A multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, Phase III study to assess the effects of ACT-064992 on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension

Published: 26-03-2008
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Primary objective• To demonstrate that either dose of ACT-064992 prolongs the time to the first morbidity or mortality event in patients with symptomatic pulmonary arterial hypertension.Secondary objectives• To demonstrate that either dose of ACT-...

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

Summary

ID

NL-OMON33990

Source
ToetsingOnline

Brief title
SERAPHIN

Condition

- Pulmonary vascular disorders

Synonym
Pulmonary hypertension; hypertension in lung arteries

Research involving

Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals Ltd.
Source(s) of monetary or material Support: Actelion Pharmaceuticals Ltd.

Intervention

Keyword: Endothelin Receptor Antagonist, Pulmonary Arterial Hypertension

Outcome measures

Primary outcome

Primary endpoint

Time from start of treatment to first morbidity or mortality event, defined as

follows:

1. Death, or

2. Atrial septostomy, or

3. Lung transplantation, or

4. Initiation of intravenous or subcutaneous prostanoids (e.g., epoprostenol,

treprostinil), or

5. Other worsening of pulmonary arterial hypertension.

Other worsening of pulmonary arterial hypertension is defined by the

combination of all of the three following components:

• A decrease in 6MWD of at least 15% from baseline that should be confirmed by

two 6-minute walk tests, performed on different days, within 2 weeks

AND

• Worsening of PAH symptoms (1)

AND

• Need for new treatment(s) for PAH (2)

1 Worsening of PAH symptoms must include at least one of the following:

* WHO functional class increased, or no change in patients in WHO class IV at baseline

* Appearance or worsening of signs/symptoms of right heart failure that did not respond to oral diuretic therapy

2 New treatments for PAH are:

* oral or inhaled prostanoids (e.g., iloprost)

* oral phosphodiesterase inhibitors (e.g., sildenafil)

* endothelin receptor antagonists (e.g., bosentan, ambrisentan, sitaxsentan) only after discontinuation of the study drug

* intravenous diuretics

Secondary outcome

Secondary endpoints

These will be analyzed in the following sequence:

1. Change from baseline to Month 6 in 6MWD

2. Change from baseline to Month 6 in modified WHO functional class

3. Time to death due to PAH or hospitalization for PAH up to EOT

4. Time to death of all causes up to EOT

Exploratory endpoints

• Time to death of all causes up to EOS

• Change from baseline to all scheduled time points in 6MWD

• Change from baseline to all scheduled time points in modified WHO functional

class

• Change from baseline to all scheduled time points in Borg dyspnea index

• Achievement and/or maintenance of a 6MWD * 380 meters at all scheduled time

points

• Change from baseline to Month 6 in N-terminal pro-B type natriuretic peptide

(NT-pro-BNP)

• Change from baseline to Month 6 and to EOT in Quality of Life assessed by the

SF-36 questionnaire

Study description

Background summary

The medication that is tested in this research is called ACT-064992. It is a new, oraly active, dual endothelin receptor antagonist. Endothelin is produced in increased amounts in patients with pulmonary arterial hypertension. It is one of the most potent vasoconstrictors. By blocking the action of endothelin, ACT-064992 may reduce the blood pressure in the lung and improve activity level and wellbeing.
The study medication, ACT-064992, belongs to the same class of drugs as bosentan (Tracleer*), the first endothelin receptor antagonist drug registered in 2002 for the treatment of pulmonary arterial hypertension.
ACT-064992 is a new, oral active, non-peptide, potent dual ETa and ETb receptor antagonist. It shows dose-dependent efficacy simular to that observed with bosetan (Tracleer) in pre-clinical models of hypertension and PAH, but ten times more potent.

Study objective

Primary objective
• To demonstrate that either dose of ACT-064992 prolongs the time to the first morbidity or mortality event in patients with symptomatic pulmonary arterial hypertension.

Secondary objectives

• To demonstrate that either dose of ACT-064992 improves exercise capacity and WHO functional class, and prolongs the time to death or hospitalization for PAH in patients with symptomatic pulmonary arterial hypertension.
• To evaluate the safety and tolerability of ACT-064992 in patients with symptomatic pulmonary arterial hypertension.

Study design

Multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, Phase III study.

Intervention

ACT-064992 tablet in a dosis of 3 or 10 mg, once daily orally or placebo. Randomisation takes place in a 1:1:1 ratio ACT-064992 3 mg : ACT-064992 10 mg : placebo.

