Protocol H6D-MC-LVHV (c)

A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension

NCT01824290

Approval Date: 13-Dec-2018

1. Protocol H6D-MC-LVHV (c)
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Tadalafil (LY450190)

Study H6D-MC-LVHV (LVHV) is a Phase 3, international, randomized, multicenter, 2-period, double-blind, placebo-controlled (Period 1), add-on (in addition to the patient's current endothelin receptor antagonist, ERA) study to evaluate tadalafil efficacy, safety, and population pharmacokinetics (PK) in pediatric patients with pulmonary arterial hypertension (PAH).

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2. Synopsis

Study Rationale

Currently there are a limited number of therapies approved for the treatment of children with pulmonary arterial hypertension (PAH); bosentan (United States [US] and European Union [EU]) and sildenafil (EU). There is a growing body of evidence, however, supporting the use of therapies approved in the adult population with PAH that has led to widespread off-label use in this pediatric population. There continues to be, however, a need for robust data to inform prescribing physicians regarding the safety and efficacy of all treatment options, including tadalafil, in the pediatric PAH population.

This is the first Phase 3 study of tadalafil for use in treating PAH in pediatric patients.

Clinical Protocol Synopsis: Study H6D-MC-LVHV

Name of Investigational Product: Tadalafil (LY450190)

Title of Study: A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension

Number of Planned Patients/Subjects:	**Phase of Development:** 3
Entered: 50 Enrolled/Randomized: 34 Completed: 30	

Length of Study: Planned first patient visit: Q1 2013
Planned last patient visit: Period 1: Q1 2019; Period 2, Q1 2021

Objectives:

Primary Objectives:

Period 1:

- The primary objective of Period 1 is 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 are developmentally capable of performing a 6-minute walk (6MW) test.

Period 2: The primary objective of Period 2 is to evaluate long-term safety of tadalafil while providing continued access to tadalafil for pediatric patients with PAH who participated in Period 1.

Secondary Objectives:

Period 1: The secondary objectives of Period 1 are as follows:

- Assess the efficacy of tadalafil compared with placebo on time to clinical worsening (CW) and the incidence of CW.
- Characterize the population pharmacokinetics (PK) of tadalafil in pediatric pulmonary arterial hypertension (PAH) patients.
- Assess the safety of tadalafil as compared with placebo.

Period 2: The secondary objective of Period 2 is to evaluate the incidence of and time to CW.

Additional Objectives:

Period 1: Additional objectives of Period 1 are as follows:

- Assess the efficacy of tadalafil compared with placebo on changes in World Health Organization (WHO) functional classification.
- 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
- Evaluate by echocardiography, changes from Day 1 to Week 24 in the following echocardiographic parameters:
  - tricuspid annular plane systolic excursion (TAPSE)
  - eccentricity index, pericardial effusion
  - maximal tricuspid regurgitant velocity
- Evaluate change from Day 1 to Week 24 in N-terminal prohormone brain natriuretic peptide (NT-Pro-BNP) concentrations.
- Assess physician- and caregiver-reported health outcome, as measured by Clinical Global Impression of Improvement (CGI-I), and in a subset of patients ≥5 years of age, Child Health Questionnaire Parent Form 28 (CHQ-PF28).

Study Design: A Phase 3, international, randomized multicenter, 2-period, double-blind, placebo-controlled, add-on (in addition to the patient's current endothelin receptor antagonist [ERA]) study to evaluate tadalafil efficacy, safety, and population PK in pediatric patients with PAH.

Screening and eligibility evaluation will be performed during an approximately 28-day period prior to randomization and the administration of tadalafil. Period 1 is a 24-week study drug treatment phase. During this study period, patients will continue to receive stable ERA therapy. Period 2 is an open-label extension (OLE) period that will evaluate the long-term safety of tadalafil while providing continued access to tadalafil for pediatric patients completing Period 1. Patients entering Period 1 of the study will be 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 to tadalafil or placebo.

Diagnosis and Main Criteria for Inclusion and Exclusion At least 34 PAH patients ≥6 months to <18 years of age with WHO functional class II or III (at screening) will be randomized to include at least 30% of patients <12 years of age.

Inclusion criteria:

- Diagnosis of PAH that is either:
  - idiopathic, including hereditary;
  - related to connective tissue disease;
  - related to anorexigen use;
  - associated with surgical repair of at least 6-month duration of simple congenital systemic to pulmonary shunt (eg, atrial septal defect, ventricular septal defect, patent ductus arteriosus)
- 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 pulmonary vascular resistance (PVR) ≥3 Wood units via right heart catheterization (RHC). In the event that a pulmonary artery wedge pressure cannot be obtained during RHC, patients with a left ventricular end diastolic pressure (LVEDP) <15 mm Hg, with normal left heart function, and absence of mitral stenosis on echocardiography can be eligible for enrollment.
- Receiving an endothelin receptor antagonist (ERA, eg, bosentan or ambrisentan) and must be on a maintenance dose with no change in dose (other than weight-based adjustments) for at least 12 weeks prior to screening and have a screening aspartate transaminase (AST)/alanine transaminase (ALT) <3 times the upper limit of normal (ULN).
- If on conventional PAH medication, including but not restricted to, anticoagulants, diuretics, digoxin, and oxygen therapy, the patient must be 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).

Main Exclusion Criteria:

- Pulmonary hypertension related to conditions other than specified above.
- History of left-sided heart disease, including any of the following:
  - clinically significant (pulmonary artery occlusion pressure [PAOP] 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 (MUGA), angiography, or echocardiography;
  - left ventricular shortening fraction < 22% by echocardiography;
  - life-threatening cardiac arrhythmias;
  - symptomatic coronary artery disease within 5 years of study entry.
- Unrepaired congenital heart disease.
- History of angina pectoris or other condition that was treated with long- or short-acting nitrates within 12 weeks before administration of study drug.
- Severe hepatic impairment, Child-Pugh Grade C.
- Severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 30 mL/min (Schwartz Formula).
- Retinal disorder (eg, hereditary retinal disorders, retinopathy of the preterm patient and other retinal disorders).
- Severe hypotension or uncontrolled hypertension as determined by the Investigator.
- Significant parenchymal lung disease or bronchopulmonary dysplasia.
- Concurrent phosphodiesterase type 5 (PDE5) inhibitor therapy (sildenafil or vardenafil) or has received PDE5 inhibitor therapy within 12 weeks prior to the first study drug 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, anti-coagulants, digoxin, and oxygen therapy within 4 weeks of screening.
- Currently receiving treatment with doxazosin, nitrates, or cancer therapy.
- 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.
- Nursing or pregnant.
- Received tadalafil therapy within 12 weeks prior to the first study drug dosing or are hypersensitive to tadalafil.
- Allergy to the excipients, notably lactose
- Unable to take orally administered tablets (without chewing, crushing or breaking) or suspension.
- Diagnosis of Down syndrome.

Investigational Product, Dosage, and Mode of Administration or Intervention: Period 1: Tadalafil, 5 mg to 40 mg, depending on treatment cohort, given once a day as 2.5 mg, 5 mg, 10 mg and 20 mg tablets or 2.5 mg/mL tadalafil suspension given orally. Period 2: Patients receiving tadalafil in Period 1 will continue at same dose in Period 2. Patients receiving placebo in Period 1 will receive tadalafil in Period 2 at the corresponding tadalafil dose in that patient's weight group. All patients in Period 2 will receive tadalafil for at least 2 years.

Planned Duration of Treatment: Approximately 2 years, 7 months: Screening Period, approximately 28 days; Period 1 treatment, 24 weeks; Period 2 treatment, 2 years.

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: Period 1: Matching placebo Period 2: No comparator during Period 2.

Criteria for Evaluation:

Efficacy:

Primary Measures (Period 1):

- The primary efficacy measure is 6MWD in meters assessed in a subset of patients ≥6 to <18 years of age who are developmentally capable of performing a 6MW test.

Secondary Measures (Period 1):

- Time to CW and the incidence of CW.

Secondary Measures (Period 2):

- Incidence of and time to CW.

Additional Measures (Period 1):

- WHO functional classification
- Cardiac MRI parameters:
  - LV ejection fraction
  - RV end diastolic volume
  - RV end systolic volume
  - RV ejection fraction
- Echocardiography parameters:
  - tricuspid annular plane systolic excursion (TAPSE)
  - eccentricity index
  - pericardial effusion
  - maximal tricuspid regurgitant velocity
- NT-Pro-BNP concentrations.

Additional Measures (Period 2):

- 6MW distance in meters measured in patients who are ≥6 years of age and who are developmentally capable of performing a 6MW test.
- WHO functional classification

Safety: Period 1: Safety during Period 1 will be assessed through AEs including abnormalities detected by ECG or physical examination, clinical chemistry and hematology panels, urinalysis, vital signs, and eye examinations. Period 2: AEs, changes in body weight and height, inhibin B biomarker (male patients only), eye examinations, Tanner scale, and intelligence tests, and concomitant medications.

Health Outcomes:

- CGI-I, CHQ-PF28 (in patients ≥5 years of age).

Pharmacokinetics: Population PK assessment of plasma tadalafil concentrations at steady-state.

Statistical Methods: Results of statistical hypothesis tests will be reported using 2-sided p-values, unless otherwise specified for a particular endpoint.

Sample Size: At least 34 patients will be stratified by weight and randomized in a 1:1 ratio to tadalafil or placebo treatment in this study (17 to placebo treatment and 17 to tadalafil treatment).

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.

Efficacy: Efficacy analyses of Period 1 data, except 6MW measurements, will include all patients who were randomized and took at least 1 dose of study medication. The analysis of 6MW data will include only the subset of randomized patients ≥6 to <18 years of age who took at least 1 dose of study medication and were capable of performing a 6MW test. Changes from Day 1 to Weeks 4, 8, 12, 16, 20, and 24 in 6MW distance will be analyzed with a mixed-effects model for repeated measures (MMRM).

Change from Day 1 of Period 1 in 6MW distance and WHO functional class will be reported for all patients who participate in Period 2.

The primary efficacy endpoint of change from baseline in 6MW distance will be analyzed using a mixed model for repeated measures (MMRM). Terms in the model will include visit, baseline 6MW measurement, PAH etiology, type of ERA therapy, and treatment group.

The proportion of patients who experience a change in WHO functional class will be summarized. Changes will also be categorized as "worsening, "no change," or "improving" over the study period. The percentages of patients in these categories will be summarized by treatment groups.

An interim analysis of 6MW data is planned in approximately Q1 2017 when approximately 50% of all randomized patients (Period 1) have baseline and Week 24 6MW measurements available for analysis. The results of this interim analysis will be reviewed by a data monitoring committee (DMC) to assess evidence of efficacy and the accuracy of study design assumptions.

The database will be locked, and data collected during Period 1 will be analyzed when all randomized patients have ended participation in Period 1. These results will be reported in a clinical study report. An addendum to the initial clinical study report will be prepared at the conclusion of Period 2 to present analyses of the **OLE** data.

Changes from Day 1 to endpoint in hemodynamic parameters collected via echocardiogram and MRI will be analyzed with analysis of covariance (ANCOVA) models. Similarly, changes in log-transformed NT-Pro-BNP values will be analyzed with an analysis of variance (ANOVA) model.

Safety: The analysis of safety will include all patients who took at least 1 dose of study medication. The differences in the percentages of patients experiencing AEs across various criteria (for example, treatment-emergent, treatment-related, serious, etc.) will be summarized.

Changes from Day 1 in clinical laboratory measurements, biomarker (inhibin B) concentrations, blood pressure, and heart rate (HR) will be analyzed with ranked ANOVA models with a term for treatment group. Differences in categorical changes will be summarized.

Changes from Day 1 in composite intelligence scores will be assessed according to the published instructions for each instrument. The numbers and percentages of patients in each treatment group with shifts in Tanner stage at Year 1 and Year 2 will be summarized.

Health Outcomes: An ANCOVA analysis will be used to examine changes from Day 1 to Weeks 16 and 24 in CHQ-PF28 scores. Patient outcome will be assessed using the CGI-I at Weeks 16 and 24 (Visits 7 and 9) using an ordinal scale with 7 response categories ranging from "Very Much Better" to "Very Much Worse". Responses will also be grouped into 3 derived categories ("Worse", "No Change", and "Better") for additional analysis. The proportion of patients in each of the 7 response categories and each of the 3 derived categories will be summarized by treatment group.

Pharmacokinetics: Plasma tadalafil concentration-time data will be pooled and evaluated using a population PK approach. The effects of body weight, age, and sex on apparent clearance (CL/F) will be explored. If the number of patients taking different types of ERA is sufficient to quantify the effect of ERA on apparent clearance, then this will also be done. Due to random PK sampling times and the low number of samples available from each individual patient, it may be necessary to combine the data from this study with the densely sampled data from Study LVIG to better characterize the population PK of tadalafil in this patient population.

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A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension

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4. Abbreviations and Definitions

Term	Definition
6MW	6-minute walk
6MWD	6-minute walk distance
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
AST	aspartate transaminase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BPH	benign prostatic hyperplasia
case report form (CRF) and electronic case report form (eCRF)	Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CC	creatinine clearance
CEC	Clinical Endpoint Committee
CGI-I	Clinical Global Impression of Improvement
cGMP	cyclic guanosine monophosphate
CHQ-PF28	Child Health Questionnaire Parent Form 28
CIOMS	Council for International Organizations of Medical Sciences
clinical research physician (CRP)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

CL/F	apparent clearance
CMH	Cochran-Mantel-Haenszel
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CW	clinical worsening
DMC	data monitoring committee
ECG	electrocardiogram
ED	erectile dysfunction
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
EMA	European Medicines Agency
end of study (trial)	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
enroll/randomize	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter/consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.
ERA	endothelin receptor antagonist
ERB	ethical review board
ERS	European Respiratory Society
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
GCP	good clinical practice

HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug application
institutional review board/ethical review board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
intention to treat (ITT)	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the Investigator is the responsible leader of the team and may be called the principal Investigator.
IXRS	interactive voice or web response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
LOCF	last observation carried forward
LV	left ventricular
LVEDP	left ventricular end diastolic pressure
MedDRA	*Medical Dictionary for Regulatory Activities*
MMRM	mixed-effects model for repeated measures
mPAP	mean pulmonary artery pressure
MRI	magnetic resonance imaging
MUGA	multigated radionucleotide angiogram
NT-Pro-BNP	N-terminal prohormone brain natriuretic peptide
OLE	open-label extension
PAH	pulmonary arterial hypertension

PAOP	pulmonary artery occlusion pressure
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PDE5	phosphodiesterase type 5
PK	pharmacokinetic(s)
PVR	pulmonary vascular resistance
QoL	quality of life
RHC	right heart catheterization
RV	right ventricular
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSARs	suspected unexpected serious adverse reactions
TAPSE	Tricuspid Annular Plane Systolic Excursion
TPO	third-party organization
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
US	United States
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organization
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension

5. Introduction

Pulmonary arterial hypertension (PAH) is a rare, chronic and progressive disease characterized by elevated pulmonary artery pressure and pulmonary vascular resistance, leading to right-heart failure and death (Rich 1998; Barst 2004). PAH can be further classified into idiopathic PAH, heritable PAH, and associated PAH. Conditions that are associated with PAH include connective tissue diseases (particularly systemic sclerosis and lupus), congenital heart disease, portal hypertension, human immunodeficiency virus (HIV) infection, and some drugs (particularly anorexigens).

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), the endothelin receptor antagonists (ERAs) (bosentan and ambrisentan), and the phosphodiesterase type 5 (PDE5) inhibitors (sildenafil and tadalafil).

While PAH is more common in the adult population, it does occur in children with a similar, if not worse, prognosis without treatment. However, with treatment the outcome appears better in children than in adults. Due to limited clinical data in children, treatment decisions are extrapolated from adult studies. Similar clinical strategies from adults have been suggested for the management of PAH in children, but these guidelines must be used with caution (McLaughlin et al. 2009a). Currently, bosentan is the only approved drug for the treatment of pediatric patients with PAH in the United States (US). In the European Union (EU), bosentan and sildenafil are approved for the same pediatric indication. There is a growing body of evidence supporting the use of therapies approved in adults that has led to widespread off-label use (Beghetti 2009). There is a need, therefore, to provide physicians with safety and efficacy results of all treatment options, including tadalafil, in the pediatric population.

Tadalafil is an orally administered, potent, and selective PDE5 inhibitor that has been investigated at doses of 2.5 mg to 100 mg (predominantly in adult men at doses of 10 mg and 20 mg on-demand, and 2.5 mg and 5 mg taken once daily). Tadalafil is currently approved in the US, EU, and Japan for the treatment of erectile dysfunction (ED), both on-demand and once daily. Tadalafil is the active ingredient of Adcirca®, that was recently approved for the treatment of PAH (pulmonary hypertension Group 1) in adults in the EU, US, Canada, and Japan. Tadalafil was also approved for the treatment of benign prostatic hyperplasia (BPH) in the US.

