Protocol 05 H6D-MC-LVIG (d)

A Multiple Ascending Dose Study of Tadalafil to Assess the Pharmacokinetics and Safety in a Pediatric Population with Pulmonary Arterial Hypertension

NCT01484431

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

Tadalafil (LY450190)

Study H6D-MC-LVIG is a Phase 1b/2, multicenter, international, open-label, multiple ascending-dose study to evaluate the safety and pharmacokinetics of tadalafil administered orally as a tablet or suspension to children with pulmonary artery hypertension (PAH). Spanning the target patient profile of ≥6 months to <18 years of age utilizing oral tadalafil doses selected to mimic typical drug exposures observed in adults with PAH with an open-label long term extension.

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2. Synopsis

Clinical Pharmacology Protocol Synopsis: Study H6D-MC-LVIG

Name of Investigational Product:
Tadalafil (LY450190)

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

Number of Planned Patients: 24 enrolled, 15 complete. At least 2 completers per weight cohort should not be taking concomitant endothelin receptor antagonists (ERAs).	**Phase of Development:** 1b/2

Length of Study: Period 1: 10 weeks (approximately 35 days at each dose level)
Period 2: Open-Label Extension (OLE): a minimum of 2 years

Objectives:
Primary Objective:

To characterize the pharmacokinetics (PK) of tadalafil in a pediatric population with pulmonary arterial hypertension (PAH) to establish an appropriate dose range for further clinical research.

Secondary Objectives:

- To assess the tolerability and safety of tadalafil in a pediatric population with PAH.
- To compare tadalafil PK profile in a pediatric population with historical adult data from Study H6D-MC-LVGY.
- To determine appropriate dose ranges for use in the evaluation of efficacy and safety of tadalafil.
- To clinically assess the palatability of the tadalafil suspension.

Open-Label Extension Objectives (Period 2):

- To evaluate long-term safety while providing continued access to tadalafil for pediatric patients completing Period 1.
- To evaluate clinical worsening (CW), defined as any of the following: death, lung or heart transplantation, atrial septostomy or Potts shunt, hospitalization due to worsening PAH, new onset syncope, initiation of new PAH therapy, or increase of 1 or more in World Health Organization (WHO) Functional Class (except for patients already in Class IV) only for patients unable to perform the 6 minute walk (6MW) test; worsening of WHO functional class by 1 or more for patients who can perform a 6MW test and who have a decrease of ≥20% in the 6 minute walk distance (for those patients who are ≥6 years of age).
- To evaluate the cardiopulmonary hemodynamic changes from baseline (Period 1) to end of 3 month treatment in Period 2 as assessed by echocardiography.

Study Design: Study LVIG is a Phase 1b/2, multicenter, international, open-label, multiple ascending-dose study to evaluate the safety and pharmacokinetics of tadalafil administered orally as a tablet or suspension to children with PAH. Eligible patients will be from 6 months to <18 years of age at time of screening. This study contains 2 study periods: PK/safety (Period 1) and an OLE (Period 2). Each patient may continue in Period 2 for at least 2 years after participating in Period 1.

Diagnosis and Main Criteria for Inclusion and Exclusion:
Pediatric patients (≥6 months to <18 years of age) at time of screening with confirmed PAH.

Patients are eligible to be included in the study only if they meet all of the following **inclusion 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 collagen vascular disease,
   - related to anorexigen use,
   - associated with surgical repair, of at least 6 month duration, of a congenital systemic-to-pulmonary shunt (for example, atrial septal defect, ventricular septal defect, patent ductus arteriosus).
3) Have a history of the diagnosis of PAH established by a resting mean pulmonary artery pressure ≥25 mm Hg, pulmonary artery wedge pressure ≤15 mm Hg, and a pulmonary vascular resistance (PVR) ≥3 Wood units via right heart catheterization. In the event that a pulmonary artery wedge pressure is unable to be obtained during right heart catheterization, patients with a left ventricular end diastolic pressure <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 I, II, or III at the time of enrollment.
5) Patients with PAH either naïve to PAH specific therapy or receiving ERAs. If on an ERA (that is, bosentan or ambrisentan), must be on a maintenance dose, with no change in dose (other than weight-based adjustments) for ≥12 weeks prior to screening and have a screening aspartate transaminase (AST) or alanine transaminase (ALT) <3 times the upper limit of normal.
6) If on conventional PAH medication, including but not restricted to, calcium channel blockers, 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) Have a chest radiograph (CXR) within 6 months of screening that shows clear lung fields or no more than mild patchy (not diffuse) interstitial infiltrates.
8) 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 a reliable method 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).
9) Written informed consent from parents or guardians (and written assent from appropriately aged patients) will be obtained prior to any study procedure being performed.

Diagnosis and Main Criteria for Inclusion and Exclusion (continued):

Patients are not eligible to be included in the study if they meet any of the following **exclusion criteria**:

10) 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.

11) History of left-sided heart disease, including any of the following:

- clinically significant (pulmonary artery occlusion pressure [PAOP] 15 to 18 mm Hg) aortic or mitral valve disease (that is, 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 as determined by the physician.

12) History of Potts Shunt within 3 months before administration of study drug.

13) Unrepaired congenital heart disease.

14) Concurrent phosphodiesterase, type 5 (PDE-5) inhibitor therapy (such as sildenafil or vardenafil) or has received PDE-5 inhibitor therapy within 24 hours prior to the first study drug dosing (baseline visit).

15) Concurrent therapy with prostacyclin or its analogues.

16) Commence or discontinue a conventional PAH medication including but not restricted to: calcium channel blockers, diuretics, anti-coagulants, digoxin, and oxygen therapy within 4 weeks prior to screening.

17) 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.

18) Currently receiving treatment with doxazosin, nitrates or cancer therapy.

19) 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.

20) Are nursing or pregnant.

21) Have a WHO functional class value of IV at the time of enrollment.

22) Have severe hepatic cirrhosis, Child-Pugh Grade C.

23) Have severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 30 mL/min/1.73 m^2 (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 Creatinine Clearance and S_{Cr} is Serum Creatinine

24) Have severe hypotension or uncontrolled hypertension as determined by the Investigator.

25) Diagnosed with a retinal disorder (for example, hereditary retinal disorders, retinopathy of the preterm and other retinal disorders).

26) Have significant parenchymal lung disease.

27) Have bronchopulmonary dysplasia.

28) Have hemoglobinopathies.

29) Have a history of drug, alcohol, or substance abuse within the past 6 months or present use, as assessed by the investigator.

30) Have previously completed or withdrawn from this study (Study LVIG), or any other study investigating tadalafil.

31) Have previously taken tadalafil within 90 days prior to the first study drug dosing (Day 1, Visit 2) or are hypersensitive to tadalafil.

32) Unable to take orally administered tablet (without chewing, crushing or breaking) or liquid suspension.

33) Investigator site personnel (or their immediate family) directly affiliated with this study. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

34) 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.

35) Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational drug or device or off-label 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.

36) Are allergic to any of the excipients, notably lactose.

37) Currently receiving treatment with soluble guanylate cyclase stimulator therapy (such as riociguat)

Study Drug, Dosage, and Mode of Administration:

Tadalafil will be administered orally in an open-label fashion. The dose of tadalafil will be escalated from low to high for each patient. For each weight cohort these 2 doses of tadalafil are determined by PK modeling such that the exposure will be expected to be similar to that observed with tadalafil 2.5 to 10 mg and 20 to 40 mg in adults. However, all of the initial doses are open to subsequent alteration based on emerging safety and PK analyses throughout the study. Although the oral route of administration is commonly used for dosing medicinal products to pediatric patients, it is acknowledged that children, especially the younger age groups, may require an age-appropriate formulation. Therefore, a ready-to-use oral suspension containing 2.0 mg/mL tadalafil will be used for the Light-weight cohorts <25 kg, nominally representing patients <8 years of age.

Tadalafil tablets; 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg (that is, two 20 mg tablets); orally; once daily.

Oral suspension formulation (2.0 mg/mL); 1 mg and 5 mg; orally; once daily.

Reference Therapy/Comparator, Dose, and Mode of Administration: Not Applicable

Planned Duration of Treatment: Tadalafil will be administered once-daily for 10 weeks in 2 sequential 5 week periods. The OLE period will last at least 2 years.

Variables

Safety: Safety will be evaluated using spontaneously reported adverse events, clinical laboratory data, vital signs, physical examinations, body weight, height, WHO functional class, IQ, Tanner score, and centralized 12-lead electrocardiograms (ECGs) as outlined in the schedule of events.

Bioanalytical: Plasma concentrations of tadalafil.

Pharmacokinetic/Pharmacodynamic: The pharmacokinetic parameters estimated during analysis will include area under the concentration-time curve (AUC), maximal concentration (C_{max}), time of C_{max} (t_{max}), apparent clearance (CL/F), apparent volume of distribution (Vz/F), and terminal half-life ($t_{½}$), as appropriate.

Exploratory: Analyses of hemodynamic data will utilize the following variables: tricuspid annular plane systolic excursion, eccentricity index, pericardial effusion, maximal tricuspid regurgitant velocity.

Health Outcomes: Not applicable.

Statistical Evaluation Methods:

Statistical: All enrolled patients who take at least 1 dose of study medication and have evaluable PK data will be included in the PK analysis. All enrolled patients who take study medication will be included in the safety analysis.

