A MULTINATIONAL, MULTICENTER STUDY TO ASSESS THE EFFECTS OF ORAL SILDENAFIL ON MORTALITY IN ADULTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH)

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

Summary

ID

NL-OMON41536

Source
ToetsingOnline

Brief title
A1481324 (209264)

Condition

- Pulmonary vascular disorders

Synonym
PAH, Pulmonary Arterial Hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Dosis, PAH, Pulmonary Arterial Hypertension, Sildenafil

Outcome measures

Primary outcome

Time to death (Mortality).

Secondary outcome

Time to first event (Clinical Worsening); and 6MWD at Months 6 and 12.

Clinical worsening for the purpose of this study is defined as:

- All-cause mortality;

- Non-elective hospital stay for worsening PAH (including but not limited to

right heartfailure [RHF], initiation of IV prostanoids, lung transplantation,

or septostomy); or

- Disease progression (defined as a reduction from baseline in the 6MWD test by

15%, confirmed by a 2nd test within 2 weeks (cannot be performed on same day)

and worsening functional class).

Study description

Background summary

A more detailed overview of the background is given in section 1 of protocol AM1 dated 18-Nov-14. Below some key paragraphs from section.

Like other PAH-targeted drugs, sildenafil was approved for use in adults based on short-term studies with improvement in exercise capacity as the primary endpoint. In these studies, no greater efficacy was achieved in the primary endpoint with the use of higher doses. Therefore, treatment with doses higher than 20 mg TID is not recommended in current US labeling. Although there are considerable data in adults with PAH with doses up to 80 mg TID from long-term, open-label extension studies, there are no controlled data and the effect of sildenafil on the risk of death is unknown.
[*]
The rationale for including the 5 mg TID dose in this trial is that the minimum effective dose of sildenafil is not known. The results of A1481244 in adults with PAH [*] indicated that the change from baseline in 6MWD was clinically significant in the 5 and 20 mg groups (mean changes of 41 m and 38 m, respectively), but smaller and not clinically significant in the 1 mg group (mean change of 14 m). Thus, in this study, a dose of 5 mg TID demonstrated a similar effect on exercise capacity as 20 mg TID. Therefore, it is important to evaluate whether doses lower than 20 mg TID might be similarly effective and relatively safer than the current recommended dose of 20 mg when used for the long-term treatment of adult PAH.

Study objective

The relative effects of sildenafil on mortality when administered at the three doses indicated above in adults with PAH will be evaluated in this clinical study. In addition, the relative effects on clinical worsening and 6-minute walking distance (6MWD) will also be assessed.

Study design

This is a randomized, double-blind, parallel-group study. Adult subjects with PAH will be randomly assigned 1:1:1 to one of three dosage groups (5 mg, 20 mg and 80 mg TID) and stratified according to PAH treatment at entry (PAH-treatment naïve vs. on PAH-treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair).

Intervention

Patient will receive study medication with a dose depending on the treatment group where they are assigned to (5, 20 or 80 mg TID). In addition, they need to take 6 placebo tablets per day.

Study burden and risks

The most common adverse reactions of Sildenafil, observed in greater than or equal to 3% of subjects, and observed more frequently than in subjects who received placebo:

* Epistaxis (nose bleeds)
* Headache
* Dyspepsia (indigestion)
* Flushing (red face)
* Insomnia (difficulty sleeping)
* Erythema (red rash)
* Dyspnea (difficulty breathing)
* Rhinitis (inflammation of the lining of the nose)
* Nasal congestion (blocked nose)
* Edema (swelling)
* Pain in extremity (arms/legs)
* Diarrhea
For more known risks of the study drug, see Attachment 3 of the Patient Information and Consent Form and the Investigator's Brochure. As with all medical research studies, there may also be risks that are currently unknown and unforeseen.

Study Procedures Risks:
Risks and possible discomforts that might be experienced from the study procedures include:
* Blood draws: A blood draw may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection. Approximately 96.3ml will be collected for patients that complete the entire study on study treatment.
* ECG: The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches.
* Chest X-ray: The risk associated with radiation exposure from having a chest X ray is minimal. The typical radiation dose to an adult from a chest radiograph is around 0.02 mSv (2 mrem), which is about the same amount of radiation you would receive by flying cross-country in an airplane.

Burden to patient:
* Take 9 tablets per day.
* Take contraceptive measures throughout the study and for 28 days after last dose of study drug.
* Not take bosentan, riociguat, nitrates or nitric oxide.
* Not take any other medications without notifying PI.
* Keep diary
* Visit the hospital and have assessments as indicated in the Schedule of Activities on page 7 of the protocol dated 25-Sep-13