PAH is associated with impaired release of nitric oxide (NO) due to little or no expression of NO synthase in the vascular endothelium of pulmonary arteries (Giaid and Saleh 1995). PDE5 is the predominant phosphodiesterase isoenzyme in the pulmonary vasculature. As such, PDE5 inhibition potentiates the nitric oxide-mediated pulmonary vasodilator and antiproliferative effects in patients (adults and children) with PAH.

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. Tadalafil 40 mg was well tolerated in the adult PAH patient population with a safety profile similar to that observed in the ED patient population.

There is limited experience with regards to the safety, tolerability, and efficacy of tadalafil in pediatric PAH patients. A recent report on tadalafil in children with PAH has demonstrated that tadalafil was well-tolerated in this patient population (Takatsuki et al. 2012). In a company-sponsored clinical trial, a single 14-year-old female patient (73 kg) received tadalafil 2.5 mg in Study LVGY. This patient completed Study LVGY and subsequently enrolled in the extension Study H6D-MC-LVGX (LVGX), in which she received tadalafil 40 mg.

It has been suggested that the clinical course of PAH in children is less predictable than in adults. If untreated, the condition may progress more rapidly in children, leading to reduced survival in children than in adults over time. Importantly, the safety and efficacy of PAH therapies approved for adults have not been robustly established in pediatric patients due to limited data in children. Given the efficacy and safety results of tadalafil for the treatment of PAH in adults (Study LVGY), and recognizing the importance of providing prescribers and patients with recommendations reflecting tadalafil experience across developmental stages, Lilly is pursuing the development of tadalafil for the treatment of PAH in patients, aged ≥6 months to <18 years.

This study, H6D-MC-LVHV (LVHV), is a phase 3, international, randomized, double-blind (Period 1), placebo-controlled (Period 1) add-on (in addition to the patient's current ERA) study to explore the efficacy, safety, and population pharmacokinetics (PK) of tadalafil administered orally once daily in children with PAH. Patients will receive study drug for 6 months in the double-blind period (Period 1), and will then be eligible to enroll into an open-label 2-year extension period (Period 2).

Study LVHV will include children who, at the time of screening, are ≥6 months of age and <18 years of age. Patients will be stratified into 3 weight cohorts (Heavy-weight, ≥40 kg; Middle-weight, ≥25 kg to <40 kg; and Light-weight, <25 kg), and then randomized to tadalafil or placebo. The dose of each weight cohort in this study will be established and may be redefined based on safety monitoring committee (SMC) and Sponsor review of the PK and safety results from Study H6D-MC-LVIG (LVIG). Study LVIG is an open-label, multiple ascending-dose study to evaluate the safety and PK of tadalafil administered orally as a tablet or suspension to children with PAH. Study LVIG includes 2 study periods: PK/safety (Period 1) and an open-label safety extension (Period 2). The primary objective of Period 1 of Study LVIG is to characterize the PK of tadalafil in a pediatric population with PAH. The objectives of Period 2 are to evaluate the long-term safety of tadalafil as well as clinical worsening (CW) of PAH in this patient population.

The study design for this study was developed to treat pediatric patients who are on stable PAH therapy of an endothelin receptor antagonist (ERA) as standard of care instead of PAH

treatment-naïve patients, as that is seen as unethical by the prescribing community, and has the agreement of the Food and Drug Administration (FDA) and European Medicines Agency (EMA). The primary efficacy measure will be 6-minute walk distance (6MWD) distance. Safety will be assessed using spontaneously reported adverse events (AEs), vital signs, laboratory analytes, electrocardiograms (ECGs), eye examinations, and concomitant medications.

More detailed information about the known benefits and risks of tadalafil may be found in the Investigator's Brochure (IB).

6. Objectives

6.1. Primary Objectives

6.1.1. Period 1

The primary objective of Period 1 is to evaluate the efficacy of tadalafil compared with placebo in improving 6MWD from baseline to Week 24, as assessed in a subset of patients ≥6 to <18 years of age who are developmentally capable of performing a 6-minute walk (6MW) test.

6.1.2. Period 2

The primary objective of Period 2 is to evaluate long-term safety of tadalafil while providing continued access to tadalafil for pediatric patients with PAH who participated in Period 1.

6.2. Secondary Objectives

6.2.1. Period 1

The secondary objectives of Period 1 are as follows:

- Assess the efficacy of tadalafil compared with placebo on time to CW and the incidence of CW.
-
- Characterize the population PK of tadalafil in pediatric PAH patients.
- Assess the safety of tadalafil compared with placebo.

6.2.2. Period 2

The secondary objective of Period 2 is to evaluate the incidence of, and time to CW.

6.3. Additional Objectives

6.3.1. Period 1

Additional objectives of Period 1 are as follows:

- Assess the efficacy of tadalafil compared with placebo on changes in WHO functional classification.
- 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
- Evaluate by echocardiography, changes from Day 1 to Week 24 in the following echocardiographic parameters:

  - tricuspid annular plane systolic excursion (TAPSE)
  - eccentricity index
  - pericardial effusion
  - maximal tricuspid regurgitant velocity
- Evaluate change from Day 1 to Week 24 in N-terminal prohormone brain natriuretic peptide (NT-Pro-BNP) concentrations.
- Assess physician- and caregiver-reported health outcome, as measured by Clinical Global Impression of Improvement (CGI-I), and in a subset of patients ≥5 years of age, Child Health Questionnaire Parent Form 28 (CHQ-PF28).

7. Investigational Plan

7.1. Summary of Study Design

Figure LVHV.7.1 illustrates the study design and the respective study periods. The Study Schedule is in Attachment 1.

This is a Phase 3, international, randomized multicenter, 2-period, double-blind (Period 1), placebo-controlled (Period 1), add-on (ie, in addition to the patient's current ERA) study to evaluate the efficacy, safety, and population PK of tadalafil in pediatric patients with PAH.

Study LVHV will enroll pediatric PAH patients ≥6 months to <18 years of age with WHO functional class II or III (Attachment 8) and who are already receiving treatment with an ERA. Patients will be randomized to receive either placebo or active drug in a 1:1 ratio, based on weight cohort, PAH etiology, and type of ERA. Patients will receive study treatment for 6 months in the double-blind period (Period 1), and then will be eligible to enroll into an open-label 2-year extension period (Period 2) during which patients will receive tadalafil.

At least 34 patients will be randomly assigned to treatment in Period 1 of this study. To achieve a representative distribution of patients' ages, enrollment will be monitored throughout the study to achieve ≥30% of all patients < 12 years of age.

Patients entering the study will be stratified into 1 of 3 weight-cohorts, based on the patient's weight at the time of the Screening visit:

Heavy-weight: ≥40 kg
Middle-weight: ≥25 kg to <40 kg
Light-weight: <25 kg

If a patient's weight changes during Period 1, such that he/she falls into a different weight cohort, he/she will continue to receive the study drug dose appropriate to his/her original weight cohort.

Patients will also be stratified by type of ERA (bosentan or other) and PAH etiology.

If a patient will be participating in Period 2, and if that patient's weight changes at the conclusion of Period 1 (at the Visit 9 or Early Termination visit) or during Period 2, such that he/she falls into a different weight cohort (defined as at least 1 kg above or below the weight cohort thresholds of 25 kg and 40 kg), then the patient's dose of study drug may be adjusted so that they are receiving the appropriate weight cohort-related dose.

Dose selection for this study will be based on pediatric PK and safety data from Study LVIG and the PK and safety data from the adult PAH development plan. The selected dose for each weight cohort will reflect exposures comparable to the approved 40-mg dose of tadalafil in adults, unless unexpected safety concerns unique to the pediatric population are revealed. Dosing of all weight cohorts is also described in Section 9.

		Study Period 1 Double-Blind Treatment N = 134 (1:1 ration, 67 per arm)													Study Period 2 Open-Label Extension							
		Tadalafil[a]													Tadalafil							
		Placebo																			
Visit	Screening[b]	2	3	4		5		6		7		8		9	10	11	12	13	14	15	16	17
Week[c]	0	Day 1	2	4		8		12		16		20		24								
Month[d]															3	6	9	12	15	18	21	24
		Stratification/Randomization																				

a Final dose to be determined after the cohort completion in Study H6D-MC-LVIG.
b Screening period is days -28 to 0.
c Weeks = ±7days.
d Months = ±10 days. Month 3 is 3 months from Visit 9; all other months (6, 9, 12, 15, 18, 21, and 24) are in relation to Visit 10.

Figure LVHV.7.1. Illustration of Study Design for Protocol H6D-MC-LVHV

Study LVHV will start to enroll patients once the appropriate PK and safety data in Study LVIG have been evaluated by a Safety Monitoring Committee (SMC). Planned tadalafil doses (Table LVHV.9.1) for all weight cohorts in Study LVHV may be redefined prior to the start of the study based on SMC and Sponsor review of the PK and safety data from Study LVIG. The safety of patients in Study LVHV will be monitored by an external data monitoring committee (DMC).

7.1.1. Screening Phase (Visit 1)

Screening and eligibility evaluations will be performed during an approximately 28-day period prior to randomizing patients to study treatment (Attachment 1). At or before Visit 1, the study and potential risks will be explained to patients and parents/legal representatives (hereafter, "parent" is used to refer to "parent" or "legal representative"). Parents will sign and date the informed consent form (ICF), and the patients will sign and date the assent document (if capable) if required by the institutional review board (IRB) or local law prior to any screening or Day 1 assessments. Qualified patients who meet inclusion and exclusion criteria will be enrolled into Period 1.

The Screening visit (Visit 1) will consist of a full clinical assessment, as detailed in the Study Schedule (Attachment 1), including a medical evaluation, assessment of PAH severity, physical examination, concomitant medications, laboratory tests, and the Clinician Global Impression of Severity (CGI-S, Day 1 only).

7.1.2. Study Period 1: Double-Blind Treatment Phase (Visits 2 to 9)

Study Period 1 is a 24-week, double-blind treatment phase that will include 8 site Visits (Attachment 1). During this study period, patients will continue to receive stable ERA therapy.

Day 1 (Visit 2) assessments that were not collected during screening will be collected prior to randomization at Day 1 (Visit 2). Patients who have completed all Day 1 (Visit 2) assessments and who meet all criteria for enrollment will be randomly assigned to either placebo or tadalafil at Day 1 (Visit 2) by an interactive voice or web response system (IXRS). Investigators will remain blinded to the patient's treatment assignment. The first dose of assigned treatment will be administered at Day 1 (Visit 2).

The 6MW test will occur on Day 1 (Visit 2), and at Weeks 4, 8, 12, 16, 20, and 24 (Visits 4 to 9) for those patients who are ≥6 years of age at Day 1 (Visit 2) and are developmentally capable of performing the test.

Echocardiography to obtain cardiopulmonary hemodynamics will occur at Day 1 (Visit 2) and Weeks 8, 16, and 24 (Visits 5, 7, and 9, respectively). Cardiac MRI to obtain cardiopulmonary hemodynamics will occur at Day 1 (Visit 2) and Week 24 (Visit 9) at selected sites that have been using MRI as routine PAH patient management. The detailed procedures for echocardiography and cardiac MRI will be provided separately to the Investigator sites.

A single blood sample will be collected at Weeks 2, 4, 16, and 24 (Visits 3, 4, 7, and 9, respectively), for analysis of plasma tadalafil concentrations (Section 10.4.1. and Attachment 1).

Safety evaluations will consist of vital signs, ECGs, physical examination, laboratory evaluations, eye examinations, and concomitant medications; these will be performed at times specified in the Study Schedule (Attachment 1). AEs will be assessed at all site visits during the study.

7.1.3. Study Period 2: Open-Label Extension (Visits 10-17)

During Period 2 the long-term safety of tadalafil in pediatric patients with PAH will be evaluated.

Patients who participated in Period 1 will be eligible to participate in Period 2. Patients who experience CW (defined in Section 10.1.2) during Period 1 will be discontinued from Period 1 and may also participate in Period 2, at the Investigator's discretion.

Investigator site visits during Period 2 will occur every 3 months in accordance with the LVHV study schedule (Attachment 1).

Period 2 will continue for at least 2 years or until the Sponsor concludes the study.

Patients receiving tadalafil in Period 1 will continue at the same dose in Period 2, unless the patient has changed his/her weight cohort at the end of Period 1 (at Visit 9 or the Early Termination visit). Patients receiving placebo in Period 1 will receive tadalafil in Period 2 at the corresponding tadalafil dose for the patient's weight cohort at entry into Period 2 (Table LVHV.9.1). During Period 2, the dose of tadalafil may be adjusted if the patient's weight changes by at least 1 kg over or below the weight cohort thresholds of 25 kg and 40 kg. If this weight change occurs, the patient's dose of study drug may be adjusted so that they are receiving the appropriate weight cohort-related dose. During this study period, patients will continue to receive stable ERA therapy, which could be adjusted at the Investigator's discretion.

Patients who experience CW (Section 10.1.2) during Period 2 will be managed according to the best treatment options, and will continue to be monitored for safety and efficacy as described in the Study Schedule (Attachment 1).

7.2. Discussion of Design and Control

Study H6D-MC-LVHV (LVHV) is a Phase 3, international, randomized, multicenter, 2-period, double-blind and placebo-controlled (Period 1), add-on study (in addition to the patient's current ERA) to evaluate tadalafil efficacy, safety, and population PK in pediatric patients with PAH. A multicenter trial is necessary to accrue the required number of pediatric patients with PAH to adequately characterize the efficacy and safety of tadalafil in this patient population in a timely manner. The efficacy and safety of tadalafil will be compared with that of placebo group during Period 1.

This study design requires patients to be receiving an ERA (such as bosentan or ambrisentan), and allows for the use of conventional PAH therapies (see Section 8.1). Endothelin receptor

antagonists 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 pediatric PAH patients to treatment with placebo alone may be viewed as unethical. To ensure that treatment assignment is balanced within type of ERA, randomization to treatment will be stratified by type of ERA (bosentan or other).

Stratification by PAH etiology is justified, as the prognosis of patients with PAH is, in part, dependent on etiology. For example, patients with PAH associated with connective tissue disease have a worse prognosis than patients with idiopathic PAH, while patients with PAH associated with congenital heart disease have a better survival (Kähler and Colleselli 2006; McLaughlin et al. 2004).

Randomization stratified by weight is considered reasonable to ensure an appropriate distribution of treatments within weight cohorts. Historically, male and female pediatric growth charts could be globally applied to clinical research based on common weight and age patterns; however, these may not be applicable to pediatric patients with PAH due to differences in disease conditions and due to a modest divergence in body weight and age patterns across geographies. Therefore, treatment randomization will be stratified by weight cohort.

This study is designed to evaluate the efficacy of tadalafil compared with placebo in pediatric patients with PAH. The primary efficacy endpoint will be the change from Baseline (Day 1) to Week 24 in 6MW distance assessed in those patients who are ≥6 years of age at Day 1 (Visit 2) and are developmentally capable of performing the test.

Due to the expected low mortality event rate in this population, mortality rate is not considered an appropriate primary endpoint in PAH studies; therefore, the use of a composite endpoint to define CW (Section 10.1.2) will provide more statistical power to detect a therapeutic effect in a limited sample population with limited individual event rates (Ventetuolo et al. 2008). The proposed definition of CW endpoint (Section 10.1.1) is similar to that used in other trials and takes into account a recent publication that offered recommendations based on historical review of PAH studies on CW as an endpoint (McLaughlin et al. 2009b). While the frequency of events of CW in patients with mild or moderate functional class (II, III) are expected to be low after 16 weeks, evaluation of this endpoint at 24 weeks (6 months) will increase the likelihood of detecting a treatment effect (Rubin et al. 2002).

Exercise capacity is an important prognostic indicator of PAH (Miyamoto et al. 2000). The distance walked during a 6MW test is the most accepted PAH exercise capacity test, as it is simple, well tolerated, and non-invasive (Peacock et al. 2010) and has therefore been the most commonly used clinical trial endpoint for PAH patients ≥6 years of age (Haworth and Beghetti 2010). For Study LVHV, it is expected that approximately 34 enrolled patients will be 6 years of age or older who are developmentally capable of performing the 6MW test. The change in 6MWD compared with placebo will be evaluated up to Week 24.

8. Study Population

Eligibility for enrollment will be based on the results of screening for the following inclusion and exclusion criteria. Entered patients who meet all of the inclusion criteria and are not excluded by an exclusion criterion will proceed to Day 1 (Visit 2), at which time patients will be randomized to treatment.

8.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] ≥6 months to <18 years of age (at screening).

[2] Currently have a diagnosis of PAH that is either:

- idiopathic, including hereditary;
- related to connective tissue disease;
- related to anorexigen use;
- associated with surgical repair of at least 6-month duration of congenital systemic to pulmonary shunt (eg, atrial septal defect, ventricular septal defect, patent ductus arteriosus)

[3] Have 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 right heart catheterization (RHC). In the event that a pulmonary artery wedge pressure cannot be obtained during RHC, patients with a left ventricular end diastolic pressure (LVEDP) <15 mm Hg, with normal left heart function, and absence of mitral stenosis on echocardiography can be eligible for enrollment.