Sample Size: No formal statistical analysis was performed to determine the sample size for this study. In order to have at least 5 completers in each weight cohort, approximately 8 patients per weight cohort for a total of up to approximately 24 may need to be enrolled, assuming a drop-out rate of approximately 30%. Tadalafil plasma concentrations from at least 5 completers per weight cohort are considered to be sufficient to characterize the PK of tadalafil in pediatric patients. Furthermore, safety and tolerability data from these patients will provide information to support the dose selection for the efficacy Study H6D-MC-LVHV.

Period 1: All enrolled patients who take at least 1 dose of study medication and have evaluable PK data will be included in the PK and the safety analysis. Prior to an individual patient being dose-escalated, the safety and PK data will be reviewed to assess the suitability of dose escalation.

Noncompartmental Pharmacokinetic Analyses: Evaluation of individual profiles during the study will be based on PK parameter estimates calculated by standard noncompartmental methods. The purpose of these analyses will be to evaluate dose escalations in individual patients, and to evaluate (as data become available) the appropriateness of the starting doses. The primary parameters for this evaluation will be area under the curve of concentration versus time (AUC) and C_{max}. Other noncompartmental parameters may be reported if appropriate.

Population Pharmacokinetic (PopPK) Analysis: The purpose of the PopPK analysis is to characterize tadalafil PK across the range of body weights and ages of patients enrolled in the study and in each cohort; to evaluate the effect of various covariates such as age, body weight, sex, and endothelin receptor antagonist (ERA) use on tadalafil exposure; and to predict appropriate dose(s) in subsequent pediatric studies of tadalafil.

After 5 Middle-weight cohort patients have completed Period 1 and prior to the Light-weight cohort patients enrolling into the study, the results of an interim analysis will be reviewed by a safety monitoring committee (SMC). The SMC will review all available study data and recommend proposed tadalafil dose levels for the Light-weight cohort. A compartmental analysis of the concentration versus time data may also be performed to support PK simulations.

Safety parameters will be listed and summarized using standard descriptive statistics by weight cohort and dose. Additional analyses will be performed if warranted by review of the data. Safety parameters that will be assessed include adverse events (AEs), serious adverse events (SAE), safety lab parameters, ECGs, body weight, height, and vital signs.

Period 2: All patients who take study medication will be included in the long-term safety analysis. Changes from baseline to endpoint in hemodynamic parameters collected by echocardiogram will be summarized. Patients will be pooled and analyzed as a single treatment group. No formal statistical testing will be conducted and only summary statistics will be presented.

Safety will be assessed through TEAEs, SAEs, body weight, height, WHO functional class, IQ, Tanner score, and reason for discontinuation.

3. Table of Contents

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

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Attachments

4. Abbreviations and Definitions

Term	Definition
6MW	6-minute walk
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) 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
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
APAH	associated pulmonary arterial hypertension
AST	aspartate transaminase
AUC	Area under the concentration versus time curve
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, Sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BMI	Body mass index: A measure of body fat based on height and weight that applies to both adult men and women.
CC	creatinine clearance
C_{max}	Maximum observed drug concentration
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.
CI	Confidence interval
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_{SS}/F	apparent clearance at steady state
C_{max}	maximum drug plasma concentration

complaint	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.
CRF/eCRF	case report form/electronic case report form: 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.
CRO	Contract research organization: A person or organization (commercial, academic, or other) contracted by the Sponsor to perform one or more of the Sponsor's trial-related duties and functions.
CSE	Clinically significant event: A moderate to severe adverse event (AE), abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject.
CW	clinical worsening
CXR	chest radiograph
CYP	cytochrome P450
ED	erectile dysfunction
ECG	Electrocardiogram
end of study (trial)	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
FPAH	heritable pulmonary arterial hypertension
GCP	good clinical practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.
ICD	informed consent document: A Lilly term used to describe (1) information regarding the trial for the subject/patient, and (2) the document that the subject/patient signs to indicate consent to participate in the clinical trial
IND	Investigational New Drug: An application to the FDA to allow testing of a new drug in humans.
INR	international normalized ratio
interim analysis	an analysis of clinical trial 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 trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IPAH	idiopathic pulmonary arterial hypertension
IQ	intelligence quotient
IRB/ERB	institutional review board/ethical review board: A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial.
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.
PD	Pharmacodynamics
PDE-5	phosphodiesterase type 5
PK	Pharmacokinetics

PopPK	population pharmacokinetics
PVR	pulmonary vascular resistance
RBC	red blood cell
REVEAL	**R**egistry to **EV**aluate **E**arly **A**nd **L**ong-term PAH Disease Management
registration	The act of assigning a registration number to the subject indicating that the [Registration center/Sponsor/principal investigator or subinvestigator] has verified that the subject meets all of the inclusion criteria and none of the exclusion criteria.
SAE	Serious adverse event: Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
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 trial. 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.
SMC	Safety monitoring committee
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.
t_{max}	Time of maximum observed concentration (C_{max})
TPO	third party organization: A TPO is an individual or organization (commercial, academic, or other) contracted by the Sponsor to provide specified services and/or deliverables.
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment.
WAIS	Wechsler Adult Intelligence Scale
WBC	white blood cell
WHO	World Health Organization
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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

5. Introduction

5.1. General Introduction

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

The pathogenesis, presentation, diagnosis and management of PAH in children is similar to that in adults, though little research has been conducted in the pediatric population. The prevalence and incidence of PAH is significantly lower in children than in adults (Rubin 1997); it has been estimated that about 0.5 per million children will be diagnosed with IPAH which accounts for about 50% of all pediatric PAH. The **R**egistry to **EV**aluate **E**arly **A**nd **L**ong-term PAH Disease Management (REVEAL Registry), a multicenter, observational, United States- (US-) based registry created to provide the characteristics and treatment patterns of patients with PAH, recently reported just 184 prevalent pediatric cases among 54 enrolling centers in the US (Barst 2008). The sex ratio between female and male is approximately 2:1 in childhood (Badesch et al. 2010) and median survival in children <16 years, prior to the introduction of specific therapies for PAH, was ≤6 months (D'Alonzo et al. 1991; Barst et al. 1999).

While sildenafil and bosentan have recently had language added to their labels pertaining to the pediatric population, there remain limited data on the safety and efficacy of the approved adult treatments in a pediatric population. Therapeutic guidelines for children have therefore generally followed those used in adults. Therapies currently approved for the treatment of PAH in adults, in various geographies around the world, include prostacyclin and its analogues (epoprostenol, trepostinil, iloprost, and beraprost), the endothelin receptor antagonists (bosentan and ambrisentan), and the phosphodiesterase type-5 (PDE-5) inhibitors (sildenafil and tadalafil).

Tadalafil is an orally administered, potent, and selective PDE-5 inhibitor currently approved in the United States, European Union, Canada and in Japan for the treatment of erectile dysfunction (ED), both on-demand (at doses of 5 mg, 10 mg and 20 mg) and once-daily (at doses of 2.5 mg and 5 mg), and for the treatment of pulmonary arterial hypertension (PAH) (at a dose of 40 mg daily).

In adults, tadalafil is rapidly absorbed after oral administration, with maximum concentrations (C_{max}) in plasma occurring at a median time of 2 hours. The rate and extent of absorption from tadalafil 10 mg and 20 mg are not influenced by food. Tadalafil is distributed into tissues, with

an apparent volume of distribution of 62.6 L. Tadalafil is cleared extensively, with metabolism by cytochrome P450 (CYP) 3A4 being the major pathway. The mean terminal elimination half-life ($t_{½}$) for tadalafil is 17.5 hours. Tadalafil pharmacokinetics are linear with respect to time and dose over a range of 2.5 to 20 mg. During tadalafil 20 mg once-daily dosing, steady-state plasma concentrations were attained within about 5 days and the degree of drug accumulation was about 1.6-fold. A tadalafil 40 mg single dose is rapidly absorbed, with C_{max} in plasma occurring at a median time of 4 hours, and within the range of that reported following a 20 mg single dose. Following tadalafil 40 mg once-daily, the apparent clearance at steady state (CL_{SS}/F) and accumulation ratios remained stationary between Day 5 and Day 10. Increases in both C_{max} and area under the concentration versus time curve (AUC) are less than proportional as the dose increases from 20 mg to 40 mg. Specifically, due to decreased bioavailability with 40 mg once-daily doses compared to lower doses, a 2-fold change in dose from 20 mg to 40 mg results in a 48% increase in exposure.

The safety and efficacy of tadalafil for the treatment of PAH in adults was investigated in a 16-week placebo-controlled study (Study H6D-MC-LVGY [LVGY]) which demonstrated that, overall, tadalafil 40 mg once-daily dosing was effective in the treatment of patients with PAH and was 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 erectile dysfunction patient population. Population pharmacokinetic (PopPK) data from Study LVGY show that exposure to tadalafil is not influenced by age, cardiovascular conditions, sex, ethnicity, PAH history or duration, creatinine clearance (CC), total serum protein, weight, warfarin, or digoxin, thereby suggesting that tadalafil can be administered without regard to these factors. Concomitant bosentan therapy increased the apparent oral clearance of tadalafil by 75%, resulting in a 35% decrease in exposure in patients receiving 40 mg tadalafil. In patients with PAH not receiving concomitant bosentan, the predicted median tadalafil exposure at steady-state was 26% higher when compared to that in healthy volunteers. There were no clinically relevant differences in mean C_{max} compared to healthy volunteers. The results suggest a potentially lower mean clearance of tadalafil in patients with PAH compared to healthy volunteers.

