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

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Primary Objectives:* For the European Union (EU) regulatory assessment, the primary objective of Period 1 is to evaluate theefficacy of tadalafil compared with placebo, as measured by time to clinical worsening (CW) in pediatricPAH patients through…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON41448

Source
ToetsingOnline

Brief title
H6D-MC-LVHV

Condition

- Pulmonary vascular disorders

Synonym
pulmonary arterial hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly

Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: pediatrics, Pulmonary Arterial Hypertension, tadalafil

Outcome measures

Primary outcome

Efficacy:

Primary Measures (Period 1):

* For the EU regulatory assessment, the primary efficacy measure is time to

first occurrence of CW.

Secondary outcome

Efficacy:

Secondary Measures (Period 1):

* Time to CW (for the US regulatory assessment) and the incidence of CW.

* 6MW distance in meters measured in a subset of patients who are *6 to <18

years of age and who are

developmentally capable of performing a 6MW test (for the EU regulatory

assessment).

Secondary Measures (Period 2):

* Incidence of and time to CW.

Additional Measures (Period 1):

* WHO functional classification

* Cardiac MRI parameters:

- LV ejection fraction

- RV end diastolic volume

- RV end systolic volume

- RV ejection fraction

* Echocardiography parameters:

- tricuspid annular plane systolic excursion (TAPSE)

- eccentricity index

- pericardial effusion

- maximal tricuspid regurgitant velocity

* NT-Pro-BNP concentrations.

Additional Measures (Period 2):

* 6MW distance in meters measured in patients who are *6 years of age and who are developmentally capable of performing a 6MW test.

* WHO functional classification

Safety: Period 1: Safety during Period 1 will be assessed through AEs including abnormalities detected by ECG or physical examination, clinical chemistry and hematology panels, urinalysis, vital signs, and eye examinations.

Period 2: AEs, changes in body weight and height, inhibin B biomarker (male patients only), eye examinations, Tanner scale, and intelligence tests, and concomitant medications.

Health Outcomes:

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

Pharmacokinetics: Population PK assessment of plasma tadalafil concentrations

at steady-state.

Study description

Background summary

Currently no therapies are approved in the United States (US) for the treatment of children with pulmonary arterial hypertension (PAH). There is a growing body of evidence, however, supporting the use of therapies approved in the adult population with PAH, that has led to widespread off-label use in this pediatric population. There continues to be, however, a need for robust data to inform prescribing physicians regarding the safety and efficacy of all treatment options, including tadalafil, in the pediatric PAH population.
This is the first Phase 3 study of tadalafil for use in treating PAH in pediatric patients.

Study objective

Primary Objectives:
* For the European Union (EU) regulatory assessment, the primary objective of Period 1 is to evaluate the efficacy of tadalafil compared with placebo, as measured by time to clinical worsening (CW) in pediatric PAH patients through Week 24.
Period 2: The primary objective of Period 2 is to evaluate long-term safety of tadalafil while providing continued access to tadalafil for pediatric patients with PAH who participated in Period 1.
Secondary Objectives:
Period 1: The secondary objectives of Period 1 are as follows:
* Assess the efficacy of tadalafil compared with placebo on time to CW (for the US regulatory assessment) and the incidence of CW.
* Assess the efficacy of tadalafil compared with placebo on 6MW distance in a subset of patients *6 to <18 years of age who are developmentally capable of performing a 6MW test (for the EU regulatory assessment).
* Characterize the population pharmacokinetics (PK) of tadalafil in pediatric pulmonary arterial

hypertension (PAH) patients.
* Assess the safety of tadalafil as compared with placebo.
Period 2: The secondary objective of Period 2 is to evaluate the incidence of, and time to CW.
Additional Objectives:
Period 1: Additional objectives of Period 1 are as follows:
* Assess the efficacy of tadalafil compared with placebo on changes in World Health Organization (WHO)
functional classification.
* Explore by cardiac magnetic resonance imaging (MRI), changes from Day 1 to Week 24 in the following
cardiac MRI parameters:
- left-ventricular (LV) ejection fraction
- right-ventricular (RV) end diastolic volume
- RV end systolic volume
- RV ejection fraction
* Evaluate by echocardiography, changes from Day 1 to Week 24 in the following echocardiographic
parameters:
- tricuspid annular plane systolic excursion (TAPSE)
- eccentricity index, pericardial effusion
- maximal tricuspid regurgitant velocity
* Evaluate change from Day 1 to Week 24 in N-terminal prohormone brain natriuretic peptide
(NT-Pro-BNP) concentrations.
* Assess physician- and caregiver-reported health outcome, as measured by Clinical Global Impression of
Improvement (CGI-I), and in a subset of patients *5 years of age, Child Health Questionnaire Parent Form
28 (CHQ-PF28).

Study design

A Phase 3, international, randomized multicenter, 2-period, double-blind, placebo-controlled, addon
(in addition to the patient*s current endothelin receptor antagonist [ERA]) study to evaluate tadalafil efficacy,
safety, and population PK in pediatric patients with PAH.
Screening and eligibility evaluation will be performed during an approximately 28-day period prior to
randomization and the administration of tadalafil. Period 1 is a 24-week study drug treatment phase. During this
study period, patients will continue to receive stable ERA therapy. Period 2 is an open-label extension (OLE)
period that will evaluate the long-term safety of tadalafil while providing continued access to tadalafil for pediatric
patients completing Period 1. Patients entering Period 1 of the study will be

stratified into 1 of 3 weight cohorts
based on their weight at the time of the screening visit (heavy-weight: *40 kg;
middle-weight: *25 kg to <40 kg;
or light-weight: <25 kg) and then be randomized to tadalafil or placebo.