Contacts

Public

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US
Scientific
Pfizer

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New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:;1. Subjects *18 and < 75 years of age with any of the following conditions:;a. Idiopathic Pulmonary Arterial Hypertension (IPAH); or;b. PAH secondary to connective tissue disease (CTD); or;c. PAH with surgical repair (at least 5 years previously) of atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA) and aorto-pulmonary window.;2. PAH must have been newly diagnosed (confirmed by right heart catheterization) within 12 months prior to randomization (mean pulmonary artery pressure (mPAP) *25 mmHg at rest, pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) *15 mmHg, and pulmonary vascular resistance (PVR) > mmHg/L/min or 320 dynes*sec/cm5);;3. No prior long term PDE-5 inhibitor treatment (Prior episodic use of PDE-5 inhibitors for erectile dysfunction or prior limited trial use (maximum of 4 weeks) provided that PDE-5 was not discontinued for lack of efficacy or adverse event does not disqualify a subject from the study);;4. PAH WHO Functional Class II-IV;;5. Baseline 6MWD *50 m.;6. Male or female subjects not of childbearing potential or female subjects of childbearing potential who agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

Female subjects who are not of childbearing potential include those who meet at least one of the following criteria:;a. Have undergone a documented hysterectomy and/or bilateral oophorectomy;;b. Have medically confirmed ovarian failure or;;c. Achieved post-menopausal status, defined as the cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum FSH level within the laboratory*s reference range for postmenopausal females.;7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures; and;8. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.

Exclusion criteria

Subjects presenting with any of the following will not be included in the study:;1. PAH secondary to any etiology other than those specified in the inclusion criteria;;2. Significant (ie, > 2+) valvular disease other than tricuspid regurgitation or pulmonary regurgitation;;3. Congenital heart disease (unless they meet inclusion criteria in Section 4.1) or pulmonary hypertension due to thromboembolism;;4. Atrial septostomy within 6 months prior to randomization (subjects who are required to undergo this procedure during the study should be withdrawn);;5. Myocardial infarction, unstable angina, cerebrovascular accident (CVA), or transient ischemic attack (TIA) within 6 months prior to randomization;;6. Acutely decompensated heart failure within 3 months prior to randomization;;7. History of cardiac arrest, respiratory arrest, hemodynamic collapse, CPR, ventricular tachycardia, ventricular fibrillation, or uncontrolled atrial fibrillation;;8. History of pulmonary embolism verified by ventilation/perfusion scan, angiogram or spiral chest computerized tomography scan;;9. Hypotension defined as systolic arterial pressure < mmHg or diastolic arterial pressure <50 mmHg after sitting for 5 minutes at either Screening or Day 1;;10. Previous long term treatment with PDE-5 inhibitors (Prior episodic use of PDE-5 for erectile dysfunction or prior limited trial use (maximum of 4 weeks) provided that PDE-5 was not discontinued for lack of efficacy or adverse event does not disqualify a subject.);;11. Treatment with bosentan or riociguat within 3 months of randomization;;12. Current treatment with nitrates or nitric oxide;;13. Initiation of new therapy for PAH < months prior to randomization or change in background treatment specific for PAH within 30 days prior to randomization (ie, ambrisentan and any other ETRA or novel agent that becomes available during the conduct of the study provided that the new agent is not a potent CYP3A inducer or inhibitor (Appendix 1) that has a clinically evident drug-drug interaction with sildenafil and/or prostanoids);;14. Change in class of supportive therapy used for adjunctive treatment of PAH within 30 days prior to randomization (eg, oxygen, calcium channel blockers, digoxin, diuretics);;15. Current treatment with potent CYP3A4 inhibitors or inducers (Appendix 1);;16. History of chronic obstructive or restrictive lung disease (eg, chronic obstructive pulmonary disease (COPD) or scleroderma) with impairment of lung function demonstrated by total lung capacity (TLC) < predicted, or forced expiratory volume (FEV1) < 60% predicted. (Subjects with these pulmonary disorders must have Pulmonary Function Tests performed prior to study entry if they have not been performed in the previous 12 months). If either TLC or FEV1 do not meet criteria above but in the Investigator*s judgment the patient does not have chronic or restrictive lung disease, the Investigator is to contact the sponsor to determine if patient can

be enrolled;;17. Within 5 years of Screening, history of malignancy (except for adequately treated basal cell or squamous cell carcinoma of the skin), human immunodeficiency virus (HIV) or any other disease likely to limit life expectancy;;18. Known allergy or adverse reaction to sildenafil or any other ingredient in Revatio®;;19. Known hereditary degenerative retinal disorders, such as retinitis pigmentosa, history of visual loss, untreated proliferative diabetic retinopathy, or history of non-arteritic ischemic optic neuropathy (NAION);;20. Known priapism, hearing loss, vision changes, or epistaxis due to any episodic use of PDE-5 inhibitor;;21. History of alcoholism or drug abuse, or prior symptoms of drug- or alcohol-related withdrawal;;22. Participation in any other experimental studies involving other drug or non-drug therapies within 30 days before the current study begins and during study participation;;23. Pregnant females; breastfeeding females; females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product;;24. Any severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial; or;25. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-09-2014
Enrollment:	5

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Revatio
Generic name:	Sildenafil Citrate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-01-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-04-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-004362-34-NL
ClinicalTrials.gov	NCT02060487
CCMO	NL47961.100.15