An aqueous, ready-to-use suspension for oral administration of 2.0 mg/mL tadalafil has been developed for use in younger children. A relative bioavailability study (Study H6D-MC-LVIF [LVIF]) has been performed in healthy adults to investigate the relative bioavailability of one 20 mg tablet compared to a suspension containing 20 mg tadalafil. Study LVIF also assessed the pharmacokinetics of the tadalafil suspension over the 20 mg to 40 mg dose range. The results from Study LVIF demonstrated that the 20 mg suspension produced a 23% lower C_{max} for tadalafil and significant delay in time of maximum observed concentration (t_{max}) of 1 hour compared to the 20 mg tablet. However, overall exposure to tadalafil was similar for the 20 mg suspension and tablet, with the 90% confidence intervals for the ratios falling within the bioequivalence limits of 0.80 to 1.25. Exposure to tadalafil during the absorption/distribution phase is lower for the 20 mg suspension compared to the 20 mg tablet, with $AUC_{(0-6)}$ and $AUC_{(0-12)}$ being 25% and 16% lower. Results indicated a less-than-dose-proportional increase in tadalafil exposure over the 20 mg to 40 mg dose range for the suspension formulation.

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 ≥6 months of age to <18 years of age.

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

5.2. Rationale and Justification for the Study

Despite the lack of therapies with an approved indication in children, there is a growing body of evidence supporting the use of therapies approved in adults that has led to widespread off-label use in children (Beghetti 2009). Therefore, there is a need to provide physicians with safety and efficacy results of all treatment options, including tadalafil, in the pediatric population.

Beyond anecdotal reports, experience with tadalafil exposure in pediatric patients does not exist, other than that in a single 14-year-old female patient (73 kg) who received tadalafil 2.5 mg in Study LVGY. This patient completed the study and subsequently enrolled in the extension Study LVGX at a dose of tadalafil 40 mg.

Given the limited safety, PK, and efficacy data in pediatric patients with PAH, the Sponsor is conducting this study. The study will assess the PK profile of tadalafil administered once-daily in tablet and suspension formulation to pediatric patients with PAH, and will assess safety and tolerance, in order to identify appropriate doses to be investigated further in a larger safety and efficacy study.

6. Objectives

6.1. Primary Objective (Period 1)

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

6.2. Secondary Objectives (Period 1)

- To assess the tolerability and safety of tadalafil in a pediatric population with PAH.
- To compare tadalafil PK profile in a pediatric population with historical adult data from Study LVGY.
- To determine appropriate dose ranges for use in the evaluation of efficacy and safety of tadalafil.
- To clinically assess the palatability of the tadalafil suspension.

6.3. Open-label Extension Objectives (Period 2):

- To evaluate long-term safety while providing continued access to tadalafil for pediatric patients completing Period 1.
- To evaluate clinical worsening (CW), defined as any of the following: death, lung or heart transplantation, atrial septostomy or Potts' shunt, hospitalization for PAH progression, new onset syncope, initiation of new PAH therapy, or increase of 1 or more in WHO Functional Class (except for patients already in Class IV; Attachment 4) only for patients unable to perform the 6MW test; worsening of WHO functional class (Attachment 4) by 1 or more for patients who can perform a 6 minute walk (6MW) test and who have a decrease of ≥ 20% in the 6 minute walk distance (for those patients who are ≥6 years of age).
- To evaluate the cardiopulmonary hemodynamic changes from baseline (Period 1) to end of 3 month treatment in Period 2 as assessed by Echocardiography.

7. Investigational Plan

7.1. Summary of Study Design

Study LVIG is a Phase 1b/2, multicenter, international, open-label, multiple ascending-dose study to evaluate the safety and pharmacokinetics of tadalafil administered orally as a tablet or suspension to children with PAH. Eligible patients will be from 6 months to <18 years of age at time of screening. This study contains 2 study periods: PK/safety (Period 1) and an open-label safety extension (OLE) (Period 2). Approximately 24 patients may be entered into this study to ensure that a minimum of 15 patients (at least 5 in each body-weight cohort, of which ≥2 are not currently receiving endothelin receptor antagonist [ERA] PAH therapy and ≥3 are treated with ERA) complete the planned progression through low and high doses of tadalafil when taking into consideration anticipated patient drop-out rates. Of the 15 completers, at least 3 patients will be ≤6 years of age and at least 2 patients will be ≤2 years of age. Period 1 is approximately 10 weeks (that is, approximately 5 consecutive weeks for each dose [low and high]) (Figure LVIG.7.1). The completer population is defined as all patients who are assigned to treatment and receive the 2 ascending dose levels of tadalafil administered once-daily and complete PK sample collection on putative steady- state of high dose. Each patient may continue into Period 2 for at least 2 years after participating in Period 1.

The body-weight cohorts are defined as:

Heavy: ≥40 kg

Middle: ≥25 kg to <40 kg

Light: <25 kg

Dosing of all weight cohorts is described in Table LVIG.9.1. Tadalafil doses were selected to mimic typical drug exposures observed in adults with PAH (Study LVGY). The Heavy-weight and Middle-weight cohorts will be enrolled concurrently. Dosing and evaluation of the Middle-weight cohort must be completed before enrolling patients in the Light-weight cohort.

The 5-week (35-day) treatment duration at each dose during Period 1 was selected to ensure sufficient time to reach steady state and allow time to process PK samples and analyze data in each patient prior to the scheduled dose escalation.

Adverse events (AEs) will be assessed on all investigator site visits during the study, and when spontaneously reported. Vital signs, electrocardiograms (ECGs), physical examination, and clinical laboratory tests will be performed at times specified in Attachment 1. Patients treated with oral suspension will also complete a questionnaire to assess the palatability of the suspension formulation during Period 1.

Dose escalation from the low to high dosing level for each patient during Period 1 may begin on approximately Day 36, approximately 5 weeks after the start of treatment. Selection of the high dose in each patient will be based on the PK data collected on Day 1 and Day 14, and on the safety data and any clinically significant physical signs or safety lab results up to approximately 4 weeks after the start of treatment. Safety and PK data will be reviewed by both the investigator

and the Sponsor before beginning the higher dose regimen. Section 8.2.2.2 specifies the dose escalation guidance to be followed during the dose escalation review. This review may result in refinement of the individual dose-escalation regimen.

When 5 patients from the Middle-weight cohort have completed Period 1, the safety, tolerability and summary of PK analyses from all patients will be reviewed by a safety monitoring committee (SMC). Based on this review, the SMC will advise Lilly as to the appropriateness of continuing the study and enrolling patients into the Light-weight cohort. The SMC will provide recommendations immediately after review.

	Period 1: PK/Safety/Tolerability					Period 2: OLE (2 years)	
				High Dose		OLE Dose	
SC	Low Dose						
Day: -28	1	14	35	49	70	71	800
PK Sampling:	X	X		X			
Visit number:	2	4	6	8	9		17

Abbreviations: OLE = open-label extension; PK = pharmacokinetic; SC = screening

Figure LVIG.7.1. Study Design

7.1.1. Study Periods

7.1.1.1. Period 1

In Period 1, tadalafil will be administered once-daily for approximately 10 weeks (~35 days at each dose level) in 2 sequential steps. Please refer to Figure LVIG.7.1.

7.1.1.2. Period 2

Period 2 will evaluate the long-term safety of tadalafil while providing continued access to tadalafil for pediatric patients completing Period 1.

The patients participating in Period 1 may enroll in the open-label extension Period 2. Period 2, will continue for at least 2 years or until the Sponsor concludes the study, whichever occurs first. At the beginning of Period 2, the starting dose for each patient may vary depending on weight cohort and tolerability but will not exceed the maximum weight range dose established in Period 1. For the first 3 months of Period 2 the target dose will deliver a tadalafil exposure equivalent to that seen with 20 mg in adults, as long as that dose does not exceed the maximum weight range, dose established in Period 1. After the first 3 months of Period 2, the dose may then be increased (as judged by the investigator), but will not exceed the maximum weight range dose established in Period 1. During Period 2, the dose for each patient might be adjusted per SMC recommendation based on more safety and efficacy information gathered during this study, or the efficacy Study LVHV. Please refer to Figure LVIG.7.1. For discontinued patients 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, regardless of seriousness or the Investigator's opinion of causation.

Clinical worsening will be evaluated during the study. Assessment of clinical worsening is defined as:

1. All-cause mortality.
2. Lung or Heart-Lung Transplantation.
3. Atrial Septostomy or Potts Shunt.
4. Hospitalization for PAH progression:
   Hospitalization for PAH progression should not be due to a potentially precipitating event such as pneumonial 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.
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 or beraprost).
   c. Increase of 1 or more in WHO Functional Class (except for patients already in Class IV; Attachment 4) only for patients unable to perform the 6MW test.
   d. Worsening of WHO functional class and a decrease of 20% in the 6MW test for those patients who are ≥6 years of age and are developmentally capable of performing the 6MW test.