[4] Have a WHO functional class value of II or III at the time of screening.

[5] All subjects must be receiving an ERA (such as bosentan or ambrisentan) and must be on a maintenance dose with no change in dose (other than weight-based adjustments) for at least 12 weeks prior to screening and have a screening aspartate transaminase (AST)/alanine transaminase (ALT) <3 times the upper limit of normal (ULN).

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

[7] Female patients of childbearing potential must test negative for pregnancy during screening. Furthermore, female patients must agree to abstain from sexual activity or to use two different reliable methods of birth control as determined by the Investigator during the study. Examples of reliable birth control methods include true abstinence as a lifestyle choice (periodic sexual abstinence method is not acceptable); the use of oral contraceptives; a reliable barrier method of birth control (diaphragms with contraceptive jelly; cervical caps with contraceptive jelly; condoms with contraceptive foam; intrauterine devices).

[8] Written informed consent from parents (and written assent from appropriately aged patients) will be obtained prior to any study procedure being performed.

8.2. Exclusion Criteria

[9] Have 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.

[10] History of left-sided heart disease, including any of the following:

- clinically significant (pulmonary artery occlusion pressure [PAOP] 15-18 mm Hg) aortic or mitral valve disease (ie, 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 (MUGA), angiography, or echocardiography;
- left ventricular shortening fraction <22% by echocardiography;
- life-threatening cardiac arrhythmias;
- symptomatic coronary artery disease within 5 years of study entry.

[11] Unrepaired congenital heart disease.

[12] Have a history of angina pectoris or other condition that was treated with long- or short-acting nitrates within 12 weeks before administration of study drug.

[13] Have severe hepatic impairment, Child-Pugh Grade C.

[14] Have severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) <30 mL/min (Schwartz Formula):

All Females and Pre-adolescent Males:

C_{cr} (mL/min/1.73 m ^{2}) = 0.55 × Height (cm) / S_{Cr} (mg/dL)

Adolescent Males:

C_{cr} (mL/min/1.73 m ^{2}) = 0.70 × Height (cm) / S_{Cr} (mg/dL)

Where C_{cr} is CC and S_{Cr} is Serum Creatinine

[15] Diagnosed with a retinal disorder (eg, hereditary retinal disorders, retinopathy of the preterm patient and other retinal disorders).

[16] Have severe hypotension or uncontrolled hypertension as determined by the Investigator.

[17] Have significant parenchymal lung disease.

[18] Have bronchopulmonary dysplasia.

[19] Concurrent PDE5 inhibitor therapy (sildenafil or vardenafil) or has received PDE5 inhibitor therapy within 12 weeks prior to the first study drug dosing (Day 1, Visit 2).

[20] Concurrent therapy with prostacyclin or its analogues within 12 weeks of screening.

[21] Commenced or discontinued a chronic conventional PAH medication including but not restricted to: diuretics, anti-coagulants, digoxin, and oxygen therapy within 4 weeks of screening.

[22] Currently receiving treatment with doxazosin, nitrates, or cancer therapy.

[23] 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.

[24] Are nursing or pregnant.

[25] Have previously completed or withdrawn from this study (LVHV), or any other study investigating tadalafil.

[26] Have received tadalafil therapy within 12 weeks prior to the first study drug dosing (Day 1, Visit 2) or are hypersensitive to tadalafil.

[27] Have allergy to the excipients, notably lactose.

[28] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or non approved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study by the Sponsor.

[29] Unable to take orally administered tablets (without chewing, crushing or breaking) or suspension.

[30] Are Investigator site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

[31] Are Lilly employees, (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[32] Diagnosis of Down syndrome.

8.2.1. Rationale for Inclusion and Exclusion of Certain Study Candidates

Inclusion criteria [1], [2], [3], and [4] are in place to ensure that PAH is properly characterized in pediatric patients.

Inclusion criteria [5] and [6] are in place to ensure that patients receiving PAH therapy(s) are stabilized with regards to their therapy(s) prior to entry into this study.

Inclusion criterion [7] is in place to prohibit inclusion of female patients who are pregnant or who are at risk of becoming pregnant.

Inclusion criterion [8] is in place to protect the safety of each patient.

Exclusion criteria [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [24], and [32] are in place to prohibit patients who have physical existing conditions that would confound the trial results and, in the case of exclusion criterion [24], to prevent undue risk to an infant or fetus.

Exclusion criteria [19], [20], [21], [22], and [23] are in place to prohibit the enrollment of patients who are taking medications that would confound the trial results.

Exclusion criteria [25], [26], and [28] are in place to prevent a previously enrolled patient from re-entering the study that may have already had study medication. This would confound the analysis.

Exclusion criteria [27] and [29] are in place to assure that the patients can take the medication in the forms that are available in this trial.

Exclusion criteria [30] and [31] are in place to prevent possible study bias from close relations.

8.3. Discontinuations

Patients who experience CW (defined in Section 10.1.2) during Period 1 may, at the Investigator's discretion, participate in Period 2, during which patients will receive open-label tadalafil treatment and standard of care as deemed by the Investigator, and will continue to be monitored for safety and efficacy (ie, CW). Patients who continue to Period 2 (because they either completed Period 1 or experienced CW in Period 1) will have all of the Week 24 (Visit 9/Early Termination) assessments performed (Attachment 1) before proceeding to Period 2.

For patients who discontinue Period 1 and who do not participate in Period 2, AEs occurring after a patient has taken the last dose of study drug will be collected for 30 days after the last dose of study drug or up to the end of Period I (whichever is longer), regardless of seriousness or the Investigator's opinion of causation. Patients who discontinue in Period 1 and who do not participate in Period 2, will have all of the Week 24 (Visit 9/Early Termination) assessments performed (Attachment 1). If a patient discontinues prior to or at Visit 8, the follow-up visit will be performed 24 weeks after the patient's initial study drug dosing (Visit 9). If a patient discontinues after Visit 8, the follow-up visit will occur 30 days after the patient has taken the last dose of study drug. This visit can be done by phone. Discontinuation of the study drug for abnormal liver tests is discussed in Section 10.3.4.1.

8.3.1. Discontinuation Procedures

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented.

8.3.2. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient will be discontinued from the study, and Lilly or its designee must be contacted.

Patients will be discontinued from the investigational product and from the study in the following circumstances:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- The subject develops a condition or begins a therapy that would have excluded entry into the study, except the following:
  - Exception: A patient receiving an ERA who develops an AST or ALT >3 times ULN may remain in the study, but must have ERA dosage adjustments and monitoring that are consistent with the adult recommendations in the respective ERA labels.
- The Investigator decides that the patient should be withdrawn. If this decision is made because of a serious adverse event (SAE) or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately (Section 10.3).

- If the patient becomes pregnant during the study, the patient must discontinue the study immediately.
- The patient, the patient's parent, or the attending physician requests that the patient be withdrawn from the study.
- The Investigator or Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- The Investigator determines that the patient is repeatedly noncompliant with study procedures and/or study drug.
- If an Investigator, study site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the Investigator must obtain specific approval from the Lilly clinical research physician (CRP).
- If the patient experiences priapism then the patient must be discontinued from the study.
- Patients requiring treatment with any of the prohibited medications.

Patients who discontinue the study early will have the Week 24 (Early Termination visit) procedures performed as shown in the Study Schedule (Attachment 1).

Patients who discontinue the study will have an Early Termination Visit performed at the time of the patient's study discontinuation, or at the earliest possible date (Attachment 1). This early termination visit will be used to collect as many data/samples as practical from the patient. The early termination data/sample collections will be the same as those collected at end of Week 24 of Period 1, or the final visit of Period 2, depending on the timing of discontinuation.

For discontinued patients during Period 1 who do not participate in Period 2, AEs occurring after a patient has taken the last dose of study drug will be collected for an additional 30 days after the last dose of study drug or up to the end of Period I (whichever is longer), regardless of seriousness or the Investigator's opinion of causation. The information can be collected by phone. Discontinued patients will not be replaced.

8.3.3. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the Investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

8.3.4. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Treatments Administered

Patients who meet all eligibility criteria will be randomized to receive tadalafil or matching placebo once daily for 24 weeks in Period 1. In Period 2, all patients will receive tadalafil in an open-label fashion. Tadalafil doses for each weight cohort will be fixed (Table LVHV.9.1).

Tadalafil tablets or tadalafil in suspension will be administered orally with water in the morning of each dose day. The ready-to-use tadalafil suspension should be mixed well by shaking and then administered within 1 hour. The study drug suspension will be directly administered into the mouth using a standard syringe. Additional dilution or combination with other substrates or vehicles is not allowed. Patients may be dosed whether or not they have eaten. Consumption of grapefruit or grapefruit juice should be avoided 1 hour prior to and after dosing.

The proposed tadalafil dose for each weight cohort for this study (Table LVHV.9.1) may be amended prior to the first enrollment into each weight cohort, based on the PK and safety data from the respective weight cohort in Study LVIG. However, the selected dose for each weight cohort is intended to reflect exposures comparable to the approved 40-mg dose of tadalafil in adults, unless unexpected safety concerns unique to the pediatric population are revealed.

During Period 1, patients, study site personnel, and the Sponsor will be blinded to the treatment assignment. During Period 2, all patients will receive tadalafil in an unblinded fashion.

The Investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient and parent, verifying that instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

Patients and/or parents will be instructed to contact the Investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.2. Materials and Supplies

Clinical trial materials will be labeled according to the country's regulatory requirements.

The dose formulations that will be used in this study consist of tadalafil tablets, 2.5, 5, 10, or 20 mg, an oral suspension formulation (2.0 mg/mL tadalafil), or matching placebo. Study medication tablets will be provided in bottles or blister.

Tadalafil oral suspension and matched placebo will be available as a ready-to-use oral suspension containing 2 mg/mL tadalafil. Tadalafil liquid suspension will be provided in a bottle and doses will be delivered to the patient using a standard syringe.

9.3. Method of Assignment to Treatment

Eligible patients will be randomized at the study level and stratified by weight cohorts of heavy, middle, or light (Section 7.1), PAH etiology (idiopathic-heritable, connective tissue/congenital heart disease, or other) and type of concomitant ERA (bosentan or other).

Assignment to treatment groups will be determined by a computer-generated random sequence using an IXRS. The IXRS will be used to assign bottles of tablets or liquid suspension containing double-blind study drug to each patient. An appropriate amount of investigational product will be assigned to each patient to cover the study visit interval. Site personnel will confirm 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.

9.4. Rationale for Selection of Doses in the Study

The dose selection strategy for pediatrics with PAH in this study will be based on data from the tadalafil clinical development program, including data from the LVIG pediatric study and Study LVGY in adults with PAH. The goal is to utilize tadalafil doses administered once-daily that deliver tadalafil exposures similar to those observed in adults receiving tadalafil 40 mg once-daily.

The proposed tadalafil dose for each weight cohort for this study (Table LVHV.9.1) may be amended prior to the first enrollment into each weight cohort, based on the PK and safety data from the respective weight cohort in Study LVIG. Additionally, if PK data from Study LVIG demonstrate a potential relationship between body weight and individual tadalafil exposure, a weight-adjusted dosing scheme (such as mg/kg) may be adopted.

Table LVHV.9.1. Planned Tadalafil Once-Daily Dosing for Study LVHV by Weight Cohort (Period 1)

Weight Cohort	Dose[a]	Tablet Strength	
		Number of Tablets[b]	
		10 mg	20 mg
Heavy	40 mg	—	2
Middle	10 mg	1	—
Light	5 mg	Volume of Oral Suspension[c]	
		2.5 mL	

a These doses may be refined if needed, when PK and safety data from the corresponding weight cohort from the LVIG pediatric study become available.

b Tadalafil or placebo administered orally with water.

c 2 mg/mL tadalafil or placebo; directly administered into the mouth using a standard syringe.

Notes: If dosage for each weight cohort is redefined, other strength of tablets, such as 2.5 mg or 5 mg, may be used to achieve the desired concentration.

If a patient's weight changes during the study, such that he/she falls into a different weight cohort category, he/she will continue to receive the study drug dose appropriate to his/her original weight cohort.

9.5. Selection and Timing of Doses

During Period 1, after the collection of all Day 1 assessments, patients will be randomized to either tadalafil or placebo at Visit 2 (Day 1). The first dose of assigned treatment will be administered at this visit. Patients and/or parents will be instructed to administer each subsequent dose (tablet or suspension) once daily, with or without food, in the morning. During Period 2, every patient will be administered tadalafil for up to 2 years.

If a daily dose is missed, the next dose should be administered the following day at the typical dosing time and a record of the missing dose should be provided to the Investigator.

9.6. Blinding

During Period 1, the IXRS will be used to assign investigational product containing double-blind study drug (tadalafil or placebo) to each patient according to body weight cohort assignment. Placebo and active drug, either tablet or liquid suspension, for a particular weight cohort will be similar in appearance and taste, and the number of tablets or the volume of liquid suspension of the study drug will be the same for each weight cohort.

The IXRS will be used to assign the appropriate package of investigational product (treatment and dose) for each visit. Patients and/or parents will be instructed to administer a fixed dose from the assigned package daily (Table LVHV.9.1).

Patients, study site personnel who record study data, and the Sponsor will be blinded to the treatment being administered to study patients. To preserve study blinding, access to the randomization table and treatment assignments will be restricted to a minimum number of Lilly personnel prior to database lock.

Emergency unblinding for AEs may be performed through the IXRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IXRS and will result in the patient being discontinued from the trial.

The Investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone.

During Period 1, if an Investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from this study.

9.7. Concomitant Therapy

Chronic use of drugs that are known potent inducers or inhibitors of CYP3A4 should be avoided. Additional drugs are to be avoided during the study, unless required to treat an AE or for the treatment of an ongoing medical problem.

If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the Investigator after consultation with a Lilly clinical pharmacologist or CRP. Any additional medication used during the course of the study must be documented. Medicines

and therapies that would prevent a patient from enrolling in the study are identified in the exclusion section of this protocol (see Section 8.2).

Patients who receive any concomitant medication listed in the exclusion criteria following randomization but before study drug administration should not receive study drug. Patients requiring treatment with any of the prohibited medications during the study will be discontinued from the study and should complete the Early Termination assessments (Attachment 1). Patients receiving prostacyclin or its analogues during Period 2 only, however, will be allowed to continue in the study.

Dosage adjustment of ERA medications and monitoring patients for aminotransferase abnormalities must be followed according to adult recommendations in the respective ERA labels.

Post-study therapy with another PDE5 inhibitor should be delayed at least 96 hours after the last dose of the study drug is administered.

Patients and/or parents will be instructed to consult with the Investigator or Study Coordinator at the study site before taking newly-prescribed medications. All non-study medications will be recorded on source documents at all visits. Non-study medications screen failures will not be reported to Lilly unless the medication is linked to an SAE or AE that the Investigator believes may have been caused by a protocol procedure.

9.8. Treatment Compliance

Every attempt will be made to select patients and/or parents who have the ability to understand and comply with instructions. To assure appropriate drug accountability, adherence will be emphasized at the start-up meeting, accountability forms will be provided in the clinical trial records' binder (or similar file), and patient adherence will be monitored throughout the study.

The Investigator will advise the patient and/or parents that the medication should be taken at approximately the same time of day. If a daily dose is missed, the next dose should be administered the following day at the typical dosing time and a record of the missing dose should be provided to the Investigator.

Each patient and/or parent will be instructed to return all study drug packaging and material to the study site at each visit. The study site will keep a record of all drug dispensed and returned throughout the study. These data will be recorded on the respective patient's electronic case report form (eCRF). Patient compliance with study drug will be assessed at each visit starting at Day 1 (Visit 2). Compliance will be assessed by direct questioning, counting returned tablets, or suspension volume reconciliation. Compliance with the prescribed regimen will be documented.

The Investigator (or designee) at each investigational site will be responsible for keeping a drug accountability log. Drug reconciliation will be performed at the end of the study.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing are summarized in the Study Schedule (Attachment 1). Analgesic cream (eg, EMLA) must be offered to minimize pain at the injection site (venipuncture). The smallest practical diameter needle is recommended, and a cannula will be used to minimize the number of needle insertions.

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

The following primary efficacy measure will be collected at the times shown in the Study Schedule (Attachment 1):

- 6MWD in meters assessed in a subset of patients who are ≥6 to <18 years of age who are developmentally capable of performing a 6MW test

10.1.2. Secondary Efficacy Measures

10.1.2.1. Period 1

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1):

- Time to CW and the incidence of CW. Patients meeting any of the following 5 major criteria would be 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 be due to a potentially precipitating event such as pneumonia hemoptysis, etc; however, if after the hospitalization is completed, the patient is discharged and the patient remains worse, then the patient can be assessed for CW.
    5. Worsening of PAH

        Patient has 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) (except for patients already in Class IV) only for patients unable to perform the 6MW test.

