LVHV. There was 1 event of a visual abnormality (photopsia) during Period 2 that was not considered to be related to tadalafil as judged by the Investigator. There were 4 subjects (all on tadalafil; 5 AEs) with uterine bleeding during the study. One of them was associated with an SAE of anaemia and required a blood transfusion. There were no AEs of priapism and none of the subjects experienced hearing abnormalities during the study. There were no pregnancies reported in the study.

At the endpoint of Period 2, the mean (median) weight increases from baseline to endpoint (Visit 17) in all subjects were 5.73 (4.95) kg and 5.16 (3.10) kg in the Pla-Tad and Tad-Tad groups, respectively. The mean change from baseline height was 9.82 cm (median: 10.5 cm) in the Pla-Tad group and 6.11 cm (median: 3 cm) in the Tad-Tad group.

There were no AEs related to ECG findings observed in the study.

During the study LVHV, no clinical information of relevance was provided as regards of intellectual ability and cognitive function assessments. Moreover, there were no clinically significant trends or changes from baseline in vital signs, eye examinations, inhibin B biomarker concentrations and Tanner score.

There were no clinically relevant mean changes from baseline to end of Period 1 (Week 24) in laboratory parameters in both placebo and tadalafil treatment groups.

Overall, the safety profile of tadalafil in Period 2 was similar to the safety profile observed in Period 1, with no new safety signals. Tadalafil safety profile observed in the study LVHV (Period 1 and 2) was consistent with the already known safety profile of tadalafil in adults with PAH.

3. Overall conclusion and recommendation

Overall, the obtained results appear to reflect a positive trend on efficacy of tadalafil in a small sample size (n=35) of paediatric subjects from 6 years of age and older with PAH (idiopathic PAH [74.3%] and PAH associated with persisting or recurrent pulmonary hypertension after repair of a congenital systemic to pulmonary shunt [25.7%]) classified as WHO functional Class II or III who were treated concomitantly with an ERA. The safety profile of tadalafil was similar in both Period 1 and Period 2 of the study, with no new safety signals. Tadalafil safety profile observed in the study LVHV (Period 1 and 2) was consistent with the already known safety profile of tadalafil in adults with PAH.

In summary, the study H6D-MC-LVHV (LVHV) conducted as a part of the PIP does not raise any major safety concern. The variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by 20 December 2021, which is agreed.

☒ **Fulfilled:**

No further action required.

Further data are expected to be submitted by the Applicant in the context of a variation application to include paediatric data in the product information. The MAH has indicated that they will submit this application by 20 December 2021, which is agreed.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Adcirca (previously Tadalafil Lilly) Active substance: tadalafil

Study title	Study number	Date of completion	Date of submission of final study report
Not applicable	Not applicable	Not applicable	Not applicable

Clinical studies

Product Name: Adcirca (previously Tadalafil Lilly) Active substance: tadalafil

Study title	Study number	Date of completion	Date of submission of final study report
H6D-MC-LVIF: Open-label, randomised, single-dose trial in healthy adult subjects to evaluate bioavailability of a tadalafil suspension (2 mg/ml) compared to marketed tadalafil film-coated tablets.	PIP study number: Study 2	March 2020	The final study report has not been submitted to the EMA under Article 46 as this was not a paediatric study.
H6D-MC-LVIG: Open-label multicentre, 2-period, multiple ascending dose trial to evaluate pharmacokinetics and safety of tadalafil administered orally in children from 6 months to less than 18 years with pulmonary arterial hypertension (PAH) with an open-label long-term extension.	PIP study number: Study 3	April 2019	The final study report has been already submitted to the EMA under Article 46.
(H6D-MC-LVHV): Randomised multicentre, double-blind, add on, 2-period study to evaluate efficacy and long-term safety of tadalafil administered once daily as a tablet or suspension to children from 6 months to less than 18 years of age with PAH with an open-label long-term extension.	PIP study number: Study 4	Period I: May 2019 Period II: March 2021	included in this submission.
Pharmacokinetic (PK) and exposure-response (ER) modelling and simulation study to support tadalafil dose recommendation for treatment of paediatric pulmonary arterial hypertension (PAH).	PIP study number: Study 7	November 2019	
Extrapolation study to evaluate the efficacy of tadalafil in paediatric pulmonary arterial hypertension (PAH) based on the change in 6 Minute Walking Distance (6MWD) observed in Study LVHV.	PIP study number: Study 8	November 2019	