7.2. Discussion of Design and Control

The pharmacokinetics of tadalafil in pediatric subjects have not been explored. This study is a multiple ascending-dose study with dosing predicted to approximate the exposures seen previously in adults with PAH (Study LVGY). In Period 1, tadalafil will be administered at 2 dose levels over 10 weeks.

Patients will be grouped by body weight so that Heavy- and Middle-weight children, in whom exposure may be more accurately predicted from the adult population, are assessed prior to enrolling Light-weight children. Light-weight children will not be exposed to tadalafil until at least 5 patients have completed from the Middle-weight cohort.

The study allows for the limited use of certain concomitant PAH medications. Endothelin receptor antagonists (that is, bosentan or ambrisentan) will be permitted, while concomitant use of prostacyclin and its analogues, and of another PDE-5 inhibitor will be contraindicated in Period 1. Adult patients with PAH who were receiving concomitant bosentan had decreased tadalafil plasma exposure; therefore, Study LVIG will enroll at least 6 subjects (2 per weight cohort) not receiving bosentan.

The concomitant use of another PDE-5 inhibitor (for example, sildenafil) or soluble guanylate cyclase stimulator (for example, riociguat) is prohibited during the study. Subjects receiving

another PDE-5 inhibitor will be required to discontinue the medication at least 24 hours prior to the baseline visit (Visit 2), which should suffice to allow for systemic elimination of the PDE-5 inhibitor (that is, at least 5 half-lives of the drug).

As the characterization of the pharmacokinetics of tadalafil is the primary objective of the study, an open-label design is considered appropriate.

7.3. Determination of Sample Size

No formal statistical analysis was performed to determine the sample size for this study. The sample size is primarily chosen to provide adequate data to characterize the PK of tadalafil in a pediatric population and to determine the dose selection for the efficacy Study LVHV.

Tadalafil plasma concentrations from at least 5 completers per weight cohort should suffice to characterize the PK of tadalafil in pediatric patients. To have at least 5 completers in each weight cohort, approximately 8 patients per weight cohort for a total of up to approximately 24 may need to be enrolled, assuming a drop-out rate of approximately 30%. Safety and tolerability data from these patients will provide information to support the dose selection for the efficacy Study LVHV. If a patient is terminated after the Day 49 PK sample collection, this patient will be defined as a completer and replacement will not occur.

8. Study Population

8.1. Criteria for Enrollment

Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, clinical laboratory tests, and ECGs. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to enrollment.

8.1.1. 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 collagen vascular disease,
- related to anorexigen use,
- associated with surgical repair, of at least 6 month duration, of a congenital systemic-to-pulmonary shunt (for example, atrial septal defect, ventricular septal defect, patent ductus arteriosus).

[3] Have a history of the diagnosis of PAH established by a resting mean pulmonary artery pressure ≥25 mm Hg, pulmonary artery wedge pressure ≤15 mm Hg, and a pulmonary vascular resistance (PVR) ≥3 Wood units via right heart catheterization. In the event that a pulmonary artery wedge pressure is unable to be obtained during right heart catheterization, patients with a left ventricular end diastolic pressure <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 I, II or III at the time of enrollment.

[5] Patients with PAH either naïve to PAH specific therapy or receiving endothelin receptor antagonists (ERA). If on an ERA (that is, bosentan or ambrisentan), must be on a maintenance dose, with no change in dose (other than weight-based adjustments) for ≥12 weeks prior to screening and have a screening aspartate transaminase (AST) or alanine transaminase (ALT) <3 times the upper limit of normal.

[6] If on conventional PAH medication, including but not restricted to, calcium channel blockers, 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] Have a chest radiograph (CXR) within 6 months of screening that shows clear lung fields or no more than mild patchy (not diffuse) interstitial infiltrates.

[8] 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 a reliable method 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).

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

8.1.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet **any** of the following criteria:

[10] 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.

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

- clinically significant (pulmonary artery occlusion pressure [PAOP] 15 to 18 mm Hg) aortic or mitral valve disease (that is, 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 as determined by the physician.

[12] History of Potts Shunt within 3 months before administration of study drug.

[13] Unrepaired congenital heart disease.

[14] Concurrent PDE-5 inhibitor therapy (such as sildenafil or vardenafil) or has received PDE-5 inhibitor therapy within 24 hours prior to the first study drug dosing (baseline visit).

[15] Concurrent therapy with prostacyclin or its analogues.

[16] Commence or discontinue a conventional PAH medication including but not restricted to: calcium channel blockers, diuretics, anti-coagulants, digoxin, and oxygen therapy within 4 weeks prior to screening.

[17] 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.

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

[19] 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.

[20] Are nursing or pregnant.

[21] Have a WHO functional class value of IV at the time of enrollment.

[22] Have severe hepatic cirrhosis, Child-Pugh Grade C.

[23] Have severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 30 mL/min/1.73 m^2 (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 Creatinine Clearance and S_{Cr} is Serum Creatinine

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

[25] Diagnosed with a retinal disorder (for example, hereditary retinal disorders, retinopathy of the preterm and other retinal disorders)

[26] Have significant parenchymal lung disease.

[27] Have bronchopulmonary dysplasia.

[28] Have hemoglobinopathies.

[29] Have a history of drug, alcohol, or substance abuse within the past 6 months or present use, as assessed by the investigator.

[30] Have previously completed or withdrawn from this study (Study LVIG), or any other study investigating tadalafil.

[31] Have previously taken tadalafil within 90 days prior to the first study drug dosing (Day 1, Visit 2) or are hypersensitive to tadalafil.

[32] Unable to take orally administered tablet (without chewing, crushing or breaking) or liquid suspension.

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

[34] 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.

[35] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational drug or device or off-label 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.

[36] Are allergic to any of the excipients, notably lactose.

[37] Currently receiving treatment with soluble guanylate cyclase stimulator therapy (such as riociguat)

8.1.3. Rationale for Inclusion and Exclusion of Certain Study Candidates

Inclusion criteria [1], [2], [3], [4], and [7] 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 criteria [8] is in place to prohibit inclusion of patients who are pregnant or who are at risk of becoming pregnant.

Inclusion criteria [9] and exclusion criteria [36] are in place to protect the safety of each patient.

Exclusion criteria [10], [11], [12], [13], [17], [20], [21], [22], [23], [24], [25], [26], [27], and [28] are in place to prohibit patients who have physical existing conditions that would confound the trial results.

Exclusion criteria [14], [15], [16], [18], and [19] are in place to prohibit the enrollment of patients who are taking medications that would confound the trial results.

Exclusion criteria [20] is in place to prevent undue risk to an infant or fetus.

Exclusion criteria [29] is in place to prevent the confounding impact that addictive drugs may have on study results.

Exclusion criteria [30], [31], and [35] 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 [32] is in place to assure that the patients can take the medication in the forms that are available in this trial.

Exclusion criteria [33] and [34] are in place to prevent possible study bias from close relations.

Exclusion criteria [37] is in place to protect the patient since the combination of PDE5 inhibitors and guanylate cyclase stimulators, such as riociguat may lead to symptomatic hypotension.

8.2. Discontinuation

8.2.1. 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.

8.2.2. Discontinuation of Individual Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Lilly clinical pharmacologist or clinical research physician and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the investigator and Lilly clinical pharmacologist or clinical research physician agree it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly clinical pharmacologist or clinical research physician does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly clinical pharmacologist or clinical research physician to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

8.2.2.1. Early Discontinuation from Study

Some possible reasons for early discontinuation of study participation:

- Enrollment in any other clinical trial involving an off-label use of an investigational drug or device or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- If Exclusion Criterion [18], [19], [20], [22 through 28], [32], [36], or [37] is observed, or develops, after entry or enrollment. In this case, the patient will be discontinued from the drug/study at the next visit or sooner in the event of a safety exclusion criterion.
    - Exception: A patient receiving an ERA who develops an AST or ALT >3 times upper limit of normal 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 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. For further information, please refer to Section 10.4, Safety Evaluations.
- The patient, the patient's legal guardian, or the attending physician requests that the patient be withdrawn from the study.
- In Period 1, the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.
- Patients experiencing clinical worsening in Period 1 (as defined in Section 7.1.1.2) will be discontinued from the study and receive standard of care. Patients in Period 2 experiencing clinical worsening (as defined in Section 7.1.1.2) will be managed at the discretion of the investigator; however, the patient may continue in 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.
- The investigator determines that the patient is repeatedly noncompliant with study procedures and/or study drug.
- If the patient experiences priapism then the patient must be discontinued from the study

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. 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 10 of Period 1, or the final visit of Period 2, depending on the timing of discontinuation.

8.2.2.2. Termination of the Dose Escalation

Dose escalation within each weight cohort will be based upon ongoing review of safety, tolerability data, and pharmacokinetic analyses. The following criteria will be employed to determine if dose escalation is appropriate:

If ANY of the following criteria are met, the patient should not have their dose escalated.

Dose levels may be repeated or reduced, if required, to better identify thresholds for tolerability.

Severe Adverse Events:

- A patient experiences an SAE related to study drug.
- Priapism (discontinue patient per Section 8.2.2.1).

- Unexpected and abnormal vaginal bleeding of moderate to severe intensity.
- Symptomatic postural hypotension considered related to study drug.
- Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) and related terms.
- Hearing loss and related terms.