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

Criteria for CW will be adjudicated by an independent, blinded study-specific Clinical Endpoint Committee (CEC). This adjudication will be used for data analysis, and will not be used to guide patient treatment.

- Population PK assessment of plasma tadalafil concentrations at steady-state.

10.1.2.2. Period 2

- Incidence of and time to CW (defined in Section 10.1.2).

10.1.3. Additional Efficacy Measures

10.1.3.1. Period 1

The following additional efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1):

- Cardiac MRI parameters:
  - LV ejection fraction
  - RV end diastolic volume
  - RV end systolic volume
  - RV ejection fraction
- NT-Pro-BNP concentrations.
- Echocardiography parameters:
  - tricuspid annular plane systolic excursion (TAPSE)
  - eccentricity index
  - pericardial effusion
  - maximal tricuspid regurgitant velocity
- WHO functional classification
- CGI-I (Attachment 4)
- CHQ-PF28 (Attachment 6) in patients ≥5 years of age

10.1.3.2. Period 2

- 6MW distance in meters measured in patients who are ≥6 years of age and who are developmentally capable of performing a 6MW test.
- WHO functional classification

10.1.4. Appropriateness of Efficacy Measures

10.1.4.1. 6MW Test

The 6MW test is the most accepted exercise capacity test and is also the most commonly used clinical trial endpoint in adult pulmonary hypertension studies. The reliable use of the 6MW test is limited in patients <6 years of age; therefore, 6MW test will be measured in patients who are ≥6 years of age and who are, in the opinion of the Investigator, developmentally capable

(mentally and physically). A 6MW test assessment will be conducted at time points specified in Attachment 1. The 6MW test will be recorded and evaluated by following 6MW test guidelines (Attachment 7). If a patient has decrease of 20% or more in 6MW distance compared with Day 1 along with worsening of WHO functional class by 1 class or more, another 6MW test will be conducted 5 to 10 days later to confirm the change. An unencouraged 6MW (Attachment 7) will be used to ensure that patients are not pressured during the test. If the 6MW test and PK are conducted on the same day, the PK blood sample should be obtained prior to the 6MW test.

10.1.4.2. Time to Clinical Worsening

Time to CW has been considered a useful endpoint for assessing the effectiveness of PAH therapies on patient's clinical status and degree of disease progression (Peacock et al. 2010). Clinical composite endpoints are increasingly gaining favor as the preferred endpoint for PAH therapy evaluation and can be used across the entire age range in the pediatric population. Because it is clinically relevant, time to CW has been used in many PAH trials as either a primary or secondary efficacy endpoint for measuring treatment effect (Haworth and Beghetti 2010). In this study, time to CW will be evaluated based on CW events that are defined in Section 10.1.2.

10.1.4.3. Echocardiography and Cardiac Magnetic Resonance Imaging (MRI)

The value of echocardiography in diagnosing pulmonary hypertension has been examined in various settings, including idiopathic pulmonary hypertension, pulmonary hypertension in systemic sclerosis, and pulmonary hypertension associated with diffuse parenchymal lung disease. Echocardiography provides both estimates of pulmonary artery pressure and an assessment of cardiac structure and function. These features justify its application as the most commonly used screening tool in patients with suspected pulmonary hypertension. In this study echocardiography will be used to evaluate changes from Day 1 to Week 24 in the parameters noted in Section 6.3.1.

Compared with echocardiography, MRI has been considered as a potential important diagnostic tool for the comprehensive evaluation of pulmonary hypertension; it has not been fully evaluated for PAH patient management.

All echocardiograms and MRIs will be transferred to a central imaging laboratory designated by Lilly. A technical expert at the central imaging laboratory will then conduct a full review of the echocardiograms and MRIs. All data from the central review will be provided to Lilly for analytical and study report purposes.

10.1.4.4. NT-Pro-BNP

NT-Pro-BNP is a 76 amino acid N-terminal fragment of brain natriuretic peptide (Bhalla et al. 2004) that might have prognostic value in patients with chronic pulmonary hypertension, and could serve as a potential indicator of the efficacy of vasodilator therapy in patients with pulmonary hypertension (Fijalkowska et al. 2006; Nagaya et al. 2000).

10.2. Health Outcome/Quality of Life Measures

The following Health Outcome measures are also considered secondary measures and will be collected at the times shown in the Study Schedule (Attachment 1).

Quality of life (QoL), as measured by CHQ-PF28 (Attachment 6) will be collected for patients aged ≥5 years old. The CHQ-PF28 is a generic QoL instrument that has been designed and normalized for children 5 to 18 years of age. The CHQ measures 14 unique physical and psychosocial concepts (Attachment 6). The CHQ-PF28 will survey the patient or parent to provide answers about the physical and psychosocial well-being of the patient.

The CGI-I Scale is a standardized assessment tool and assesses the patient's improvement or worsening from Day 1 (Attachment 4). The CGI-I is intended to allow clinicians to rate a patient's improvement from Day 1, taking into account the patient's clinical condition and the severity of side effects compared to the patient's condition at the beginning of the trial.

The CGI-S (Attachment 5) provides an overall rating of the illness severity at baseline and as such, will be collected at Baseline only.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The Investigator is responsible for the appropriate medical care of patients during the study.

The Investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

10.3.1. Period 1

Safety during Period 1 will be evaluated using reported AEs (which will include 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. Tadalafil concentrations and protocol clinical laboratory data may be collected for patients reporting an SAE.

10.3.2. Period 2

Safety during period 2 will be evaluated by monitoring AEs, body weight and height, eye examinations, concomitant medications, Tanner scale, and intellectual ability and cognitive functioning assessment. Testicular integrity toxicity will be checked by monitoring changes in inhibin B biomarkers in male patients from 9 years to less than 18 years of age. Inhibin B levels in patients below the age of 9 years must be collected in an exploratory manner. Tadalafil concentrations and protocol clinical laboratory data may be collected for patients reporting an SAE.

10.3.3. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to investigational product or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via eCRF/electronic data entry.

Any clinically significant findings from ECGs, labs, vital sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, investigational product, and/or drug delivery system via electronic data entry.

Study site personnel must alert Lilly or its designee within 24 hours of the Investigator **unblinding** a patient's treatment group assignment for any reason.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via electronic data entry the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.3.1. Serious Adverse Events

Serious adverse event (SAE) collection begins after the patient has signed informed consent and has received investigational product. If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will NOT be collected unless the Investigator feels the event may have been caused by a protocol procedure.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of Investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the Investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events occurring after a patient has taken the last dose of investigational product will be collected 30 days after the last dose of investigational product, regardless of the Investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the Investigator feels the events were related to either investigational product, or drug delivery system, or a protocol procedure.

Potential study endpoints (that is, CW as defined in Section 10.1.2), that meet serious criteria, will not be reported as an SAE unless deemed by the Investigator to be possibly related to study drug.

Information on SAEs expected in the study population independent of drug exposure and, that will be assessed by the sponsor in aggregate at least twice a year during the course of the trial, may be found in the IB.

Additional laboratory samples and a blood sample for tadalafil concentration analysis may be collected as needed at time of an SAE.

10.3.3.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

10.3.4. Safety Measures

10.3.4.1. Hepatic Monitoring

ALT and AST elevations may occur with the use of ERA medications. If a study patient experiences elevated ALT or AST >3X upper limit of normal (ULN) or elevated total bilirubin >2X ULN, the patient should have ERA dosage adjustments and monitoring that are consistent

with the adult recommendations in the respective ERA labels. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities.

To ensure patient safety and to comply with regulatory guidance, the Investigator is to consult with the Lilly designated medical monitor regarding the collection of additional, specific recommended clinical information and follow-up laboratory tests, if a study patient experiences elevated ALT or AST >3X ULN or elevated total bilirubin >2X ULN.

Guidelines for the evaluation and management of patient with abnormal liver tests will be provided in the Investigator training document.

Discontinuation of the study drug for abnormal liver tests should be considered by the Investigator after consultation with the Lilly designated medical monitor when a patient meets one of the following conditions:

- ALT or AST >8 X ULN
- ALT or AST >5 X ULN for more than 2 weeks
- ALT or AST >3 X ULN and total bilirubin level >2 X ULN or prothrombin time >1.5 X ULN
- ALT or AST >3 X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

10.3.4.2. Vital Signs

Blood pressure and heart rate (HR) will be measured as specified in the Study Schedule (Attachment 1) and as clinically indicated. Blood pressure will be measured after the patient has been in a supine position for at least 2 minutes, using the same arm for each measurement (Attachment 3). The interpretation of diastolic and systolic measurements are left to the discretion of the Investigator.

10.3.4.3. Eye Examination

An eye examination will be performed according to the Study Schedule (Attachment 1). The examination includes patient medical eye history, external eye examination and retinal examination using an ophthalmoscope. There are no clinical data on treatment-related effect on eyes with tadalafil in pediatric population. Studies during the nonclinical development of tadalafil and the clinical adult population did not indicate treatment-related effect on retina. Since this is the first study to investigate tadalafil in the pediatric population, general eye safety monitoring was deliberately included as one of safety parameters to ensure there is no effect on retinas in the pediatric PAH population.

10.3.4.4. Inhibin Monitoring

Inhibin B will be collected by a single blood draw at the times indicated in the Study Schedule (Attachment 1) from all male patients. Inhibin B is being monitored to check for potential testicular integrity toxicity. In patients below the age of 9 years, this will be an exploratory assessment and results are blinded.

10.3.4.5. Collection of Electrocardiograms

For each subject, a single 12-lead digital ECG will be collected locally according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed when needed to ensure high quality records.

ECGs will be interpreted by a qualified physician (the Investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified. The Investigator (or qualified designee) must document his/her review of the ECG printed at the time of collection.

After enrollment, any clinically significant changes from baseline in the patient's ECG will be recorded as an AE in the patient's eCRF.

10.3.4.6. Intellectual Ability and Cognitive Functioning Assessment

The patient's intellectual ability (intelligence quotient, IQ) will be assessed at Day 1 (Visit 2, prior to first dose of study drug), and after 1 year and 2 years following treatment initiation. The Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) is the preferred instrument for IQ assessment. Due to age restrictions of the WISC-IV, the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) and Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) Test may also be used as detailed below. Patients may be assessed with a different scale at subsequent visits depending on their age.

- Patients who are aged 2 years 6 months through 5 years 11 months at Day 1 (Visit 2) will be administered the WPPSI-III at Day 1 (Visit 2) and follow-up visits. For patients who completed the WPPSI-III at Visit 2, they will be administered the WISC-IV at any subsequent visit if their age exceeds or if they are older than 7 years 3 months.
- Patients who are aged 6 years 0 months through 15 years 11 months at Day 1 (Visit 2) will be administered the WISC-IV at Day 1 (Visit 2) and follow-up visits. For patients whose age exceeds 16 years 11 months at subsequent visits, the WAIS-IV will be administered.
- Patients who are ages 16 years 0 months or older at Day 1 (Visit 2) will be administered the WAIS-IV at Day 1 (Visit 2) and all subsequent visits.

If the recommended versions of the IQ scales listed above are not available in the patients' primary language, the site may use the most recent version of the available scale in that geography. Investigator or site study personnel should ensure the instrument administrator/examiner and interpreter, either at the Investigator site or from an external evaluation service, meet the qualification, training, and interpretation requirements per the instrument manual. The IQ scales will be administered at the times according to the Study

Schedule (Attachment 1). Comprehensive reporting of the patient's IQ is not required in this study.

Patients will not be excluded from the study if none of the recommended instruments are available in the patient's primary language or if no qualified examiner is available to conduct the evaluation. Not obtaining an intellectual ability assessment for this study will not be a protocol violation, but notification of this must be provided to the Lilly research physician prior to the patient's enrollment.

10.3.4.6.1. Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV)

The fourth edition of the WISC assessment (WISC-IV) is administered to children ranging from 6 years to 16 years, 11 months. It contains 10 core subtests and 5 additional tests, and takes 60 to 90 minutes to complete. In this study, the 10 core subtests needed to derive a Full Scale IQ score are required to be completed: Block Design, Similarities, Digit Span, Picture Concepts, Coding, Vocabulary, Letter-Number Sequencing, Matrix Reasoning, Comprehension, and Symbol Search. The scaled score for each subtest and Full Scale IQ composite score are required to be entered into the eCRF.

10.3.4.6.2. Wechsler Adult Intelligence Scale -Fourth Edition (WAIS-IV)

The WAIS–IV structure was modified to align with the WISC–IV and to reflect current theory regarding cognitive ability. The WAIS-IV is used as an intelligence measure for persons aged 16 to 90 years and 11 months. The anticipated time for completion of WAIS-IV is approximately 60 to 90 minutes. In this study, the 10 core subtests needed to derive a Full Scale IQ score are required to be completed: Vocabulary, Similarities, Information, Symbol Search, Coding, Visual Puzzles, Block Design, Digit Span, Arithmetic, and Matrix Reasoning. The scaled scores for each subtest and Full Scale IQ composite score are required to be entered into the eCRF.

10.3.4.6.3. Wechsler Preschool and Primary Scale of Intelligence Test - 3rd Edition (WPPSI-III)

The WPPSI-III is an intelligence test designed for children aged 2 years 6 months to 7 years 3 months. The anticipated time for completion of WPPSI-III is approximately 25 to 60 minutes. In this study, the core subtests needed to compute a Full Scale IQ score are required to be completed. For ages 2 years 6 months to 3 years 11 months, these 4 core subtests are: Receptive Vocabulary, Information, Block Design, and Object Assembly. For children ages 4 years 0 months to 7 years 3 months, these 7 core subtests are: Information, Vocabulary, Word Reasoning, Block Design, Matrix Reasoning, Picture Concepts, and Coding. The scaled score for each subtest and Full Scale IQ score are required to be entered into the eCRF.

10.3.5. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study. In addition, the DMC will review safety data periodically, as outlined in the DMC charter.

Lilly will review SAEs within time frames mandated by company procedures and will review trends, laboratory analytes, and AEs at periodic intervals. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review trends and laboratory analytes periodically.

The Lilly CRP will monitor blinded safety data throughout the course of the study. A DMC independent of Lilly will monitor unblinded safety data throughout the course of the study by periodic reviews of safety data, as outlined in the DMC charter.

The Lilly CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist as appropriate. In the event that Lilly safety monitoring uncovers an issue that needs to be evaluated further by unblinding at the group level, the safety concern will be communicated to the DMC. The DMC will review the unblinded data and conduct appropriate analyses of the safety data, as deemed necessary.

10.3.6. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

Lilly collects product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Investigators are instructed to report product complaints as they would for products in the marketplace.

The Investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the Investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 9 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. Fewer invasive sampling may actually occur, but this will not require a protocol amendment.

Section 12.2.8 summarizes the Plasma tadalafil concentration-time data analyses.

10.4.1. Samples for Standard Laboratory Testing

Blood and Urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests including chemistry, hematology, coagulation, and urinalysis panels will be performed. A urine pregnancy test will be performed (if applicable). Clinical laboratory tests will be analyzed by a central laboratory; however, pregnancy testing may be repeated locally during the study, if indicated by the Investigator. Attachment 2 lists the specific tests that will be performed for this study.

Laboratory analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Exploratory Work

Genetic testing is a mandatory part of this study. Genetic material derived from samples may be tested for drug metabolism enzyme polymorphisms, transporter polymorphisms, association of genetic variants with PAH, and variance in response to tadalafil. Pharmacogenetic data will not be provided back to the Investigator nor will it be shared with patients in the trial.

10.4.2.1. Samples for Genetic Testing

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow, a 0.5 mL blood sample will be collected on a DNA filter paper (FTA card) for pharmacogenetic analysis. It is a one-time collection, as noted in the Study Schedule (Attachment 1).

Samples will be stored and analysis may be performed on genetic variants thought to play a role in endothelial cell dysfunction, blood pressure and intracellular levels of cyclic guanosine monophosphate (cGMP) (including but not limited to GNB3, ACE, ENOS, PDE5) to evaluate their association with observed clinical outcomes to LY450190.

In the event of an unexpected AE or the observation of unusual response, the samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY450190. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will be used only for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Samples will be identified by the patient number (coded) and stored for up to 15 years after the last subject visit for the study at a facility selected by the Sponsor. The sample and any data generated from it can only be linked back to the patient by Investigator site personnel.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the Investigators and Study Coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection.
- Verify the quality of the data.

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly Medical Quality Assurance (MQA) personnel, its designated representatives, or regulatory agencies at any time. Auditors will make every effort to provide Investigators ample notification of upcoming audits.

A central laboratory will be used to maintain consistency of methods and to compile laboratory data across study sites and/or across studies.

The following measures will be taken for drug accountability:

- Drug accountability will be emphasized at start-up meetings.
- A drug accountability form will be provided in the clinical study records binder or similar file.
- Drug accountability will be checked during monitoring visits.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the Investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system. Some or all of a patient's data (for example, rating scales, daily dosing schedules, subject diaries, or event diaries) may be entered into the electronic data capture (EDC) system directly via an eCRF

at the time that the information is obtained. In instances where no prior written or electronic record of the data exists, the eCRF will serve as the source document.