Intervention

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

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

Study burden and risks

There are risks involved with the use of the medicinal product tadalafil. There are also risks involved with the study procedures. Most of these are part of the standard care. An overview is provided in the SIS-ICF.
There may also be other unknown risks involved with the medication and study procedures and their combination. Patients taking part could benefit from taking part in this study, but this is not necessarily the case. Knowledge derived from this study can help patients in the future by providing physicians information needed to make a well informed decision on treatment options.

Contacts

Public
Eli Lilly

Lilly Corporate Center NA
Indianapolis IN 46285
US
Scientific
Eli Lilly

Lilly Corporate Center NA
Indianapolis IN 46285

US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

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 connective tissue disease;;*related to anorexigen use;;*associated with surgical repair of at least 6-month duration of congenital systemic to pulmonary shunt (eg, atrial septal defect, ventricular septal defect, patent ductus arteriosus);[3] Have a history of a diagnosis of PAH established by a resting mean pulmonary artery pressure (mPAP) *25 mm Hg, pulmonary artery wedge pressure *15 mm Hg, and a PVR *3 Wood units via right heart catheterization (RHC). In the event that a pulmonary artery wedge pressure cannot be obtained during RHC, patients with a left ventricular end diastolic pressure (LVEDP)<15 mm Hg, with normal left heart function, and absence of mitral stenosis on echocardiography can be eligible for enrollment.;[4] Have a WHO functional class value of II or III at the time of screening.;[5] All subjects must be receiving an ERA (such as bosentan or ambrisentan) and must be on a maintenance dose with no change in dose (other than weight-based adjustments) for at least 12 weeks prior to screening and have a screening aspartate transaminase (AST)/alanine transaminase (ALT) <3 times the upper limit of normal (ULN).;[6] If on conventional PAH medication, including but not restricted to, anticoagulants, diuretics, digoxin, and oxygen therapy, the patient must be on stable doses with no changes (other than weight-based adjustments) for at least 4 weeks before screening. ;[7] Female patients of childbearing potential must test negative for pregnancy during screening. Furthermore, female patients must agree to abstain from sexual activity or to use two different reliable methods of birth control as determined by the Investigator during the study. Examples of reliable birth control methods include true abstinence as a lifestyle choice (periodic sexual abstinence method is not acceptable); the use of oral contraceptives; a reliable barrier method of birth control (diaphragms with contraceptive jelly; cervical caps with contraceptive jelly; condoms with contraceptive foam; intrauterine devices).;[8] Written informed consent from parents (and written assent from appropriately aged patients) will be

obtained prior to any study procedure being performed.

Exclusion criteria

[1] Pulmonary hypertension related to conditions other than specified in inclusion criteria.;[2] History of left-sided heart disease, including any of the following:;- clinically significant (pulmonary artery occlusion pressure [PAOP] 15 18 mm Hg) aortic or mitral valve disease (i.e., aortic stenosis, aortic insufficiency, mitral stenosis, moderate or greater mitral regurgitation);;- pericardial constriction;;- restrictive or congestive cardiomyopathy;;- left ventricular ejection fraction < 40% by multigated radionucleotide angiogram (MUGA), angiography, or echocardiography;;- left ventricular shortening fraction < 22% by echocardiography;;- life-threatening cardiac arrhythmias;;- symptomatic coronary artery disease within 5 years of study entry.;[3] History of atrial septostomy or Potts Shunt within 3 months before administration of study drug.;[4] Unrepaired congenital heart disease.;[5] History of angina pectoris or other condition that was treated with long- or short-acting nitrates within 12 weeks before administration of study drug.;[6] WHO functional class value of either I or IV at the time of screening.;[7] Severe hepatic impairment, Child-Pugh Grade C.;[8] Severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 30 mL/min (Schwartz Formula);[9] Retinal disorder (e.g., hereditary retinal disorders, retinopathy of the preterm patient and other retinal disorders);[10] Severe hypotension or uncontrolled hypertension as determined by the Investigator.;[11] Significant parenchymal lung disease.;[12] Bronchopulmonary dysplasia.;[13] Concurrent PDE5 inhibitor therapy (sildenafil or vardenafil) or has received PDE5 inhibitor therapy within 24 hours prior to the first study drug dosing.;[14] Concurrent therapy with prostacyclin or its analogues.;[15] Previously completed or withdrawn from this study (LVHV), or any other study investigating tadalafil.;[16] Commenced or discontinued a chronic PAH medication including but not restricted to: calcium channel blockers, diuretics, anti-coagulants, digoxin, and oxygen therapy within four weeks of screening.;[17] Currently receiving treatment with doxazosin, nitrates, or cancer therapy.;[18] 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.;[19] History of loss of vision in 1 eye because of nonarteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous phosphodiesterase type 5 (PDE5) inhibitor exposure.;[20] Concurrent soluble guanylate cyclase stimulator therapy (such as riociguat) or has received soluble guanylate cyclase stimulator therapy within 12 weeks prior to first study drug dosing (Day 1, Visit 2)

Study design

Design

Study phase: 3

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-03-2014
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adcirca
Generic name:	Tadalafil
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cialis
Generic name:	Tadalafil
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tadalafil oral suspension
Generic name:	Tadalafil oral suspension

Ethics review

Approved WMO

Date:	31-05-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	18-10-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	26-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-002354-23-NL
CCMO	NL43901.042.13