In the event of an SAE related to study drug, other than precautionary inpatient observation, dosing will be suspended for the patient pending notification of the ethical review board (ERB) and appropriate regulatory authorities. Dosing will only resume after the ERB, investigator, and Sponsor agree on the appropriateness of further dosing.

Should an individual patient meet either of the PK criteria below on Day 1 or Day 14, then the patient may not increase to the high dose level.

Pharmacokinetic Results:

- An observed tadalafil C_{max} exceeds the mean C_{max} of 700 ng/mL measured during 40 mg once-daily dosing to adult patients with PAH (Study LVGY).
- An AUC (0-24) exceeds the mean AUC (0-24) of 13,700 ng•hr/mL measured during 40 mg once-daily dosing to adult patients with PAH (Study LVGY).

8.2.3. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for any reason.

8.2.4. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for any reason. Additionally, the study may be discontinued at the recommendation of the Safety Monitoring Committee.

9. Treatment

9.1. Rationale for Selection of Dose

In Period 1, it is planned that tadalafil once-daily doses will initially be administered as pre-defined fixed doses (Table LVIG.9.1) selected to mimic typical tadalafil exposures in adults at doses of 2.5 mg to 40 mg. However, all of these initial doses are open to alteration based on emerging safety and PK analyses throughout the study. Each cohort will begin with the lower of 2 doses and escalate to the high dose following approximately 5 weeks at the lower dose level. Pharmacokinetic samples will be collected per the Study Schedule (Attachment 1) such that these data (in addition to safety and tolerability data) will be available prior to planned dose escalation, thus allowing the opportunity to refine any individual's dose progression.

At the beginning of Period 2, the dose may vary depending on weight cohort and tolerability for each individual from Period 1. During Period 2, the dose for each patient might be adjusted per SMC recommendation as more safety and efficacy information become available during this study or the efficacy Study LVHV. For the first 3 months of Period 2 the target dose will deliver a tadalafil exposure equivalent to that seen with 20 mg in adults, as long as that dose does not exceed the maximum weight range dose established in Period 1. After the first 3 months of Period 2 the dose may then be increased (as judged by the investigator), but will not exceed the maximum weight range dose established in Period 1.

Table LVIG.9.1. Planned Tadalafil Once-Daily Dosing in Period 1 for Study LVIG

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

[a] Tadalafil administered once daily in suspension formulation for Light-weight cohort.

From the exposure-response relationship developed in adults with PAH, patients who benefited most from tadalafil treatment received doses of at least 20 mg of tadalafil once daily, irrespective of the PK influence of bosentan and other disease or patient-specific factors. Therefore, typical tadalafil exposures following administration of 20 mg and 40 mg once daily to adults were identified as reasonable targets for selection of maximum doses investigated in pediatrics.

Based on these data from the tadalafil clinical development programs, the dose selection strategy for pediatrics is to define tadalafil doses that may support once-daily administration and maintain mean concentrations within those typically reported from adults with PAH given comparable or slightly higher doses of tadalafil (Table LVIG.9.1). This is expected to provide an opportunity to evaluate dose-dependent trends in pediatrics while minimizing significant excursions of tadalafil concentrations above the highest typically observed in most adult patients (<90th percentile).

The doses selected should provide tadalafil concentrations within the range of those produced by 5 mg to 10 mg (low dose) or 20 mg to 40 mg (high dose) of tadalafil administered to adults with PAH.

Detailed information of the known benefits and risks of tadalafil is provided in the IB.

9.2. Study Drug Formulations

Table LVIG.9.2 presents the planned initial oral administration dosing of tadalafil tablets or suspension in pediatric patients with PAH. If additional doses are required, they will be achieved by utilizing the minimum number of tadalafil tablets possible.

Table LVIG.9.2. Tadalafil Study Drug Regimens

Tablet Dose:	5 mg	7.5 mg	10 mg	20 mg	40 mg
Tablets:	1 × 5 mg	1 × 5 mg and 1 × 2.5 mg	1 × 10 mg	1 × 20 mg	2 × 20 mg
Suspension Dose:	1 mg	3 mg	5 mg		
Volume[a]:	0.5 mL	1.5 mL	2.5 mL		

[a] Volume of a tadalafil pediatric suspension (2 mg tadalafil/ml).

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

The formulations for use include the authorized 2.5 mg, 5 mg, 10 mg and 20 mg Cialis® tablets, and an oral tadalafil suspension formulation (2.0 mg tadalafil/mL). No placebo tablets or placebo suspension will be used. All formulations will be administered orally, once daily.

Tadalafil film-coated tablets: Tadalafil tablets will be used for the Middle- and Heavy-weight cohorts. In addition to tadalafil, the tablets contain lactose monohydrate as a diluent, hydroxypropyl cellulose as a binder, croscarmellose sodium as a disintegrant, microcrystalline cellulose as a disintegrant and dry binder, sodium lauryl sulfate as a wetting agent, and magnesium stearate as a lubricant. The film coatings consist of lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow ferric oxide and red ferric oxide in the color mixtures. Tadalafil tablets will be provided in either a blister pack or bottle. It is stable when stored at room temperature.

Tadalafil oral suspension: Although the oral route of administration is commonly used for dosing medicinal products to pediatric patients, it is acknowledged that children, especially the younger age groups, may require an age-appropriate formulation. Therefore, a ready-to-use oral suspension containing 2.0 mg/mL tadalafil will be used for the Light-weight cohorts <25 kg, nominally representing patients <8 years of age. The suspension contains 2.0 mg/mL of tadalafil in a ready-to-use suspension vehicle. The aqueous vehicle is preserved with sodium benzoate. The suspension contains the inactive ingredients Avicel RC 591, xanthan gum, polysorbate 80, colloidal silicon dioxide, simethicone emulsion, sorbitol solution, sodium citrate, and citric acid. The suspension is artificially cherry flavored and sweetened with sucralose. Tadalafil oral suspension is stable when stored at room temperature.

Tadalafil liquid suspension will be provided in a plastic bottle and doses will be delivered to the patient using a standard syringe.

Tadalafil is not affected by food, and therefore the pediatric formulation can be administered with or without food.

9.3. Study Drug Administration

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

All clinical trial material provided to the investigator will be stored in a secure place, and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the study drugs will be fully documented and verified by a second person. Detailed records of the amounts of study drug received, dispensed and remaining at the end of the study will be maintained.

Either 1 or 2 tablets of tadalafil, or 0.5 or 2.5 mL of 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 will be directly administered into the mouth with the required suspension volume by 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.

9.4. Specific Restrictions/Requirements

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

The informed consent document (ICD) will be used to explain the risks and benefits of study participation to the patient and/or parent/legal representative in simple terms before the patient is entered into the study, and to document that the patient and/or parent/legal representative is satisfied with their 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 and/or parent/legal representative. This includes obtaining the appropriate signatures and dates on the ICD and assent document, if applicable, prior to the performance of any protocol procedures and prior to the administration of study drug.

A parent or legal representative must give informed consent for a child to participate in this study.

Throughout the study, the patient may be subject to medical assessment and review of compliance with restrictions before continuing in the study. The patient should continue to meet the inclusion and exclusion criteria at the start of each dosing period, including restrictions related to contraception and medication use.

9.4.1. Special Treatment Considerations

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. During Period 1, patients who wish to begin or add a new concomitant medication for the treatment of PAH will be discontinued from the study. However, additional or new concomitant medication for the treatment of PAH will be allowed in Period 2.

9.5. Blinding

Study LVIG is an open-label multiple ascending dose study and therefore will not be blinded for treatment.

9.6. Concomitant Therapy

Chronic use of drugs that are known potent inducers, or inhibitors of cytochrome P450 3A4 (CYP3A4) should be prohibited. 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 a patient may be at the discretion of the investigator after consultation with a Lilly clinical research scientist or clinical research physician. 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 8.1.2), such as:

- Prostacyclin or its analogues.
- Concurrent PDE-5 inhibitor (other than study medication)
- Nitrates
- Doxazosin or Other cancer chemotherapy
- Antiretroviral therapy (protease inhibitors), systemic ketoconazole, or systemic itraconazole.
- Potent systemic CYP3A4 inhibitors and inducers
- Guanylate cyclase stimulators, such as riociguat

Patients who receive any concomitant medication listed in the exclusion criteria following enrollment and before study drug administration should not receive study drug. During Period 1, patients requiring treatment with any of the prohibited medications during the study will be discontinued from the study and will complete a termination visit.

For patients receiving bosentan, dosage adjustment and monitoring for those developing aminotransferase abnormalities must be followed according to the approved Tracleer (bosentan) labeling information.

Post-study therapy with another PDE-5 inhibitor should be delayed at least 96 hours after the last dose of the study drug is administered.

Patients 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 for patients who screen fail will not be reported to Lilly unless the medication is linked to an SAE or adverse event of which the Investigator believes may have been caused by a protocol procedure.

10. Pharmacokinetic, Pharmacodynamic, and Safety Data Collection

10.1. Pharmacokinetic and Pharmacodynamic Evaluations

10.1.1. Samples for Pharmacokinetic Measurements

Blood samples of a maximum of 0.5 mL each will be collected into appropriate tubes predose and 2, 4, 8, 12, and 24 hours postdose, and used to determine the plasma concentrations of tadalafil. One trough PK sample will also be collected at Visit 10 to evaluate the tadalafil exposure after 3 months of treatment during Period 2. The actual date and 24-hour clock time of each sampling will be recorded. Analgesic cream (e.g., eutectic mixture of local anesthetics [EMLA]) must be offered to minimize pain at the venipuncture site. The smallest practical diameter needle is recommended, and a cannula may be used to minimize the number of needle insertions.