Case report form (CRF) data will be encoded and stored in a clinical trial database.

Data managed by a central vendor, such as laboratory, echocardiogram, and MRI data will be stored electronically in the central vendor's database system. Laboratory data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the eCRF will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary efficacy measure is 6MWD and will be evaluated in this study during Period 1.

At least 34 patients will be stratified by weight and randomized in a 1:1 ratio to tadalafil or placebo treatment in this study (17 to placebo treatment and 17 to tadalafil treatment).

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.

12.2. Statistical and Analytical Plans

The Statistical Analysis Plan will include additional details regarding the statistical analyses of data from this study.

12.2.1. General Considerations

Efficacy analyses of Period 1 data, except 6MW measurements, will include all patients who were randomized and took at least 1 dose of study medication. The analysis of 6MW data will include only the subset of randomized patients ≥6 to <18 years of age who took at least 1 dose of study medication and were able to perform a 6MW test. Patients will be analyzed according to the randomized treatment assignment. Patients with no post Day 1 data for a particular efficacy endpoint will be excluded from the analysis of that endpoint. Additional sensitivity analyses utilizing imputed values for missing post Day 1 data may be conducted for specific endpoints. Safety analyses will include all randomized patients who took at least 1 dose of study medication.

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 25^{th} percentile, median and 75^{th} percentile will be presented for variables that are analyzed using rank-transformed data.

Given the small sample size, no formal comparison will be made between treatment groups. Hence, the overall treatment difference p-value and the visit-wise p-values will not be reported.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Patient Disposition

The number and percentage of patients screened and randomly assigned to treatment will be presented by investigative site and weight cohort. Reasons for screen failure will be summarized. The final disposition of randomized patients and reasons for early discontinuation will be summarized for Period 1 and Period 2.

12.2.3. Patient Characteristics

Patient characteristics will be summarized for each treatment group. Patient characteristics at Day 1 will include age, sex, race, ethnicity, weight cohort, weight (kg), height (cm), and Tanner score.

Day 1 disease characteristics that will be summarized include PAH etiology, duration of PAH, prior PAH therapies received, type of concomitant ERA therapy, WHO functional class, and 6MW. Additionally, patient disease severity at Day 1 as assessed by CGI-S will be summarized.

Day 1 data are defined as the most recent data collected prior to randomization.

12.2.4. Concomitant Therapy

Previous and concomitant therapies will be coded using the World Health Organization Drug Dictionary (WHO Drug). Previous therapies are those therapies that started and stopped prior to the first dose of study medication. Concomitant therapies are those therapies that started on or after the first dose of study medication or those therapies that started prior to the first dose of study medication and were ongoing when the first dose of study medication was given. Previous and concomitant therapies will be summarized by drug class and therapy name by treatment group for all randomized patients. Summaries will consist of the number and percent of patients taking a drug from each drug class and therapy name.

12.2.5. Treatment Compliance

Treatment compliance will be assessed in Period 1 by reconciling the number of doses of study treatment dispensed at Visits 2 through 8 with the number of doses returned at Visits 3 through 9, and in Period 2 by reconciling the number of doses dispensed at Visits 9 through 16 with the number of doses returned Visits 10 through 17. Treatment compliance at each visit will be calculated as the number of doses of treatment taken during a visit interval divided by the number of days in the visit interval. Overall treatment compliance for a study period will be defined as the number of doses of treatment taken during the study period divided by the number of days that the patient was actively participating in the study period.

12.2.6. Primary Outcome and Methodology

The primary efficacy endpoint of change from baseline (Day 1) in 6MW distance will be analyzed at Weeks 4, 8, 12, 16, 20, and 24 with a mixed effects model for repeated measures (MMRM). This analysis will include only patients who are ≥6 to <18 years of age and are developmentally able to complete 6MW testing during Period 1. Factors in the MMRM model include visit, baseline 6MWD, PAH etiology, type of endothelin receptor antagonist (ERA) therapy, and treatment group. Within the model, the effect of PAH etiology will only be

included if there are at least 3 patients per treatment arm at each PAH aetiology level. Similarly, the effect of ERA therapy will only be included if there are at least 3 patients per treatment arm at each ERA therapy level.

As the study has a limited number of patients enrolled, an inspection of the model estimated mean change in 6MWD and corresponding CIs will be used instead of significance testing to ensure whether they are trending in the right direction. The overall treatment difference p-value and the visit-wise p-values will not be reported.

These objectives will be assessed and results reported at the end of Period 1.

12.2.7. Efficacy Analyses

Secondary and additional efficacy endpoints will include all patients who were randomized to treatment and took at least 1 dose of study medication.

The proportion of patients who experience a change in WHO functional class will be summarized. Changes will also be categorized as "worsening, "no change," or "improving" over the study period.

The incidence of CW (Section 10.1.2) will be summarized as the number and percentage of patients in each treatment group who experience at least one criterion of the CW definition during the study period.

Changes from Day 1 to endpoint in hemodynamic parameters collected via echocardiography and MRI will be analyzed with analysis of covariance (ANCOVA) models. Models will include terms for Day 1 value, weight cohort, PAH etiology, type of ERA therapy, and treatment group.

These objectives will be analyzed and results reported at the end of Period 1. No adjustments for multiple comparisons will be made for the analysis of these endpoints.

During Period 2, the incidence and time to first occurrence of CW during Period 2 will be assessed. The percentage of patients who participate in Period 2 and who experience one of the CW criteria will be summarized. In addition, change from Day 1 of Period 1 in 6MW and WHO functional class will be reported for all patients who participate in Period 2.

Changes from Day 1 in NT-Pro-BNP values will be analyzed with an analysis of variance (ANOVA) model. NT-Pro-BNP values will be log-transformed for analysis. Day 1 values for NT-Pro-BNP concentrations will be the last value collected prior to randomized treatment assignment at Day 1 (Visit 2).

12.2.8. Pharmacokinetic Analyses

Plasma tadalafil concentration-time data will be pooled and evaluated using a population PK approach. The model structure to be used for this evaluation is expected to be the same model structure determined to be suitable for tadalafil PK data in pediatric patients in Study LVIG. The effects of body weight, age, and sex on apparent clearance will be explored. If the number of patients taking different types of ERA is sufficient to quantify the effect of ERA on apparent clearance, then this will also be done. Due to random PK sampling times and the low number of

samples available from each individual patient, it may be necessary to combine the data from this study with the densely sampled data from Study LVIG to better characterize the population PK of tadalafil in this patient population.

12.2.9. Health Outcome/Quality of Life Analyses

An ANCOVA analysis will be used to examine changes from Day 1 to Weeks 16 and 24 in CHQ-PF28 scores. The models will include terms for Day 1 score, Day 1 value, weight cohort, PAH etiology, type of ERA therapy, and treatment group.

Patient outcome will be assessed using the CGI-I at Weeks 16 and 24 (Visits 7 and 9) using an ordinal scale with 7 response categories ranging from "Very Much Better" to "Very Much Worse." Responses will also be grouped into 3 derived categories ("Worse," "No Change," and "Better") for additional analysis. The proportion of patients in each of the 7 response categories and each of the 3 derived categories will be summarized by treatment group.

12.2.10. Safety Analyses

Safety during Period 1 will be assessed through AEs including abnormalities detected by ECG or physical examination, clinical chemistry and hematology panels, urinalysis, vital signs, eye examinations, and concomitant medications. During Period 2, safety will be monitored using AEs, changes in body weight and height, inhibin B biomarker (male patients only), eye examinations, Tanner scale, and intelligence tests. The analysis of safety will include all patients who took at least 1 dose of study medication.

Adverse events will be coded using the Medical *Dictionary for Regulatory Activities* (MedDRA) preferred term. Treatment-emergent AEs (TEAEs) are defined as events that first occurred or worsened after the first dose of study medication on Day 1 (Visit 2). Treatment-related adverse events are defined as events that are determined to be possibly or probably treatment-related by the Investigator. The percentages of patients experiencing AEs across various criteria (for example, treatment-emergent, treatment-related, serious, etc.) will be displayed by treatment groups.

Changes from Day 1 in clinical laboratory measurements, inhibin B biomarker concentrations, blood pressure, and HR will be analyzed with ranked ANOVA models with a term for treatment group. Observed laboratory values and changes from Day 1 in laboratory values will be evaluated for categorical changes based on normal ranges and displayed by treatment groups. Changes from Day 1 in composite intelligence scores will be assessed according to the published instructions for each instrument. The numbers and percentages of patients in each treatment group with shifts in Tanner stage at Year 1 and Year 2 will be summarized. Day 1 values for laboratory data, vital signs, body weight and height, inhibin B biomarker, Tanner scale, and intelligence tests will be the last values collected prior to randomized treatment assignment at Day 1 (Visit 2).

12.2.11. Subgroup Analyses

Subgroup analyses will be conducted as deemed appropriate and necessary. Detailed descriptions of the subgroup variables will be provided in the statistical analysis plan.

12.2.12. Interim Analyses

The database will be locked and data collected during Period 1 will be analyzed when all randomized patients have ended participation in Period 1. This will not be considered an interim lock per se, as it will be the final lock for Period 1. These results will be reported in a clinical study report. An additional clinical study report will be prepared at the conclusion of Period 2 to present analyses of the OLE data.

Summaries of patient safety data, including reported and adjudicated clinical endpoint events, will be monitored by a DMC throughout the study. In addition, an interim analysis of the 6MW data is planned. The interim analysis is planned to occur in approximately Q1 2017. Heavy- and mid-weight cohorts, likely to be comprised of patients ≥6 to <18 years of age who are developmentally able to complete the 6MW test, will be the first cohorts to enroll in Study LVHV. As a result, it is expected that approximately 50% of all randomized patients will have 6MW test scores at baseline and Week 24 at the time of the planned interim analysis. This would provide 65% power to detect a 35 m difference in change in 6MW distance with a standard deviation of 60 m and a 0.05 significance level. The results of this interim analysis will be reviewed by the DMC for Study LVHV for evidence of efficacy and to confirm the accuracy of study design assumptions. Other efficacy endpoints may be examined at the time of the interim analysis, as appropriate.

Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their patients.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The Investigator is responsible for ensuring that the patient and/or parent understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an Investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

The study site's ERB(s) should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1. consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. ICH GCP Guideline [E6]
3. applicable laws and regulations

The Investigator or designee will promptly submit the protocol to applicable ERB(s).

Tadalafil is being studied in the US under a US Investigational New Drug (IND) application. The US IND number is 112,329 (pediatric PAH).

All or some of the obligations of the sponsor will be assigned to a third-party organization (TPO).

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in PAH, pediatric cardiology, or internal medicine, will participate as Investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal Investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report coordinating Investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The Investigator with the most enrolled patients will serve as the clinical study report coordinating Investigator. If this Investigator is unable to fulfill this function, another Investigator will be chosen by Lilly to serve as the clinical study report coordinating Investigator.

The sponsor's responsible medical officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol LVHV Study Schedule

Study Schedule Protocol H6D-MC-LVHV

		Period 1								Period 2				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET[a]**	**10-12**	**13**	**14-16**	**17**	
Description of event LVHV	**Screening Day -28 to 0**	**Day 1**	**Wk2 ± 7days**	**Wk 4 ± 7days**	**Wk8 ± 7days**	**Wk12 ± 7days**	**Wk16 ± 7days**	**Wk20 ± 7days**	**Wk 24 ± 7days**	**Every 3 months ±10 days**	**1 Year ±10 days**	**Every 3 months ±10 days**	**2 Year ±10 days**	**Follow-up[b]**
Informed Consent	X													
Medical History	X													
PAH etiology	X													
OB/GYN History[c]	X													
CXR (within 6 months of screening)	X													
WHO Functional Class	X			X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X				X			X					
Eye Examination[d]	X								X				X	
6MW Test[e]		X		X	X	X	X	X	X		X		X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X								X		X		X	
Weight	X	X	X	X		X	X		X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X					
ECG (single)[f]	X				X				X					
Urinalysis	X			X			X		X					
Urine Pregnancy Test[g]	X													
Urine Drug Screen[f]	X													
Safety Lab Tests: Chemistry, hematology, Coagulation[h]	X[i]			X			X		X					
NT-Pro-BNP		X					X		X					
Inhibin B biomarker (for male patients)		X									X		X	
CHQ-PF28 (≥ 5 yrs. old)		X					X		X					
DNA (PGx) Sample		X[j]												
PK (tadalafil concentration)[k,l]			X[m]	X[m,n]			X[m,n]		X[m.n]					

		Period 1								Period 2				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET[a]**	**10-12**	**13**	**14-16**	**17**	
Description of event LVHV	**Screening Day -28 to 0**	**Day 1**	**Wk2 ± 7days**	**Wk 4 ± 7days**	**Wk8 ± 7days**	**Wk12 ± 7days**	**Wk16 ± 7days**	**Wk20 ± 7days**	**Wk 24 ± 7days**	**Every 3 months ±10 days**	**1 Year ±10 days**	**Every 3 months ±10 days**	**2 Year ±10 days**	**Follow-up[b]**
CGI-S		X												
CGI-I							X		X					
Intelligence Test (WISC-IV, WAIS-IV, or WPPSI-III[o])		X									X		X	
Tanner Score		X									X[p]		X	
Echocardiography		X			X		X		X					
Cardiac MRI[q]		X							X					
Pre-existing Conditions and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Drug Return and Accounting			X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: 6MW = 6-minute walk; CHQ-PF28 = Child Health Questionnaire Parent Form 28; CGI-I = Clinical Global Impression of Improvement questionnaire; CGI-S = Clinical Global Impression of Severity questionnaire; CXR = chest radiography; DNA (Pgx) = deoxyribonucleic acid pharmacogenetics; ECG = 12 –lead electrocardiogram; ERA = endothelial receptor antagonists; ET = early termination; NT-Pro-BNP = N-terminal prohormone brain natriuretic peptide; MRI = magnetic resonance imaging; OB-GYN = obstetrics-gynecology; PAH = pulmonary arterial hypertension; PK = pharmacokinetics; SAE = serious adverse event; WAIS = Wechsler Adult Intelligence Scale; WHO = World Health Organization; WISC = Wechsler Intelligence Scale for Children; Wk=week; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

a. Patients who continue to Period 2 (because they completed or discontinued Period 1), will have all of the Week 24 (Visit 9/ET Visit) assessments performed before proceeding to Period 2. Patients, who discontinue Period 1 and do not participate in Period 2, will also have all of the Week 24 (Visit 9/ET Visit) assessments performed.
b. This follow-up visit will be conducted only for patients who discontinue from the study during Period 1 and will not participate in Period 2. If a patient discontinues prior to or at Visit 8, the follow-up visit will be performed 24 weeks after the patient's initial study drug dosing (Visit 9). If a patient discontinues after Visit 8, the follow-up visit will occur 30 days after the patient has taken the last dose of study drug. This visit can be done by phone.
c. Including family history of menarche.
d. Eye examination includes patient medical eye history, external eye examination and retinal examination using ophthalmoscopy.
e. 6MW test will be performed for those patients ≥6 years of age and who are, in the opinion of the Investigator developmentally capable (mentally and physically) of performing a 6MW test. Patient with worsening of WHO functional class by 1 class or more and a decrease of ≥20% in the 6MW distance, another 6MW will be repeated 5 to 10 days later to confirm the change. An unencouraged 6-MW will be used to ensure that patients are not pressured during the test. A separate "practice" 6MW test must be done before or during Visit 2 (Day 1).
f. To be performed locally. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
g. Local pregnancy test for females of child bearing potential; may be repeated at Investigator's discretion throughout the trial.
h. Additional samples may be collected as needed at time of SAE reporting and clinical worsening. Digoxin, warfarin, ERA and coagulation tests should be carried out using the Investigator's standard of care.
i. Screening laboratory exam includes measured or estimated creatinine clearance (See Section 8.2).
j. If not collected at this visit, the sample could be collected at a following visit.
k. The sampling times relative to dosing should vary as much as possible across the PK sampling visits.
l. At the time of any SAE, a blood sample for tadalafil concentration analysis may be collected.
m. Obtain and record the patient's weight at each PK sampling visit.
n. The PK blood sample should be obtained prior to the 6MW test.
o. WISC-IV is to be administered for patients ranging from 6 years 0 months through 15 years 11 months, WAIS-IV is to be used for patients 16 years 0 months and older, and WPPSI is to be used for patients 2 years 6 months to 5 years 11 months at Visit 2 and up to 7 years and 3 months for the follow up visit. The Intelligence test may be performed prior to Visit 2.
p. If patient has Tanner Score 5 on all criteria, the following Tanner Score evaluation will not be required.
q. Participation for MRI assessment will be based on selection of specific sites that have been using MRI as routine PAH patient management.