Study burden and risks

At screening there will be a standard physical examination, a complete laboratory tests. Also an ECG will be done. Monthly messuremens of liver functionswill be done. For women of child baring potential a pregnacy test will be done. After 6 months a right heart catheterization will be performed. On visit 1, month 6 and at the en d of treatment a quality of life questionair will have to be completed. The ECG will be repeated on month 6 visit and at the end of treatment. Complete laboratory assessment will be done on month 3 and further every 6 months.

Most right and left catheterisations are performed without any complications. Only rarely adverse events occur, like heamatoma at the place of catheter entry, or deviations of the hartritme. Real complications like clumping of blood in the bloodstream. There is also a risk of bruises due to venapunctions. Adverse events of ACT-064992 as recorded in the investigator brochure version 6, August 2009, pages 77 - 103 (also see E9).

The conduction of this trial can be justified because Pulmonary Arterial Hypertension is a serious disease which can not be cured and might lead to death within a few years. An accurate monitoring with a quick intervention c.q. medication adjustment is the general guideline within this group of patients. In this trial also will be evaluated what the effect of ACT-064992 is on the morbidity and mortality in this group of patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed informed consent prior to initiation of any study mandated procedure.
2. Patients with symptomatic pulmonary arterial hypertension (PAH) in modified WHO functional class II to IV.
3. Patients with the following types of PAH belonging to groups 1.1 to 1.3 of the Venice classification:
a. Idiopathic (IPAH);
b. Familial (FPAH); or
c. Related to:
i. Collagen vascular disease;
ii. Simple, congenital systemic-to-pulmonary shunts at least 1 year post surgical repair;
iii. HIV infection; or
iv. Drugs and toxins.

4. PAH diagnosis confirmed by hemodynamic evaluation performed prior to randomization and showing all of the following:
a. Mean pulmonary artery pressure (mPAP) > 25 mmHg at rest;
b. Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) <= 15 mmHg; and
c. Pulmonary vascular resistance (PVR) at rest >= 320 dyn-sec/cm5.
* For patients who participate in the pharmacokinetic/ pharmacodynamic substudy, hemodynamic evaluation must have been performed within 3 months prior to randomization.
* For all other patients, hemodynamic evaluation must have been performed within 1 year prior to randomization.
5. 6-minute walk distance (6MWD) >= 50 m.
6. Men or women >= 12 years of age (women of childbearing potential must have a negative pre-treatment serum pregnancy test and must use a reliable method of contraception).

Exclusion criteria

1. PAH associated with portal hypertension, thyroid disorders, glycogen storage disease, Gaucher**s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders or splenectomy.
2. PAH associated with non corrected simple congenital systemic-to-pulmonary shunts, and combined and complex systemic-to-pulmonary shunts, corrected or non corrected.
3. PAH associated with significant venous or capillary involvement (PCWP > 15 mmHg), known pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis.
4. Persistent pulmonary hypertension of the newborn.
5. Pulmonary Hypertension belonging to groups 2 to 5 of the Venice classification.
6. Moderate to severe obstructive lung disease: forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) < 70% and FEV1 < 65% of predicted value after bronchodilator administration.
7. Moderate to severe restrictive lung disease: total lung capacity (TLC) < 60% of predicted value.
8. Moderate to severe hepatic impairment, i.e., Child-Pugh Class B or C.
9. Estimated creatinine clearance < 30 mL/min
10. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal.
11. Hemoglobin < 75% of the lower limit of the normal range.
12. Systolic blood pressure < 100 mmHg.
13. Acute or chronic physical impairment (other than dyspnea), limiting the ability to comply with study requirements.
14. Pregnant or breast-feeding.
15. Known concomitant life-threatening disease with a life expectancy < 12 months.
16. Body weight < 40 kg.
17. Any condition that prevents compliance with the protocol or adherence to therapy.
18. Recently started (< 8 weeks prior to randomization) or planned cardio-pulmonary rehabilitation program based on exercise.
19. Treatment with endothelin receptor antagonists (ERAs) within 3 months prior to

randomization.
20. Systemic treatment within 4 weeks prior to randomization with cyclosporine A or tacrolimus, everolimus, sirolimus (calcineurin or mTOR inhibitors).
21. Treatment with CYP3A inducers within 4 weeks prior to randomization.
22. Known hypersensitivity to drugs of the same class as the study drug, or any of their excipients.
23. Planned treatment, or treatment, with another investigational drug within 1 month prior to randomization.

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):	20-10-2008
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine

Ethics review

Approved WMO

Date:	26-03-2008

Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-07-2008
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-09-2008
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-10-2008
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-12-2008
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-03-2009
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-06-2009
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-08-2009
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	11-11-2009
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-01-2010
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-10-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-11-2011
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	EUCTR2007-002440-14-NL
CCMO	NL20580.100.08