Additional blood samples may be drawn if needed for safety purposes and/or if warranted and agreed upon between the investigator and Sponsor or its designee. Instructions for collection and handling of blood samples will be provided by the Sponsor or its designee.

10.1.2. Bioanalysis

Samples will be analyzed at a laboratory approved by the Sponsor. Tadalafil concentrations will be assayed using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method.

Bioanalytical samples collected to measure tadalafil concentrations will be retained for a maximum of 1 year following last patient visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein binding work.

10.1.3. Pharmacodynamic Evaluations

Not applicable.

10.2. 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 pregnancy test will be performed if applicable. Other clinical laboratory tests will be analyzed by a central laboratory. Attachment 2 lists the specific tests that will be performed for this study.

Investigators must document their review of each safety laboratory report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results

are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

Attachment 3 provides a summary of the blood sampling volumes.

10.3. Exploratory Work

10.3.1. 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 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 cGMP (including but not limited to GNB3, ACE, ENOS, PDE-5) 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.

10.4. Safety Evaluations

Period 1

- Safety will be evaluated using spontaneously reported adverse events, clinical laboratory data, vital signs, physical examinations, body weight, height, and ECGs.
- Change from baseline to endpoint as measured by WHO functional classification and six minute walk test (for patients ≥6 years of age); and
- Percent increase in N-terminal prohormone brain natriuretic peptide (NT-Pro-BNP) concentrations.

Period 2

Safety will be evaluated at each study visit by monitoring treatment-emergent adverse events, SAEs, WHO functional class, and reasons for discontinuation. Body weight, height, 6MW test, IQ, and Tanner score will also be collected in Period 2 as defined in the Study Schedule (Attachment 1). Tadalafil concentrations and protocol clinical laboratory data will be collected for patients when reporting an SAE.

10.4.1. Safety Measures

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.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study. Further routine medical assessments may take place during the study as clinically indicated.

10.4.1.1. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Study Schedule and as clinically indicated (Attachment 1). Physical examinations will include an eye examination. In addition, Tanner Stage will be assessed at the time of specified in Protocol Attachment 1.

10.4.1.2. Vital Signs

Blood pressure and heart rate (HR) will be measured as specified in the Study Schedule and as clinically indicated (see Attachment 1 and Attachment 5). After the initial or subsequent increase in tadalafil dose, blood pressure and HR will be measured at 30 minutes, 60 minutes, and then hourly for 6 hours post dose.

Blood pressure and HR should be measured after the patient has been in supine position for at least 2 minutes.

Additional vital signs may be measured during each study period if warranted and agreed upon between the Sponsor and investigator. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be also be measured if clinically indicated.

10.4.1.3. Body Weight and Height

Body weight and height will be recorded as specified in the Study Schedule and as clinically indicated (Attachment 1).

10.4.1.4. Electrocardiograms

Twelve-lead ECGs will be obtained according to the Study Schedule (Attachment 1). Additional ECGs may be obtained during each study period if warranted.

Electrocardiograms 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, for immediate patient management and to determine whether the patient meets entry criteria. If the ECG shows a clinically important change, then the investigator should assess if the patient can continue in the study.

The ECGs will subsequently be electronically transmitted to the centralized ECG vendor designated by Lilly for storage. Some or all ECGs may be over read by a medically-qualified professional (for example, cardiologist) to assess clinically significant findings on the automated ECG readings. Should an over read occur, the rationale and strategy for cardiologist assessment of ECG abnormalities will be documented in the final study report.

If an over read ECG is returned from the centralized ECG vendor, the investigator or qualified designee is responsible to determine if any change to the subject's management is needed and must document his/her review by signing and dating the over read ECG. Any clinically significant findings that result in a diagnosis should be recorded on the case report form (CRF). Any clinically significant findings that do not result in a diagnosis should be commented on and appropriately documented.

If there are differences in ECG interpretation between the investigator or qualified designee and the ECG vendor cardiologist, the investigator or qualified designee's interpretation will prevail for study entry and immediate subject management purposes, and the ECG vendor cardiologist's interpretation will prevail for data analysis purposes.

10.4.1.5. Special Procedure

10.4.1.5.1. Eye Examination

Eye examinations will be performed according to the Study Schedule (Attachment 1). The examination includes patient medical history, external eye examination and retinal examination using an ophthalmoscope.

10.4.1.5.2. Inhibin Monitoring

Inhibin B monitoring will be collected according to the Study Schedule (Attachment 1) from all male patients. In patients below the age of 9 years, this will be an exploratory assessment.

10.4.1.5.3. Intellectual Ability and Cognitive Functioning Assessment

The patient's intellectual ability (intelligence quotient; IQ) will be assessed at 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 Test (WPPSI-III) 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 Visit 2 will be administered the WPPSI-III at 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 7 years 3 months.
- Patients who are aged 6 years 0 months through 15 years 11 months at Visit 2 will be administered the WISC-IV at Visit 2 and follow-up visits. For patients whose age exceeds 16 years 11 months at subsequent visits, then the WAIS-IV will be administered.
- Patients who are ages 16 years 0 months or older at Visit 2 will be administered the WAIS-IV at 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.

10.4.1.5.4. 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 60-90 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, Symbol Search. The scaled score for each subtest and Full Scale IQ composite score are required to be entered into the eCRF.

10.4.1.5.5. 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 60-90 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.

10.4.1.5.6. 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 25-60 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.

10.4.1.5.7. Palatability Questionnaire

Subjects who are at least 3 years of age treated with oral suspension will complete a questionnaire to assess the palatability of the suspension formulation at times according to the Study Schedule (Attachment 1).

10.4.1.5.8. 6-Minute Walk (6MW) Test

The 6MW test is the most accepted exercise capacity test and is also the most commonly used clinical trial endpoint in adult PAH 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 developmentally able (mentally and physically) in the opinion of the investigator. An un-encouraged 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 (see Attachment 6). A practice of 6MW test may be conducted prior to the first of 6MW test performance for each patient. If a patient has decrease of 20% or more in 6 minute walk distance compared with baseline, another 6MW test will be conducted 5 to 10 days later to confirm the change.

10.4.1.5.9. Echocardiograph

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 baseline (Visit 2) to end of 3 month treatment in Period 2 (Visit 10).

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

10.4.2. Adverse Events

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

Cases of pregnancy that occur during maternal or paternal exposures to study drug or drug delivery system should be reported. Data on fetal outcome and breastfeeding 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 informed consent document (ICD) 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.

Any clinically significant findings from physical examinations (including eye examinations), ECGs, labs, vital sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

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

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

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.

10.4.3. Serious Adverse Events

Previously planned (prior to signing of ICD) 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 or subject 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 study drug will be collected for 30 days after the last dose of study drug, 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 study drug, drug delivery system, or a protocol procedure.

10.4.4. Safety Monitoring

The Lilly clinical pharmacologist or clinical research physician will monitor safety data throughout the course of the study. In addition, a Safety Monitoring Committee will undertake periodic reviews of the data, as outlined in the Safety Monitoring Committee's 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 will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review trends and laboratory analytes.

10.4.5. Complaint Handling

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

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

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.

10.5. Appropriateness and Consistency of Measurements

The AE profile of tadalafil taken as needed or once daily in patients with ED is similar to that in patients with PAH. The current safety measures should be adequate to evaluate safety concerns of tadalafil administered once daily in the treatment of PAH in pediatric patients.

10.6. Compliance

Every attempt will be made to select patients who have the ability to understand and comply with instructions. During Period 2, compliance for each visit interval is defined as taking between 80% and 120% of the prescribed study drug. Patients who are significantly noncompliant with study drug may be discontinued from the study. Drug accountability records will be maintained by the study site.

The specifications in this protocol for the timings of safety and pharmacokinetic sampling are given as targets, to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and pharmacokinetic information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the lab requisition.

Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

11. Data Management Methods

11.1. 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/or use standard computer edits to detect errors in data collection.
- verify the quality of the data.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the Sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

11.2. Data Capture Systems

11.2.1. Case Report Form

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.

Case report form data collected by the third party organization (TPO) will be encoded by the TPO and stored electronically in the TPO's database system. Validated data will subsequently be transferred to the Sponsor's data warehouse, using standard Lilly file transfer processes.

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

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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

11.2.2. Ancillary Data

Central laboratory data will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the contract laboratory to the Lilly generic labs system and then to TPO's system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly generic labs system and then to TPO's system.

Electrocardiogram data will be stored electronically in the central database system of Lilly's central review organization.

The Echocardiogram data will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central laboratory to the Lilly generic labs system and then to TPO's system.

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

12. Pharmacokinetic, Pharmacodynamic, and Safety Data Analyses

12.1. Data Analysis Plans

12.1.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or designee.

Pharmacokinetic analyses will be conducted on the full pharmacokinetic analysis set that includes all data from all enrolled patients who receive at least one dose of tadalafil and have an evaluable PK profile. Analyses will be according to the treatment the patient actually received. Safety analyses will be conducted for all enrolled patients who take study medication, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Analyses will be fully detailed in the statistical analysis plan (SAP).