Attachment 2. Protocol LVHV Clinical Laboratory Tests

Clinical Laboratory Tests Performed at Screening and during the Study

Hematology:	Clinical Chemistry:
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Calcium
Mean cell volume (MCV)	Phosphorus
Mean cell hemoglobin (MCH)	Magnesium
Mean cell hemoglobin concentration (MCHC)	Blood urea nitrogen (BUN)
Leukocytes (WBC)	Total bilirubin
Absolute counts of:	Alanine transaminase/Serum glutamic pyruvic transaminase (ALT/SGPT)
Neutrophils	Aspartate transaminase/Serum glutamic oxaloacetic transaminase (AST/SGOT)
Lymphocytes	Creatinine
Monocytes	
Eosinophils	
Basophils	
Platelets	Urine drug screen[a]
	Urine Pregnancy test (women of childbearing potential) [a]
Urinalysis:	Coagulation
Specific gravity	Prothrombin time (PT),
pH	International normalized ratio (INR)
Protein	
Glucose	
Ketones	NT-Pro-BNP
Bilirubin	Inhibin B[b]
Urobilinogen	
Blood	

Abbreviations: NT-Pro-BNP = N-terminal prohormone-brain natriuretic peptide; RBC = red blood cells; WBC = white blood cells.

a Testing will be performed by a local lab.

b Male subjects only.

Attachment 3. Protocol LVHV Blood Pressure Collection Protocol

According to the American Heart Association (AHA) blood pressure is most conveniently measured in children by the auscultation method using a standard sphygmomanometer. Therefore, the investigation sites will be encouraged to use this method rather than automated devices. An exception is allowed in the case of young infants in whom auscultation is difficult and in intensive care settings where frequent measurements are needed.

Correct blood pressure measurement in children requires a cuff which is appropriate for the size of the child's upper arm. This will require a cuff bladder that covers 80% of the 100% of the circumference of the arm. Thus the recommended size for infants is 6×12 cm and the recommended size for older children is 9×18 cm. A standard adult cuff, a large adult cuff and a thigh cuff for leg blood pressure measurement and for use in children with very large arms should also be available.

Blood pressure will be measured after the patient has been in a supine position for at least 2 minutes, using the same arm for each measurement. The interpretation of diastolic and systolic measurements is left to the discretion of the Investigator.

Attachment 4. Protocol LVHV Clinical Global Impression of Improvement (CGI-I)

The Clinical Global Impression of Improvement (CGI-I) Scale (Guy 1976) is a standardized assessment tool and assesses the patient's improvement or worsening from Day 1. The CGI-I is intended to allow clinicians to rate a patient's improvement from Day 1, taking into account the patient's clinical condition and the severity of side effects compared to the patient's condition at the beginning of the trial. The Global Improvement subscale ranges from 1 (very much improved) to 7 (very much worse).

The following is the CGI-I question the will be used in this trial:

How would you rate the overall improvement in this patient's symptoms of pulmonary arterial hypertension compared to patient's condition at the beginning of the trial?

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

Attachment 5. Clinician Global Impression of Severity (CGI-S)

Considering your clinical experience with this particular population, how severe are your patient's pulmonary arterial hypertension symptoms at this time?

[1] Normal.

[2] Mild.

[3] Moderate.

[4] Severe.

Attachment 6. Protocol LVHV Child Health Questionnaire – Parent Form (CHQ-PF28)

The Child Health Questionnaire Parent Form 28 (CHQ-PF28) measures 14 unique physical and psychosocial concepts. The questionnaire groups questions of like subject matter into nine sections. The questions use context adjusted scales to rate current condition (such as excellent, very good, good, fair, poor). The questionnaire has nine sections that characterize the child's health, physical activities, behavior, self esteem, and family condition.

The following are the sections in the CHQ-PF28:

- Child's global health
- Physical activities
- Everyday activities
- Pain
- Behavior
- Well being
- Self esteem
- Your child's health
- You and your family

Attachment 7. Protocol LVHV Guidelines for Conduct of Unencouraged 6-Minute Walk Test

(modified from *Am J Respir Crit Care Med*. 2002; 166:111-7)

The test should be conducted along a long, flat, enclosed corridor with a hard surface that is seldom traveled. If weather permits, the test may be conducted outdoors. The corridor must be as quiet as possible while the test is underway to minimize external interference. The distance that the patient has to walk before changing directions must be 30 meters in length, so as not to artificially reduce the distance walked during the test. The length of the corridor should be marked every 3 meters and turnaround points should be marked with a brightly colored cone. A starting line, which marks the beginning and end of each 60-meter lap, should be marked on the floor with brightly colored tape.

1. Before starting the test, record all pertinent information surrounding the test, i.e., starting location, length of hallway, direction the subject will be walking, time of test, patient's general condition/feeling on the day of the test, and any other physical or medical information that may potentially influence the results of the test.

2. Instruct the patient as follows:

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

   (Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.)

   "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

   Start now, or whenever you are ready."

3. Have the patient stand at the starting point. Simultaneously, give the patient a signal to start walking as quickly as possible, record the start time, and continue timing for the 6-minute period.

4. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap

counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like: then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timing of the 6-minute Period 1 is complete, the patient should be instructed to stop walking and the time recorded. The patient must not move the final location until the person conducting the test marks that location. Once the patient's final location has been marked, allow the patient to leave the test course.

Measure the distance from the starting point to the final location and calculate the distance walked as follows:

Distance walked = (number of "laps" completed) x (length of 1 "lap" in meters) + (distance of any partial lap).

Record the distance walked by the patient.

If a subject uses oxygen during the Day 1 6-minute walk test, subsequent 6-minute walk tests must be conducted with the subject using oxygen. Similarly, subjects performing the 6-minute walk test on room air at Day 1 should have subsequent 6-minute walk tests performed while on room air.

Attachment 8. Protocol LVHV World Health Organization (WHO) Functional Classification

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Attachment 9. Protocol LVHV Blood Sampling Summary

This table summarizes the maximum number of samples (venipunctures) and volumes for all sampling (screening, standard laboratory, drug concentration, pharmacogenetic, pharmacokinetic, biomarker, and exploratory) and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol H6D-MC-LVHV Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample (mL)	Maximum Number Samples	Maximum Total Amount (mL)
Standard laboratory tests[a,b]	Blood	6.3	4	25.2
Pharmacokinetic samples[a]	Blood	0.5	4	2
Pharmacogenetic samples	Blood	0.5	1	0.5
Inhibin B[c]	Blood	2.5	3	7.5
NT-Pro-BNP[d]	Blood	2.5	3	7.5
Total	Blood	12.3	15	42.7

Abbreviations: NT-Pro-BNP = N-terminal prohormone brain natriuretic peptide.

A Additional samples may be drawn if needed for safety purposes.

b Includes hepatic monitoring. Unscheduled hepatic monitoring testing may be performed in patients with treatment emergent hepatic abnormalities as part of patient follow-up, in consultation with Lilly Designated Medical Monitor.

c Male subjects only. The total blood volume for female subjects will be 37.2 mL in maximum.

d NT-Pro-BNP can be performed with clinical chemistry. If it is not performed with the clinical chemistry, then 2.5 mL blood required.

Attachment 10: Protocol Amendment H6D-MC-LVHV(c) Summary of Changes

Overview

Protocol H6D-MC-LVHV (A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension) has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table. In addition, minor typographical corrections not affecting content have been also made in the document.

Amendment Summary for Protocol H6D-MC-LVHV Amendment (c)

Section # and Name	Description of Change	Brief Rationale
Synopsis	Multiple	The synopsis has been modified to encompass changes in study rationale (bosentan and sildenafil are now approved treatments for children with pulmonary arterial hypertension [PAH]), objectives, study design, and statistical analysis.
5. Introduction	Added bosentan as a US- and EU-approved treatment for pulmonary arterial hypertension (PAH) in children.	Since the previous protocol amendment, bosentan has been approved in the United States for treatment of PAH in children.
6.1. Primary Objectives 6.1.1. Period 1	Removed clinical worsening (CW) as primary objective for EU and made 6-minute walk distance (6MWD) the primary objective for both US and EU throughout the protocol.	CW is not feasible in this study as a primary objective.
6.2. Secondary Objectives 6.2.1. Period 1	Removed 6-minute walk (6MW) as a secondary objective for the EU regulatory assessment throughout the protocol.	6MW distance was changed to a primary objective for the European Union.
7.1. Summary of Study Design	Changed number of enrolled patients.	The previous goal for number of enrolled patients in this study was not feasible.
10.1.1. Primary Efficacy Measures and 10.1.2.1 Period 1	Moved criteria for CW from Primary Efficacy Measures to Secondary Efficacy Measures Period 1 (Section 10.1.2.1).	Text was moved for added clarity and consistency.

12. Sample Size and Statistical Methods	Changed Determination of Sample Size, General Considerations, Primary Outcome and Methodology, Efficacy Analyses, Health Outcome/Quality of Life Analyses, Safety Analyses, and Subgroup Analyses.	Updated Sample Size and Statistical Methods sections to reflect the changes to number of enrolled patients and study objectives, including, but not limited to, adjusting the calculated study power and removing subgroup analyses.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

1. Protocol H6D-MC-LVHV (~~b~~c)
A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension

Confidential Information

The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of tadalafil (LY450190), unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries. This document and its associated attachments are subject to United States Freedom of Information Act (FOIA) Exemption 4.

Tadalafil (LY450190)

Study H6D-MC-LVHV (LVHV) is a Phase 3, international, randomized, multicenter, 2-period, double-blind, placebo-controlled (Period 1), add-on (in addition to the patient's current endothelin receptor antagonist, ERA) study to evaluate tadalafil efficacy, safety, and population pharmacokinetics (PK) in pediatric patients with pulmonary arterial hypertension (PAH).

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 12 June 2012
Amendment (a) Electronically Signed and Approved by Lilly: 27 Sep 2012
Amendment (b) Electronically Signed and Approved by Lilly: 14 Dec 2012
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

~~Approval Date: 14-Dec-2012 GMT~~

2. Synopsis

Study Rationale

Currently ~~no therapies are~~ there are a limited number of therapies approved ~~in the United States (US)~~ for the treatment of children with pulmonary arterial hypertension (PAH); bosentan (United States [US] and European Union [EU]) and sildenafil (EU). There is a growing body of evidence, however, supporting the use of therapies approved in the adult population with PAH~~,~~ that has led to widespread off-label use in this pediatric population. There continues to be, however, a need for robust data to inform prescribing physicians regarding the safety and efficacy of all treatment options, including tadalafil, in the pediatric PAH population.

This is the first Phase 3 study of tadalafil for use in treating PAH in pediatric patients.

Clinical Protocol Synopsis: Study H6D-MC-LVHV

Name of Investigational Product: Tadalafil (LY450190)	
Title of Study: A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension	
Number of Planned Patients/Subjects: Entered: ~~200~~50 Enrolled/Randomized: ~~134~~ 34 Completed: ~~121~~ 30	**Phase of Development:** 3
Length of Study: Planned first patient visit: Q1 2013 Planned last patient visit: Period 1: Q1 2019; Period 2, Q1 2021	

Objectives:

Primary Objectives:

Period 1:

- ~~For the United States (US) regulatory assessment, t~~The primary objective of Period 1 is to evaluate the efficacy of tadalafil compared with placebo in improving 6-minute walk distance (6MWD) ~~distance~~ from Baseline to Week 24, as assessed in a subset of patients ≥6 to <18 years of age who are developmentally capable of performing a 6-minute walk (6MW) test.
- ~~For the European Union (EU) regulatory assessment, the primary objective of Period 1 is to evaluate the efficacy of tadalafil compared with placebo, as measured by time to clinical worsening (CW) in pediatric PAH patients through Week 24.~~

Period 2: The primary objective of Period 2 is to evaluate long-term safety of tadalafil while providing continued access to tadalafil for pediatric patients with PAH who participated in Period 1.

Secondary Objectives:

Period 1: The secondary objectives of Period 1 are as follows:

- Assess the efficacy of tadalafil compared with placebo on time to clinical worsening (CW) ~~(for the US regulatory assessment)~~ and the incidence of CW.
- ~~Assess the efficacy of tadalafil compared with placebo on 6MW distance in a subset of patients ≥6 to <18 years of age who are developmentally capable of performing a 6MW test (for the EU regulatory assessment).~~
- Characterize the population pharmacokinetics (PK) of tadalafil in pediatric pulmonary arterial hypertension (PAH) patients.
- Assess the safety of tadalafil as compared with placebo.

Period 2: The secondary objective of Period 2 is to evaluate the incidence of~~,~~ and time to CW.

Additional Objectives:

Period 1: Additional objectives of Period 1 are as follows:

- Assess the efficacy of tadalafil compared with placebo on changes in World Health Organization (WHO) functional classification.
- 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
- Evaluate by echocardiography, changes from Day 1 to Week 24 in the following echocardiographic parameters:
  - tricuspid annular plane systolic excursion (TAPSE)
  - eccentricity index, pericardial effusion
  - maximal tricuspid regurgitant velocity

- Evaluate change from Day 1 to Week 24 in N-terminal prohormone brain natriuretic peptide (NT-Pro-BNP) concentrations.
- Assess physician- and caregiver-reported health outcome, as measured by Clinical Global Impression of Improvement (CGI-I), and in a subset of patients ≥5 years of age, Child Health Questionnaire Parent Form 28 (CHQ-PF28).

Study Design: A Phase 3, international, randomized multicenter, 2-period, double-blind, placebo-controlled, add-on (in addition to the patient's current endothelin receptor antagonist [ERA]) study to evaluate tadalafil efficacy, safety, and population PK in pediatric patients with PAH.

Screening and eligibility evaluation will be performed during an approximately 28-day period prior to randomization and the administration of tadalafil. Period 1 is a 24-week study drug treatment phase. During this study period, patients will continue to receive stable ERA therapy. Period 2 is an open-label extension (OLE) period that will evaluate the long-term safety of tadalafil while providing continued access to tadalafil for pediatric patients completing Period 1. Patients entering Period 1 of the study will be 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 to tadalafil or placebo.

Diagnosis and Main Criteria for Inclusion and Exclusions ~~-~~ At least ~~134~~ 34 PAH patients ≥6 months to <18 years of age with WHO functional class II or III (at screening) will be randomized~~,~~ to include at least ~~50%~~ 30% of patients <12 years of age~~and at least 20% of patients <6 years of age.~~

Inclusion criteria:

- Diagnosis of PAH that is either:
  - idiopathic, including hereditary;
  - related to connective tissue disease;
  - related to anorexigen use;
  - associated with surgical repair of at least 6-month duration of simple congenital systemic to pulmonary shunt (eg, atrial septal defect, ventricular septal defect, patent ductus arteriosus)
- 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 pulmonary vascular resistance (PVR) ≥3 Wood units via right heart catheterization (RHC). In the event that a pulmonary artery wedge pressure cannot be obtained during RHC, patients with a left ventricular end diastolic pressure (LVEDP) <15 mm Hg, with normal left heart function, and absence of mitral stenosis on echocardiography can be eligible for enrollment.
- Receiving an endothelin receptor antagonist (ERA, eg, bosentan or ambrisentan) and must be on a maintenance dose with no change in dose (other than weight-based adjustments) for at least 12 weeks prior to screening and have a screening aspartate transaminase (AST)/alanine transaminase (ALT) <3 times the upper limit of normal (ULN).
- If on conventional PAH medication, including but not restricted to, anticoagulants, diuretics, digoxin, and oxygen therapy, the patient must be 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).

Main Exclusion Criteria:

- Pulmonary hypertension related to conditions other than specified above.
- History of left-sided heart disease, including any of the following:
  - clinically significant (pulmonary artery occlusion pressure [PAOP] 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 (MUGA), angiography, or echocardiography;
  - left ventricular shortening fraction < 22% by echocardiography;
  - life-threatening cardiac arrhythmias;
  - symptomatic coronary artery disease within 5 years of study entry.
- Unrepaired congenital heart disease.
- History of angina pectoris or other condition that was treated with long- or short-acting nitrates within 12 weeks before administration of study drug.
- Severe hepatic impairment, Child-Pugh Grade C.
- Severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 30 mL/min (Schwartz Formula).
- Retinal disorder (eg, hereditary retinal disorders, retinopathy of the preterm patient and other retinal disorders).
- Severe hypotension or uncontrolled hypertension as determined by the Investigator.
- Significant parenchymal lung disease or bronchopulmonary dysplasia.
- Concurrent phosphodiesterase type 5 (PDE5) inhibitor therapy (sildenafil or vardenafil) or has received PDE5 inhibitor therapy within 12 weeks prior to the first study drug 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, anti-coagulants, digoxin, and oxygen therapy within 4 weeks of screening.
- Currently receiving treatment with doxazosin, nitrates, or cancer therapy.
- 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.
- Nursing or pregnant.
- Received tadalafil therapy within 12 weeks prior to the first study drug dosing or are hypersensitive to tadalafil.
- Allergy to the excipients, notably lactose
- Unable to take orally administered tablets (without chewing, crushing or breaking) or suspension.
- Diagnosis of Down syndrome.

Investigational Product, Dosage, and Mode of Administration or Intervention: Period 1: Tadalafil, 5 mg to 40 mg, depending on treatment cohort, given once a day as 2.5 mg, 5 mg, 10 mg and 20 mg tablets or 2.5 mg/mL tadalafil suspension given orally. Period 2: Patients receiving tadalafil in Period 1 will continue at same dose in Period 2. Patients receiving placebo in Period 1 will receive tadalafil in Period 2 at the corresponding tadalafil dose in that patient's weight group. All patients in Period 2 will receive tadalafil for at least 2 years.

Planned Duration of Treatment: Approximately 2 years, 7 months: Screening Period, approximately 28 days; Period 1 treatment, 24 weeks; Period 2 treatment, 2 years.

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: Period 1: Matching placebo Period 2: No comparator during Period 2.

Criteria for Evaluation:

Efficacy:

Primary Measures (Period 1):

- ~~For the US regulatory assessment, t~~The primary efficacy measure is 6MWD ~~distance~~ in meters assessed in a subset of patients ≥6 to <18 years of age who are developmentally capable of performing a 6MW test.
- ~~For the EU regulatory assessment, the primary efficacy measure is time to first occurrence of CW.~~

Secondary Measures (Period 1):

- Time to CW ~~(for the US regulatory assessment)~~ and the incidence of CW.
- ~~6MW distance in meters measured in a subset of patients who are ≥6 to <18 years of age and who are developmentally capable of performing a 6MW test (for the EU regulatory assessment).~~

Secondary Measures (Period 2):

- Incidence of and time to CW.

Additional Measures (Period 1):

- WHO functional classification
- Cardiac MRI parameters:
  - LV ejection fraction
  - RV end diastolic volume
  - RV end systolic volume
  - RV ejection fraction
- Echocardiography parameters:
  - tricuspid annular plane systolic excursion (TAPSE)
  - eccentricity index
  - pericardial effusion
  - maximal tricuspid regurgitant velocity
- NT-Pro-BNP concentrations.

Additional Measures (Period 2):

- 6MW distance in meters measured in patients who are ≥6 years of age and who are developmentally capable of performing a 6MW test.
- WHO functional classification

Safety: Period 1: Safety during Period 1 will be assessed through AEs including abnormalities detected by ECG or physical examination, clinical chemistry and hematology panels, urinalysis, vital signs, and eye examinations. Period 2: AEs, changes in body weight and height, inhibin B biomarker (male patients only), eye examinations, Tanner scale, and intelligence tests, and concomitant medications.

Health Outcomes:

- CGI-I, CHQ-PF28 (in patients ≥5 years of age).

Pharmacokinetics: Population PK assessment of plasma tadalafil concentrations at steady-state.

Statistical Methods: Results of statistical hypothesis tests will be reported using 2-sided p-values, unless otherwise specified for a particular endpoint.

Sample Size: ~~The sample size of 34 randomized patients will provide 80% power to detect a hazard ratio of 3.6 in time to first incidence of CW during the 24 week Period 1 follow up, based on a two sided 0.3 significance level and assumptions of an estimated placebo event rate for CW during Period 1 of 15%, and an estimated discontinuation rate for causes other than CW during Period 1 of 10%. In addition, a sample size of 134 patients is expected to include at least 96 patients (48 per treatment arm) who are able to complete the 6MW test, which will provide 80% power to detect a placebo-adjusted mean difference in change in 6MW distance of 35m with a standard deviation of 60m and a two-sided significance level of 0.05.~~ At least 34 patients will be stratified by weight and randomized in a 1:1 ratio to tadalafil or placebo treatment in this study (17 to placebo treatment and 17 to tadalafil treatment).

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 6MW 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.

Efficacy: Efficacy analyses of Period 1 data, except 6MW measurements, will include all patients who were randomized and took at least 1 dose of study medication. The analysis of 6MW data will include only the subset of randomized patients ≥6 to <18 years of age who took at least 1 dose of study medication and were capable of performing a 6MW test. Changes from Day 1 to Weeks 4, 8, 12, 16, 20, and 24 in 6MW distance will be analyzed with a mixed-effects model for repeated measures (MMRM).

~~The primary efficacy endpoint of time to first occurrence of CW during Period 1 will be analyzed using a Cox proportional hazard model. Comparisons between treatment groups will be assessed for significance at a 0.3 alpha level. The incidence of CW will be summarized as the number and percentage of patients in each treatment group who experience at least 1 criterion of the CW definition during the study period. A Fisher's exact test will be used to compare the incidence rates. The percentage of patients who participate in Period 2 and who experience one of the CW criteria will be summarized. In addition, e~~Change from Day 1 of Period 1 in 6MW distance and WHO functional class will be reported for all patients who participate in Period 2.

The primary efficacy endpoint of change from baseline in 6MW distance will be analyzed using a mixed model for repeated measures (MMRM). Terms in the model will include visit, baseline 6MW measurement, PAH etiology, type of ERA therapy, and treatment group.

The proportion of patients who experience a change in WHO functional class will be summarized.~~analyzed using a Cochran-Mantel-Haenszel (CMH) test.~~ Changes will also be categorized as "worsening, "no change," or "improving" over the study period. The percentages of patients in these categories will be summarized by~~compared between~~ treatment groups~~ with a chi-square test~~.

An interim analysis of 6MW data is planned in approximately Q1 2017 when approximately 50% of all randomized patients (Period 1) have baseline and Week 24 6MW measurements available for analysis. The results of this interim analysis will be reviewed by a data monitoring committee (DMC) to assess evidence of efficacy and the accuracy of study design assumptions.

The database will be locked, and data collected during Period 1 will be analyzed when all randomized patients have ended participation in Period 1. These results will be reported in a clinical study report. An addendum to the initial clinical study report will be prepared at the conclusion of Period 2 to present analyses of the OLE data.

Changes from Day 1 to endpoint in hemodynamic parameters collected via echocardiogram and MRI will be analyzed with analysis of covariance (ANCOVA) models. Similarly, changes in log-transformed NT-Pro-BNP values will be analyzed with an analysis of variance (ANOVA) model.

Safety: The analysis of safety will include all patients who took at least 1 dose of study medication. The differences in the percentages of patients experiencing AEs across various criteria (for example, treatment-emergent, treatment-related, serious, etc.) will be summarized~~assessed by Fisher's exact tests~~.

Changes from Day 1 in clinical laboratory measurements, biomarker (inhibin B) concentrations, blood pressure,

and heart rate (HR) will be analyzed with ranked ANOVA models with a term for treatment group. Differences in categorical changes will be summarized~~assessed by Fisher's exact tests~~.

Changes from Day 1 in composite intelligence scores will be assessed according to the published instructions for each instrument. The numbers and percentages of patients in each treatment group with shifts in Tanner stage at Year 1 and Year 2 will be summarized.

Health Outcomes: An ANCOVA analysis will be used to examine changes from Day 1 to Weeks 16 and 24 in CHQ-PF28 scores. Patient outcome will be assessed using the CGI-I at Weeks 16 and 24 (Visits 7 and 9) using an ordinal scale with 7 response categories ranging from "Very Much Better" to "Very Much Worse". Responses will also be grouped into 3 derived categories ("Worse", "No Change", and "Better") for additional analysis. The proportion of patients in each of the 7 response categories and each of the 3 derived categories will be summarized by treatment group. ~~Differences between treatment groups will be tested using a CMH test.~~

Pharmacokinetics: Plasma tadalafil concentration-time data will be pooled and evaluated using a population PK approach. The effects of body weight, age, and sex on apparent clearance (CL/F) will be explored. If the number of patients taking different types of ERA is sufficient to quantify the effect of ERA on apparent clearance, then this will also be done. Due to random PK sampling times and the low number of samples available from each individual patient, it may be necessary to combine the data from this study with the densely sampled data from Study LVIG to better characterize the population PK of tadalafil in this patient population.

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4. Abbreviations and Definitions

Term	Definition
6MW	6-minute walk
6MWD	6-minute walk distance

…

5. Introduction

Pulmonary arterial hypertension (PAH) is a rare, chronic and progressive disease characterized by elevated pulmonary artery pressure and pulmonary vascular resistance, leading to right-heart failure and death (Rich 1998; Barst 2004). PAH can be further classified into idiopathic PAH, heritable PAH, and associated PAH. Conditions that are associated with PAH include connective tissue diseases (particularly systemic sclerosis and lupus), congenital heart disease, portal hypertension, human immunodeficiency virus (HIV) infection, and some drugs (particularly anorexigens).

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), the endothelin receptor antagonists (ERAs) (bosentan and ambrisentan), and the phosphodiesterase type 5 (PDE5) inhibitors (sildenafil and tadalafil).

While PAH is more common in the adult population, it does occur in children with a similar, if not worse, prognosis without treatment. However, with treatment the outcome appears better in

children than in adults. Due to limited clinical data in children, treatment decisions are extrapolated from adult studies. Similar clinical strategies from adults have been suggested for the management of PAH in children, but these guidelines must be used with caution (McLaughlin et al. 2009a). Currently, ~~no therapies are~~ bosentan is the only approved drug for the treatment of pediatric patients with PAH in the United States (US). In the European Union (EU), bosentan and s~~S~~ildenafil ~~is the only drug that has been~~ are approved ~~in the European Union (EU) for the treatment of pediatric PAH patients~~for the same pediatric indication. There is a growing body of evidence supporting the use of therapies approved in adults~~,~~ that has led to widespread off-label use (Beghetti 2009). There is a need, therefore, to provide physicians with safety and efficacy results of all treatment options, including tadalafil, in the pediatric population.

Tadalafil is an orally administered, potent, and selective PDE5 inhibitor that has been investigated at doses of 2.5 mg to 100 mg (predominantly in adult men at doses of 10 mg and 20 mg on-demand, and 2.5 mg and 5 mg taken once daily). Tadalafil is currently approved in the US, EU, and Japan for the treatment of erectile dysfunction (ED), both on-demand and once daily. Tadalafil is the active ingredient of Adcirca®, that was recently approved for the treatment of PAH (pulmonary hypertension Group 1) in adults in the EU, US, Canada, and Japan. Tadalafil was also approved for the treatment of benign prostatic hyperplasia (BPH) in the US.

PAH is associated with impaired release of nitric oxide (NO) due to little or no expression of NO synthase in the vascular endothelium of pulmonary arteries (Giaid and Saleh 1995). PDE5 is the predominant phosphodiesterase isoenzyme in the pulmonary vasculature. As such, PDE5 inhibition potentiates the nitric oxide-mediated pulmonary vasodilator and antiproliferative effects in patients (adults and children) with PAH.

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. Tadalafil 40 mg was well tolerated in the adult PAH patient population with a safety profile similar to that observed in the ED patient population.

There is limited experience with regards to the safety, tolerability, and efficacy of tadalafil in pediatric PAH patients. A recent report on tadalafil in children with PAH has demonstrated that tadalafil was well-tolerated in this patient population (Takatsuki et al. 2012). In a company-sponsored clinical trial, a single 14-year-old female patient (73 kg) received tadalafil 2.5 mg in Study LVGY. This patient completed Study LVGY and subsequently enrolled in the extension Study H6D-MC-LVGX (LVGX), in which she received tadalafil 40 mg.

It has been suggested that the clinical course of PAH in children is less predictable than in adults. If untreated, the condition may progress more rapidly in children, leading to reduced survival in children than in adults over time. Importantly, the safety and efficacy of PAH therapies approved for adults have not been robustly established in pediatric patients due to limited data in children. Given the efficacy and safety results of tadalafil for the treatment of PAH in adults

(Study LVGY), and recognizing the importance of providing prescribers and patients with recommendations reflecting tadalafil experience across developmental stages, Lilly is pursuing the development of tadalafil for the treatment of PAH in patients, aged ≥6 months to <18 years.

This study, H6D-MC-LVHV (LVHV), is a phase 3, international, randomized, double-blind (Period 1), placebo-controlled (Period 1) add-on (in addition to the patient's current ERA) study to explore the efficacy, safety, and population pharmacokinetics (PK) of tadalafil administered orally once daily in children with PAH. Patients will receive study drug for 6 months in the double-blind period (Period 1), and will then be eligible to enroll into an open-label 2-year extension period (Period 2).

Study LVHV will include children who, at the time of screening, are ≥6 months of age and <18 years of age. Patients will be stratified into 3 weight cohorts (Heavy-weight, ≥40 kg; Middle-weight, ≥25 kg to <40 kg; and Light-weight, <25 kg), and then randomized to tadalafil or placebo. The dose of each weight cohort in this study will be established and may be redefined based on safety monitoring committee (SMC) and Sponsor review of the PK and safety results from Study H6D-MC-LVIG (LVIG). Study LVIG is an open-label, multiple ascending-dose study to evaluate the safety and PK of tadalafil administered orally as a tablet or suspension to children with PAH. Study LVIG includes 2 study periods: PK/safety (Period 1) and an open-label safety extension (Period 2). The primary objective of Period 1 of Study LVIG is to characterize the PK of tadalafil in a pediatric population with PAH. The objectives of Period 2 are to evaluate the long-term safety of tadalafil as well as clinical worsening (CW) of PAH in this patient population.

The study design for this study was developed to treat pediatric patients who are on stable PAH therapy of an endothelin receptor antagonist (ERA) as standard of care instead of PAH treatment-naïve patients, as that is seen as unethical by the prescribing community, and has the agreement of the Food and Drug Administration (FDA) and European Medicines Agency (EMA). The primary efficacy measure will be 6-minute walk distance (6MWD) distance~~for US regulatory assessment, and time to CW for EU regulatory assessment~~. Safety will be assessed using spontaneously reported adverse events (AEs), vital signs, laboratory analytes, electrocardiograms (ECGs), eye examinations, and concomitant medications.

More detailed information about the known benefits and risks of tadalafil may be found in the Investigator's Brochure (IB).

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6. Objectives

6.1. Primary Objectives

6.1.1. Period 1

~~For the US regulatory assessment, t~~The primary objective of Period 1 is to evaluate the efficacy of tadalafil compared with placebo in improving 6MWD ~~distance~~ from baseline to Week 24, as

assessed in a subset of patients ≥6 to <18 years of age who are developmentally capable of performing a 6-minute walk (6MW) test.

~~For the EU regulatory assessment, the primary objective of Period 1 is to evaluate the efficacy of tadalafil compared with placebo, as measured by time to CW (as defined in Section 10.1.1) in pediatric PAH patients through Week 24.~~

6.1.2 Period 2

The primary objective of Period 2 is to evaluate long-term safety of tadalafil while providing continued access to tadalafil for pediatric patients with PAH who participated in Period 1.

6.2 Secondary Objectives

6.2.1 Period 1

The secondary objectives of Period 1 are as follows:

- Assess the efficacy of tadalafil compared with placebo on time to CW ~~(for the US regulatory assessment)~~ and the incidence of CW.
- ~~Assess the efficacy of tadalafil compared with placebo on 6MW distance in a subset of patients ≥6 to <18 years of age who are developmentally capable of performing a 6MW test (for the EU regulatory assessment).~~
- Characterize the population PK of tadalafil in pediatric PAH patients.
- Assess the safety of tadalafil compared with placebo.

…

7. Investigational Plan

7.1 Summary of Study Design

Figure LVHV.7.1 illustrates the study design and the respective study periods. The Study Schedule is in Attachment 1.

This is a Phase 3, international, randomized multicenter, 2-period, double-blind (Period 1), placebo-controlled (Period 1), add-on (ie, in addition to the patient's current ERA) study to evaluate the efficacy, safety, and population PK of tadalafil in pediatric patients with PAH.

Study LVHV will enroll pediatric PAH patients ≥6 months to <18 years of age with WHO functional class II or III (Attachment 8) and who are already receiving treatment with an ERA. Patients will be randomized to receive either placebo or active drug in a 1:1 ratio, based on weight cohort, PAH etiology, and type of ERA. Patients will receive study treatment for 6 months in the double-blind period (Period 1), and then will be eligible to enroll into an open-label 2-year extension period (Period 2) during which patients will receive tadalafil.

At least ~~134~~ 34 patients will be randomly assigned to treatment in Period 1 of this study. To achieve a representative distribution of patients' ages, enrollment will be monitored throughout

the study to achieve ~~≥50%~~ ≥30% of all patients < 12 years of age~~ and ≥ 20% of all patients < 6 years of age~~.

Patients entering the study will be stratified into 1 of 3 weight-cohorts, based on the patient's weight at the time of the Screening visit:

Heavy-weight: ≥40 kg
Middle-weight: ≥25 kg to <40 kg
Light-weight: <25 kg

If a patient's weight changes during Period 1, such that he/she falls into a different weight cohort, he/she will continue to receive the study drug dose appropriate to his/her original weight cohort.

Patients will also be stratified by type of ERA (bosentan or other) and PAH etiology.