12.1.2. Study Participant Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

12.1.3. Study Participant Characteristics

The patient's age, sex, weight, height, or other demographic characteristics will be recorded and may be used in the pharmacokinetic and safety analyses as quantitative or classification variables.

12.1.4. Pharmacokinetic Analyses

12.1.4.1. Noncompartmental Pharmacokinetic Analyses

Evaluation of individual profiles during the study will be based on PK parameter estimates calculated by standard noncompartmental methods of analysis. The purpose of these analyses will be to evaluate dose escalations in individual patients, and to evaluate (as data become available) the appropriateness of the starting doses listed in Table LVIG.9.1. The primary parameters for this evaluation will be area under the curve of concentration versus time (AUC) and C_{max}. Other noncompartmental parameters may be reported if appropriate.

12.1.4.2. Population Pharmacokinetic (PopPK) Analysis

Pharmacokinetic data will be analyzed using an appropriate population-based method across all patients at the end of the study, and also across all Middle-weight and available Heavy-weight patients at the time of the SMC evaluation to proceed with dosing in the Light-weight cohort. The purpose of the PopPK analysis is to characterize tadalafil PK across the range of body weights and ages enrolled in the study and in each cohort; to evaluate the effect of various covariates such as age, body weight, sex, and ERA use on tadalafil exposure; and to predict appropriate dose(s) in subsequent pediatric studies of tadalafil. A one compartment model has

been shown to be suitable for data in adults, and will be used in pediatric patients if also shown to be suitable for the data collected during the study. The appropriateness of other models may also be explored. Details regarding the PopPK analysis will be described in a separate analysis plan.

12.1.5. Pharmacodynamic Analyses

Not applicable.

12.1.6. Pharmacokinetic/Pharmacodynamic Analyses

Not Applicable.

12.1.7. Safety Analyses

12.1.7.1. Clinical Evaluation of Safety

All study drug and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with study drug as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

12.1.7.2. Statistical Evaluation of Safety

Safety parameters will be listed and summarized overall and by weight cohort. Safety parameters to be assessed include AEs, safety lab parameters, vital signs, physical examination data, body weight, height, WHO functional class, IQ, Tanner score, 6MW test results, and ECG data. Serious adverse events including deaths and discontinuations due to adverse events will be summarized by weight cohort with counts of the number of patients and percentages. A summary of all treatment emergent adverse events (TEAE) will be presented by system organ class and preferred term. The frequency and percentage of TEAEs will be presented for each weight cohort. Continuous laboratory data will be summarized by weight cohort and visit. Additional analysis will be performed if warranted upon review of the data.

12.1.8. Exploratory Analyses

Palatability questionnaire data and NT-Pro-BNP collected during the study will be summarized. Changes from baseline to endpoint (defined as the end of the first 3 months of treatment in Period 2) in hemodynamic parameters (tricuspid annular plane systolic excursion, eccentricity index, pericardial effusion, maximal tricuspid regurgitant velocity) collected via echocardiogram will be summarized.

12.2. Interim Analyses

Interim analyses are planned for this study.

Study sites will receive information about interim results ONLY if they need to know for the safety of their patient or for dose escalation.

If an additional unplanned interim analysis is deemed necessary, the Lilly clinical research scientist or CRP/investigator will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

12.2.1. Individual Dose Escalation Analysis

The purpose of these analyses will be to evaluate dose escalations in individual patients for the appropriateness of the high doses listed in Table LVIG.9.1

Investigator-level clinical data and lab reports regarding AEs, clinical signs and abnormal laboratory tests, and PK results will be reviewed by the sponsor, the sponsor designee, and investigator to support decisions to escalate to the high dose level for each patient without QA/QC or output from the Sponsor's database. The specifics about the timing of the interim analyses and the procedures for deciding the next dose are described in the Study Design section of the protocol.

12.2.2. Cohort Analysis

The purpose of the PopPK analysis is to characterize tadalafil PK across the range of body weights and ages of patients enrolled in the study and in each cohort; to evaluate the effect of various covariates such as age, body weight, sex, and ERA use on tadalafil exposure; and to predict appropriate dose(s) in subsequent pediatric studies of tadalafil.

These analyses will take place after 5 Middle-weight cohort patients have completed Period 1, and prior to the Light-weight cohort patients enrolling into the study. The SMC will review all available study data, including both safety and PK data, and recommend tadalafil dose levels for the Light-weight cohort. A similar review will occur when 5 patients from the Heavy -weight cohort have completed Period 1 of Study LVIG. Additionally, the SMC will review all available study data after the completion of the Light-weight cohort and at least annually until the end of the study.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

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

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

The investigator is ultimately responsible for ensuring that informed consent is given by each patient or parent/legal representative before the study is started. This includes obtaining the appropriate signatures and dates on the ICD prior to the performance of any protocol procedures and prior to the administration of study drug.

A parent or legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the parent or 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 subjects or their legal representatives.

13.2. Ethical Review

Lilly must agree with all ICDs before they are submitted to the ERB and are used at investigative sites(s). All ICDs must be compliant with the International Conference on Harmonization guideline on good clinical practice (GCP). Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations, and performed in accordance with a written process approved by Lilly.

The investigator will provide Lilly with documentation of ERB approval of the protocol and the ICD *before* the study may begin at the investigative site(s). 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 ERB(s) will review the protocol as required.

The investigator will supply the following to the study site's ERB(s):

- the current IB or package labeling and updates during the course of the study
- ICD
- 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) the International Conference on Harmonisation (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 United States (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 contract research organization (CRO).

An identification code assigned by the investigator 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

Site-specific contact information may be provided in a separate document.

13.3.2. Protocol Signatures

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 final report coordinating investigator or designee will sign the 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 final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

The Sponsor's responsible medical officer will sign 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.

14. References

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Attachment 1. Protocol LVIG Study Schedule

Visit*	1	2	3	4	5	6	7	8	9	10-12	13	14-16	17	Follow -up[o]
Description of event LVIG	Screening Day -28 to 0	Day 1	Wk1 Day 7 ± 3days	Wk 2 Day 14 ± 3days	Wk4 Day 28 ± 3days	Wk5 Day 35 ± 3days	Wk 6 Day 42 ± 3days	Wk7 Day 49 ± 3days	Wk 10 Day 70 ± 3days	Every 3 months ±10 days	1 Year ±10 days	Every 3 months ±10 days	2 Year ±10 days	Last dose + 30 days
Informed Consent	X													
Medical history	X													
Pulmonary Function test[l]	X													
OB/GYN history[a]	X													
CXR (within 6 months of screening)	X													
WHO Functional class	X								X	X	X	X	X	
Physical Examination	X	X				X			X					
Eye Examination[b]	X								X				X	
6-minute walk test[h]		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	
Vital signs	X	X[c]		X		X[c]		X	X					
ECG (single)	X								X					
Urine Pregnancy test[d]	X								X		X		X	
Urine drug screen	X													
NT-Pro-BNP		X							X					
Safety lab tests: Chemistry, hematology, Coagulation[e]	X			X				X	X					
Urinalysis	X								X					
DNA (PGx) Sample		X[f]												
PK[g]		X		X				X		X[m]				
Inhibin B (for male patients)		X									X		X	
WISC-IV or WAIS-IV or WPPSI-III[k]		X									X		X	
Tanner Score[i]		X									X		X	

Pre-existing conditions and adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Extended study visit		X		X				X						
Palatability Questionnaire[j]		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	
Echocardiography[n]		X								X				

Attachment 1 Protocol LVIG Study Schedule

Study Schedule Protocol H6D-MC-LVIG (Period 1 and Period 2 [beginning after Visit 9])

Abbreviations: CXR = chest radiography; ECG = 12 –lead electrocardiogram; NT-Pro-BNP = N-terminal prohormone brain natriuretic peptide; PK = pharmacokinetics; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children; WPPSI= Wechsler Preschool and Primary Scale of Intelligence; WHO = World Health Organization; Wk=week.

a Including family history of menarche.

b Eye Examination includes patient medical history, external eye examination and retinal examination using an ophthalmoscopy.

c Heart rate and blood pressure (systolic/diastolic) at pre-dose, 30 minutes, 60 minutes, then hourly for 6 hours post dose.

d Pregnancy test: only females of child bearing potential, may be repeated at investigator's discretion throughout the trial.

e Collect if needed for clinical worsening. At time of SAE reporting, hematology, coagulation, and serum chemistry samples might be collected from the patient. Digoxin, warfarin, and ERA blood sampling should be carried out using the Investigator's standard of care. The coagulation can be carried out for patients on warfarin.

f If not collected at this visit, the sample could be collected at following visit.

g PK Sampling will be as follows: pre-dose, 2.0 hr, 4.0 hr, 8.0 hr, 12.0 hr, 24.0 hrs post-dose. This will require an extended study visit. The nominal sampling window is ±5% of the nominal collection times.

h 6MW test will be performed for those patients ≥6 years of age. If patient has decrease of ≥20% in 6MW distance compared with baseline, another 6MW test will be conducted 5 to 10 days later to confirm the change.

i If patient has Tanner Score 5 on all criteria, the following Tanner Score evaluation will not be required.

j Light-weight cohort only and ≥ 3 years of age.

k WISC IV is to be used for patients ranging from 6 years to 16 years 11 months, WAIS IV is to be used for patients 16 years and older, and WPPSI-III 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 visits. The IQ tests may be performed prior to Visit 2, but must be performed prior to study drug dosing.

l Pulmonary Function test will be performed for those patients ≥6 years of age.

m Visit 10 only. PK sample at Visit 10 is a trough monitoring PK sampling.

n Echocardiography will be performed at baseline prior to initiation of study drug dosing (Visit 2) and at Visit 10 (3 months after initiation of Period 2) at those sites that have the capability of echocardiography.

o This follow up visit will be conducted only for those patients who are discontinued from study during Period 1 and will not participate in Period 2. This visit can be done by phone.