If a patient will be participating in Period 2, and if that patient's weight changes at the conclusion of Period 1 (at the Visit 9 or Early Termination visit) or during Period 2, such that he/she falls into a different weight cohort (defined as at least 1 kg above or below the weight cohort thresholds of 25 kg and 40 kg), then the patient's dose of study drug may be adjusted so that they are receiving the appropriate weight cohort-related dose.

Dose selection for this study will be based on pediatric PK and safety data from Study LVIG and the PK and safety data from the adult PAH development plan. The selected dose for each weight cohort will reflect exposures comparable to the approved 40-mg dose of tadalafil in adults, unless unexpected safety concerns unique to the pediatric population are revealed. Dosing of all weight cohorts is also described in Section 9.

…

7.2. Discussion of Design and Control

Study H6D-MC-LVHV (LVHV) is a Phase 3, international, randomized, multicenter, 2-period, double-blind and placebo-controlled (Period 1), add-on study (in addition to the patient's current ERA) to evaluate tadalafil efficacy, safety, and population PK in pediatric patients with PAH. A multicenter trial is necessary to accrue the required number of pediatric patients with PAH to adequately characterize the efficacy and safety of tadalafil in this patient population in a timely manner. The efficacy and safety of tadalafil will be compared with that of placebo group during Period 1.

This study design requires patients to be receiving an ERA (such as bosentan or ambrisentan), and allows for the use of conventional PAH therapies (see Section 8.1). Endothelin receptor antagonists 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 pediatric PAH patients to treatment with placebo alone may be viewed as unethical. To ensure that treatment assignment is balanced within type of ERA, randomization to treatment will be stratified by type of ERA (bosentan or other).

Stratification by PAH etiology is justified, as the prognosis of patients with PAH is, in part, dependent on etiology. For example, patients with PAH associated with connective tissue disease have a worse prognosis than patients with idiopathic PAH, while patients with PAH associated with congenital heart disease have a better survival (Kähler and Colleselli 2006; McLaughlin et al. 2004).

Randomization stratified by weight is considered reasonable to ensure an appropriate distribution of treatments within weight cohorts. Historically, male and female pediatric growth charts could be globally applied to clinical research based on common weight and age patterns; however, these may not be applicable to pediatric patients with PAH due to differences in disease conditions and due to a modest divergence in body weight and age patterns across geographies. Therefore, treatment randomization will be stratified by weight cohort.

This study is designed to evaluate the efficacy of tadalafil compared with placebo in pediatric patients with PAH. ~~For the US regulatory agency, t~~The primary efficacy endpoint will be the change from Baseline (Day 1) to Week 24 in 6MW distance assessed in those patients who are ≥6 years of age at Day 1 (Visit 2) and are developmentally capable of performing the test. ~~For the EU regulatory agency, the primary endpoint will be the time to CW through Week 24.~~

Due to the expected low mortality event rate in this population, mortality rate is not considered an appropriate primary endpoint in PAH studies; therefore, the use of a composite endpoint to define CW (Section 10.1.2) will provide more statistical power to detect a therapeutic effect in a limited sample population with limited individual event rates (Ventetuolo et al. 2008). The proposed definition of CW endpoint (Section 10.1.2) is similar to that used in other trials and takes into account a recent publication that offered recommendations based on historical review of PAH studies on CW as an endpoint (McLaughlin et al. 2009b). While the frequency of events of CW in patients with mild or moderate functional class (II, III) are expected to be low after 16 weeks, evaluation of this endpoint at 24 weeks (6 months) will increase the likelihood of detecting a treatment effect (Rubin et al. 2002).

Exercise capacity is an important prognostic indicator of PAH (Miyamoto et al. 2000). The distance walked during a 6MW test is the most accepted PAH exercise capacity test, as it is simple, well tolerated, and non-invasive (Peacock et al. 2010) and has therefore been the most commonly used clinical trial endpoint for PAH patients ≥6 years of age (Haworth and Beghetti 2010). For Study LVHV, it is expected that approximately ~~75% of the 134~~ 34 enrolled patients will be 6 years of age or older who are developmentally capable of performing the 6MW test. The change in 6MWD ~~distance~~ compared with placebo will be evaluated up to Week 24.

…

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measures

The following primary efficacy measure~~s~~ will be collected at the times shown in the Study Schedule (Attachment 1):

- ~~For the US regulatory assessment, t~~The ~~primary efficacy measure for this study is~~ 6MWD ~~distance~~ in meters assessed in a subset of patients who are ≥6 to <18 years of age ~~and~~ who are developmentally capable of performing a 6MW test~~.~~
- ~~For the EU regulatory assessment, the primary efficacy measure for this study is time to first occurrence of CW. Patients meeting any of the following 5 major criteria would be considered to have met the definition of CW:~~
- ~~All cause mortality~~
- ~~Lung or Heart Lung Transplantation~~
- ~~Atrial Septostomy or Potts Shunt~~
- ~~Hospitalization for PAH progression~~
- ~~Hospitalization for PAH progression should not be due to a potentially precipitating event such as pneumonia hemoptysis etc.; however, if after the hospitalization is completed, the patient is discharged and the patient remains worse, then the patient can be assessed for clinical worsening.~~
- ~~Worsening of PAH~~
- ~~Patient has any of the following criteria:~~
- ~~New-onset syncope.~~
- ~~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).~~
- ~~Increase of 1 or more in WHO Functional Class (Attachment 8) (except for patients already in Class IV) only for patients unable to perform the 6MW test.~~
- ~~Worsening of WHO functional class and a decrease of 20% in the 6MW test (confirmed 5 to 10 days later) for those patients who are ≥6 years of age and are developmentally capable of performing the 6MW test.~~
- ~~Criteria for clinical worsening will be adjudicated by an independent, blinded study-specific Clinical Endpoint Committee (CEC). This adjudication will be used for data analysis, and will not be used to guide patient treatment.~~

10.1.2. Secondary Efficacy Measures

~~The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1).~~

10.1.2.1. Period 1

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1):

- Time to CW ~~(for the US regulatory assessment)~~ and the incidence of CW ~~(defined in Section 10.1.1)~~. Patients meeting any of the following 5 major criteria would be 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 be due to a potentially precipitating event such as pneumonia hemoptysis, etc; however, if after the hospitalization is completed, the patient is discharge and the patient remains worse, then the patient can be assessed for CW.
5. Worsening of PAH

   Patient has 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) (except for patients already in Class IV) only for patients unable to perform the 6MW test.
   d. Worsening of WHO functional class and a decrease of 20% in the 6MW test (confirmed 5 to 10 days later) for those patients who are ≥6 years of age and are developmentally capable of performing the 6MW test.

Criteria for CW will be adjudicated by an independent, blinded study-specific Clinical Endpoint Committee (CEC). This adjudication will be used for data analysis, and will not be used to guide patient treatment.

- ~~6MW distance in meters measured in subset of patients who are ≥6 to <18 years of age and who are developmentally capable of performing a 6MW test (for the EU regulatory assessment).~~
- Population PK assessment of plasma tadalafil concentrations at steady-state.

…

10.3.5. Safety Monitoring

The Lilly ~~clinical research physician~~CRP will monitor safety data throughout the course of the study. In addition, the DMC will review safety data periodically, as outlined in the DMC charter.

Lilly will review SAEs within time frames mandated by company procedures and will review trends, laboratory analytes, and AEs at periodic intervals. The Lilly ~~clinical research physician~~CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review trends and laboratory analytes periodically.

The Lilly ~~Clinical Research Physician~~CRP will monitor blinded safety data throughout the course of the study. A DMC independent of Lilly will monitor unblinded safety data throughout the course of the study by periodic reviews of safety data, as outlined in the DMC charter.

The Lilly ~~clinical research physician~~CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist as appropriate. In the event that Lilly safety monitoring uncovers an issue that needs to be evaluated further by unblinding at the group level, the safety concern will be communicated to the DMC. The DMC will review the unblinded data and conduct appropriate analyses of the safety data, as deemed necessary.

…

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

~~Two different primary endpoints~~ The primary efficacy measure is 6MWD and will be evaluated in this study during Period 1. ~~For the US regulatory assessment, the primary efficacy measure is 6MW distance. For the EU regulatory assessment, the primary efficacy measure is time to first occurrence of CW.~~

~~A total of 134~~ At least 34 patients will be stratified by weight and randomized in a 1:1 ratio to tadalafil or placebo treatment in this study (~~67~~ 17 to placebo treatment and ~~67~~ 17 to tadalafil treatment). ~~The statistical significance of each endpoint will be established using separate error-spending functions.~~

~~The sample size of 134 randomized patients will provide 80% power to detect a hazard ratio of 3.6 in time to first incidence of CW during the 24 week Period 1 follow-up. This estimate is based on a two-sided 0.3 significance level, an assumption of an exponential parameter of 0.0271 for the placebo treatment group (that is, an estimated placebo event rate for CW during Period 1 of 15% and an estimated tadalafil event rate for CW during Period 1 of 4.4%) and a common exponential censoring parameter for both treatment groups of 0.0176 (that is, an estimated discontinuation rate for causes other than CW during Period 1 of 10%).~~

With 2 patients not having postbaseline 6MWD, ~~A~~ a sample size of ~~134~~ 32 randomized patients is assumed to be~~to include at least 96 patients (48 per treatment arm) who are~~ ≥6 to <18 years of age ~~and~~ 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. ~~These data will provide 80% power to detect a placebo-adjusted mean difference in change in 6MW distance of 35 m with a standard deviation of 60 m and a two-sided significance level of 0.05.~~

12.2. Statistical and Analytical Plans

The Statistical Analysis Plan will include additional details regarding the statistical analyses of data from this study.

12.2.1. General Considerations

Efficacy analyses of Period 1 data, except 6MW measurements, will include all patients who were randomized and took at least 1 dose of study medication. The analysis of 6MW data will

include only the subset of randomized patients ≥6 to <18 years of age who took at least 1 dose of study medication and were able to perform a 6MW test. Patients will be analyzed according to the randomized treatment assignment. Patients with no post Day 1 data for a particular efficacy endpoint will be excluded from the analysis of that endpoint. Additional sensitivity analyses utilizing imputed values for missing post Day 1 data may be conducted for specific endpoints. Safety analyses will include all randomized patients who took at least 1 dose of study medication.

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 rank-transformed data.

~~Results of statistical hypothesis tests will be reported using two-sided p-values, unless otherwise specified for a particular endpoint.~~Given the small sample size, no formal comparison will be made between treatment groups. Hence, the overall treatment difference p-value and the visit-wise p-values will not be reported.

…

12.2.6. Primary Outcome and Methodology

The primary efficacy endpoint ~~for the US regulatory assessment~~ of change from baseline (Day 1) in 6MW distance will be analyzed at Weeks 4, 8, 12, 16, 20, and 24 with a mixed effects model for repeated measures (MMRM). This analysis will include only patients who are ≥6 to <18 years of age and are developmentally able to complete 6MW testing during Period 1. Factors in the MMRM model include visit, baseline 6MWD, PAH etiology, type of endothelin receptor antagonist (ERA) therapy, and treatment group. Within the model, the effect of PAH etiology will only be included if there are at least 3 patients per treatment arm at each PAH etiology level. Similarly, the effect of ERA therapy will only be included if there are at least 3 patients per treatment arm at each ERA therapy level.~~Terms in the model will include visit, baseline (Day 1) 6MW distance, PAH etiology, type of ERA therapy, and treatment group. Treatment effects will be reported as least-squares means and associated confidence intervals with the overall treatment effect p-value interpreted for evidence of efficacy.~~

~~The primary efficacy endpoint for the EU regulatory assessment of time to first occurrence of CW (Section 10.1.1) during Period 1 will be analyzed using a Cox proportional hazard model. The analysis model will include terms for weight cohort, PAH etiology, type of ERA therapy, and treatment group. Comparisons between treatment groups will be assessed for significance at a 0.3 alpha level.~~

As the study has a limited number of patients enrolled, an inspection of the model mean change in 6MWD and corresponding CIs will be used instead of significance testing to ensure whether

they are trending in the right direction. The overall treatment difference p-value and the visit-wise p-values will not be reported.~~Kaplan-Meier plots of the proportion of patients without CW over time will be presented for all subjects and by treatment group and weight cohort. Analyses of CW will use adjudicated data reported by the CEC.~~

These objectives will be ~~analyzed~~ assessed and results reported at the end of Period 1.

12.2.7. Efficacy Analyses

Secondary and additional efficacy endpoints will include all patients who were randomized to treatment and took at least 1 dose of study medication.

The proportion of patients who experience a change in WHO functional class will be summarized.~~analyzed using a Cochran-Mantel-Haenszel (CMH) test.~~ Changes will also be categorized as "worsening, "no change," or "improving" over the study period.~~ The percentages of patients in these categories will be compared between treatment groups with a chi-square test.~~

The incidence of CW (Section 10.1.2) will be summarized as the number and percentage of patients in each treatment group who experience at least one criterion of the CW definition during the study period.~~ A Fisher's exact test will be used to compare the incidence rates.~~

Changes from Day 1 to endpoint in hemodynamic parameters collected via echocardiography and MRI will be analyzed with analysis of covariance (ANCOVA) models. Models will include terms for Day 1 value, weight cohort, PAH etiology, type of ERA therapy, and treatment group.

These objectives will be analyzed and results reported at the end of Period 1. No adjustments for multiple comparisons will be made for the analysis of these endpoints.

During Period 2, the incidence and time to first occurrence of CW during Period 2 will be assessed. The percentage of patients who participate in Period 2 and who experience one of the CW criteria will be summarized. In addition, change from Day 1 of Period 1 in 6MW and WHO functional class will be reported for all patients who participate in Period 2.

Changes from Day 1 in NT-Pro-BNP values will be analyzed with an analysis of variance (ANOVA) model. NT-Pro-BNP values will be log-transformed for analysis. Day 1 values for NT-Pro-BNP concentrations will be the last value collected prior to randomized treatment assignment at Day 1 (Visit 2).

…

12.2.9. Health Outcome/Quality of Life Analyses

An ANCOVA analysis will be used to examine changes from Day 1 to Weeks 16 and 24 in CHQ-PF28 scores. The models will include terms for Day 1 score, Day 1 value, weight cohort, PAH etiology, type of ERA therapy, and treatment group.

Patient outcome will be assessed using the CGI-I at Weeks 16 and 24 (Visits 7 and 9) using an ordinal scale with 7 response categories ranging from "Very Much Better" to "Very Much

Worse."~~.~~ Responses will also be grouped into 3 derived categories ("Worse", ~~"~~; "No Change", ~~"~~; and "Better") for additional analysis. The proportion of patients in each of the 7 response categories and each of the 3 derived categories will be summarized by treatment group. ~~Differences between treatment groups will be tested using a CMH test.~~

12.2.10. Safety Analyses

Safety during Period 1 will be assessed through AEs including abnormalities detected by ECG or physical examination, clinical chemistry and hematology panels, urinalysis, vital signs, eye examinations, and concomitant medications. During Period 2, safety will be monitored using AEs, changes in body weight and height, inhibin B biomarker (male patients only), eye examinations, Tanner scale, and intelligence tests. The analysis of safety will include all patients who took at least 1 dose of study medication.

Adverse events will be coded using the Medical *Dictionary for Regulatory Activities* (MedDRA) preferred term. Treatment-emergent AEs (TEAEs) are defined as events that first occurred or worsened after the first dose of study medication on Day 1 (Visit 2). Treatment-related adverse events are defined as events that are determined to be possibly or probably treatment-related by the Investigator. The ~~differences in the~~ percentages of patients experiencing AEs across various criteria (for example, treatment-emergent, treatment-related, serious, etc.) will be displayed by treatment groups~~analyzed using Fisher's exact test~~.

Changes from Day 1 in clinical laboratory measurements, inhibin B biomarker concentrations, blood pressure, and HR will be analyzed with ranked ANOVA models with a term for treatment group. Observed laboratory values and changes from Day 1 in laboratory values will be evaluated for categorical changes based on normal ranges and displayed by treatment groups. ~~Differences in categorical changes will be assessed by Fisher's exact tests.~~ Changes from Day 1 in composite intelligence scores will be assessed according to the published instructions for each instrument. The numbers and percentages of patients in each treatment group with shifts in Tanner stage at Year 1 and Year 2 will be summarized. Day 1 values for laboratory data, vital signs, body weight and height, inhibin B biomarker, Tanner scale, and intelligence tests will be the last values collected prior to randomized treatment assignment at Day 1 (Visit 2).

12.2.11. Subgroup Analyses

Subgroup analyses will be conducted as deemed appropriate and necessary. Detailed descriptions of the subgroup variables will be provided in the statistical analysis plan.

~~Additional analyses will examine time to first incidence of CW and change in 6 MW distance within subgroups defined by weight cohort, ERA type, and PAH etiology. The subgroup-by-treatment interaction p-values will be examined to determine if there is evidence that treatment effects change across levels of the specified subgroup. Additional analyses of within subgroup treatment effects may be performed to investigate and quantify significant interactions.~~

~~This study is not powered to detect differences within these subgroups. As such, all results of subgroup analyses will be considered exploratory.~~

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