* Some visits may be conducted in the patient's home by qualified study personnel, as agreed on a per patient basis by the Sponsor. Visit 3, Visit 5, and Visit 7 may be conducted by phone.

Note that the first visit during Period 2 (Visit 10) is 3 months after Visit 9.

Attachment 2. Protocol LVIG Clinical Laboratory Tests

Laboratory Tests[a] 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 [optional]
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	Ethanol testing [a]
Basophils	Urine drug screen[a]
Platelets	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 LVIG Blood Sampling Summary

This table summarizes the maximum number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories and bioanalytical assays) during the study. A protocol amendment would not be required for fewer venipunctures and/or less blood draws (volume) or additional blood drawn for safety purposes.

Subjects in all weight cohorts

Purpose	Maximum Blood volume per sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Clinical laboratory tests[a]	6.3	4	25.2
PK Drug assays	0.5	19	9.5
Inhibin B[b]	2.5	3	7.5
NT-Pro-BNP	2.5	1	2.5
Pharmacogenomic Sample (PGx)	0.5	1	0.5
Total			45.2

[a] Includes 3 blood samples: hematology, coagulation, clinical chemistry; additional samples may be drawn if needed for safety purposes.

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

Attachment 4. World Health Organization (WHO) Functional Classification

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Attachment 5. Protocol LVIG 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 mercury 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.

It is preferred that the children should be in a supine position. The interpretation of diastolic and systolic measurements is left to the discretion of the investigator.

Attachment 6. Protocol LVIG Guidelines for Conduct of Un-encouraged 6-Minute Walk Test

(modified from *Am J Respir Crit Care Med*. 2002;166:111-117).

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 is **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.

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 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.

Attachment 7.
Protocol Amendment H6D-MC-LVIG(d) Summary
A Multiple Ascending Dose Study of Tadalafil to Assess the Pharmacokinetics and Safety in a Pediatric Population with Pulmonary Arterial Hypertension

Overview

Protocol H6D-MC-LVIG, A Multiple Ascending Dose Study of Tadalafil to Assess the Pharmacokinetics and Safety in a Pediatric Population with Pulmonary Arterial Hypertension, has been amended. The new protocol is indicated by Amendment(d) 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 as follows:

- The wording in the Summary of Study Design (Section 7.1) has been changed to provide the minimum number of completers ≤6 years of age and the minimum number of completers ≤2 years of age; the maximum number that was included in the previous version of the protocol ("but not more than 4 patients" and "but not more than 3 patients," respectively) has been deleted. This modification will leverage the potential additional patient enrollment in this age group to better understand the PK and safety.
- Guanylate cyclase stimulators, such as riociguat, were added as concomitant medicines that are excluded and should prevent a patient from enrolling in the study. The combination of guanylate cyclase stimulators and tadalafil could suddenly cause a drop in blood pressure which may result in dizziness or fainting. Therefore, exclusion criterion [37] has been added to exclude any patients who are taking guanylate cyclase stimulators, such as riociguat. Also, riociguat was added to Section 9.6 (Concomitant Therapy) as a concomitant medicine that would prevent a patient from enrolling in the study.
- Text in Section 8.2.2 (Discontinuation of Individual Patients) has been changed to align with the current required language related to criteria for enrollment required per Lilly SEQS/MQS.
- Text in the footnote section of the Study Schedule (Attachment 1) has been modified for clarification of the beginning of Period 2.
- Corrected typos and clarified various other minor items in the protocol.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

Minor typographical/grammatical errors were corrected throughout the protocol.

Abbreviations were defined throughout the protocol.

2. Synopsis

Diagnosis and Main Criteria for Inclusion and Exclusion

Patients are not eligible to be included in the study if they meet any of the following ~~exclusion criteria~~**exclusion criteria**:

[14] Concurrent PDE-5 inhibitor therapy (such as sildenafil or vardenafil) or has received PDE-5 inhibitor therapy within 24 hours prior to the first study drug dosing (baseline visit).

[23] Have severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 30 mL/min/1.73 m^2 (Schwartz Formula):

All Females and Pre-adolescent Males:
Ccr (mL/min/1.73 m2) = 0.55 × Height (cm) / SCr (mg/dL)
Adolescent Males:
Ccr (mL/min/1.73 m2) = 0.70 × Height (cm) / SCr (mg/dL)
Where C_{cr} is Creatinine Clearance and S_{Cr} is Serum Creatinine

[37] Currently receiving treatment with soluble guanylate cyclase stimulator therapy (such as riociguat). Exclusion criteria [37] has been added.

7.1. Summary of Study Design

… Of the 15 completers, at least 3~~, but not more than 4~~ patients will be ≤6 years of age and at least 2~~, but not more than 3~~ patients will be ≤2 years of age.

7.2. Discussion of Design and Control

… The concomitant use of another PDE-5 inhibitor (for example, sildenafil) or soluble guanylate cyclase stimulator (for example, riociguat) is prohibited during the study. Subjects receiving another PDE-5 inhibitor will be required to discontinue the medication at least 24 hours prior to the baseline visit (Visit 2), which should suffice to allow for systemic elimination of the PDE-5 inhibitor (that is, at least 5 half-lives of the drug).

8.1.2. Exclusion Criteria

[14] Concurrent PDE-5 inhibitor therapy (such as sildenafil or vardenafil) or has received PDE-5 inhibitor therapy within 24 hours prior to the first study drug dosing (baseline visit).

[23] Have severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 30 mL/min/1.73 m^2 (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 Creatinine Clearance and S_{Cr} is Serum Creatinine

[37] Currently receiving treatment with soluble guanylate cyclase stimulator therapy (such as riociguat). Exclusion criteria [37] has been added.

8.1.3. Rationale for Inclusion and Exclusion of Certain Study Candidates

Exclusion criteria ~~and~~ [30], [31], and [35] 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 [32] is in place to assure that the patients can take the medication in the forms that are available in this trial.

Exclusion criteria [33] and [34] are in place to prevent possible study bias from close relations.

Exclusion criteria [37] is in place to protect the patient since the combination of PDE5 inhibitors and guanylate cyclase stimulators, such as riociguat may lead to symptomatic hypotension.

8.2.2. Discontinuation of Individual Patients

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

~~or its designee must be contacted.~~ If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Lilly clinical pharmacologist or clinical research physician and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the investigator and Lilly clinical pharmacologist or clinical research physician agree it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly clinical pharmacologist or clinical research physician does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly clinical pharmacologist or clinical research physician to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

8.2.2.1. Early Discontinuation from Study

- If Exclusion Criterion [18], [19], [20], [22 through 28], [32], ~~or~~ [36], or [37] is observed, or develops, after entry or enrollment. In this case, the patient will be discontinued from the drug/study at the next visit or sooner in the event of a safety exclusion criterion.
    - Exception: A patient receiving an ERA who develops an AST or ALT >3 times upper limit of normal 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.

9.6. Concomitant Therapy

Medicines and therapies that would prevent a patient from enrolling in the study are identified in the exclusion section of this protocol (see Section 8.1.2), such as:

- Prostacyclin or its analogues.
- Concurrent PDE-5 inhibitor (other than study medication)
- Nitrates
- Doxazosin or Other cancer chemotherapy
- Antiretroviral therapy (protease inhibitors), systemic ketoconazole, or systemic itraconazole.
- Potent systemic CYP3A4 inhibitors and inducers
- Guanylate cyclase stimulators, such as riociguat

Attachment 1: Protocol LVIG Study Schedule (footnotes)

Study Schedule Protocol H6D-MC-LVIG (Period 1 and Period 2 [beginning ~~with~~ after Visit ~~9~~10])

Abbreviations: CXR = chest radiography; ECG = 12 –lead electrocardiogram; NT-Pro-BNP = N-terminal prohormone brain natriuretic peptide; PK = pharmacokinetics; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children; WPPSI= Wechsler Preschool and Primary Scale of Intelligence; WHO = World Health Organization; Wk=week.

a Including family history of menarche.

b Eye Examination includes patient medical history, external eye examination and retinal examination using an ophthalmoscopy.

c Heart rate and blood pressure (systolic/diastolic) at pre-dose, 30 minutes, 60 minutes, then hourly for 6 hours post dose.

…

o This follow up visit will be conducted only for those patients who are discontinued from study during Period 1 and will not participate in Period 2. This visit can be done by phone.

* Some visits may be conducted in the patient's home by qualified study personnel, as agreed on a per patient basis by the Sponsor. Visit 3, Visit 5, and Visit 7 may be conducted by phone.

Note that the first visit during Period 2 (Visit 10) is 3 months after Visit 9.

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