A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension

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Primary objective* To demonstrate the effect of ACT-293987 on time to first morbidity and mortality (MM) event in patients with pulmonary arterial hypertension (PAH).Secondary objective * To evaluate the effect of ACT-293987 on exercise capacity and...

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

Summary

ID

NL-OMON39263

Source
ToetsingOnline

Brief title
GRIPHON (Prostacyclin (PGI2) Receptor agonist In PAH)

Condition

- Pulmonary vascular disorders

Synonym
Pulmonary arterial hypertension; hypertension in lung arteries

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Prostacyclin Receptor agonist, Pulmonary arterial Hypertension

Outcome measures

Primary outcome

Primary endpoint

Time to first CEC-confirmed morbidity and mortality (MM) event, up to 7 days

after last study drug intake defined as:

* Death (all-cause mortality)

or

* Hospitalization for worsening of PAH

or

* Worsening of PAH resulting in need for lung transplantation or balloon atrial

septostomy

or

* Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to

worsening of PAH

or

* Disease progression (patients in modified NYHA/WHO functional class II-III at

baseline) confirmed by :

* decrease in 6MWD from Baseline (* 15%, confirmed by two tests on different

days within 2 weeks) and

* worsening of NYHA/WHO functional class

or

* Disease progression (patients in modified NYHA/WHO functional class III-IV at baseline) confirmed by :

* decrease in 6MWD from Baseline (* 15%, confirmed by 2 tests on different days within 2 weeks) and

* need for additional PAH specific therapy.

MM events will be adjudicated in a blinded fashion by an independent Critical Event Committee.

Secondary outcome

Secondary endpoints

* Change from baseline to Week 26 in 6MWD measured at trough

* Absence of worsening from Baseline to Week 26 in modified NYHA/WHO functional class

* Change from Baseline to Week 26 in Borg dyspnea index

* Time to death up to Study Closure

* Change from Baseline to Week 26 in the sub-scale *Breathlessness* of the *Symptoms* score in the CAMPHOR questionnaire (at selected centers) (not in the Netherlands)

* Change from Baseline to Week 26 in the *Symptoms* score of the CAMPHOR questionnaire (at selected centers) (not in the Netherlands)

Study description

Background summary

The medication that is tested in this research is called ACT-293987. It is a non-prostanoid IP receptor agonist. It is much more specific and more potent in the activation of the human IP receptor then the currently available IP receptor agonists.
Patients with PAH have been shown to have deficiency of prostacyclin and of PGI2 synthase causing an imbalance in prostacyclin (PGI2) and thromboxane A2 (TXA2), it's physiological antagonist. These findings led to the rationale that targeting the PGI2 pathway with IP receptor agonists could be benificial. Prostacyclin (epoprostenol) and analogs like treprostinil (intravenous, subcutaneous and inhaled) and iloprost (inhaled) have already been approved for PHA. An orally available medicinal product, such as ACT-293987, can provide a significant contribution in the treatment options for these patients.

Study objective

Primary objective
* To demonstrate the effect of ACT-293987 on time to first morbidity and mortality (MM) event in patients with pulmonary arterial hypertension (PAH).

Secondary objective
* To evaluate the effect of ACT-293987 on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH.
* To evaluate the safety and tolerability of ACT-293987 in patients with PAH.

Study design

Multicentre, double-blind, randomised, placebo-controlled Phase 3 study.

Intervention

Patients will receive an ACT-293987 tablet or placebo twice daily, in the morning and in the evening. At weekly intervals (scheduled phone calls or visits), patients will be up-titrated in increments of 200 µg b.i.d. until reaching the individual maximum tolerated dose (MTD) within the dose range of up to maximally 1600 *g b.i.d.
If the investigator identifies a tolerability concern for a patient, the patient's dose will be reduced to the previous dose level.
At Week 12 (scheduled phone call), the MTD for each patient should be finally determined and this dose must then be kept unchanged for the last 14 weeks (from Week 12 on) until the Week 26 (Visit 5) assessment of the primary endpoint, change in 6MWD.

Randomisation takes place in a 1:1 ratio ACT-293987:placebo.

Study burden and risks

At screening and at baseline there will be a standard physical examination and a complete laboratory tests. For women of child baring potential a pregnacy test will be done.
At baseline an ECG will be done. The ECG and complete laboratory tests will be repeated on week 4, week 8, week 16, month 6, further every 6 months and also at the end of the study. The risks to subjects associated with participation in the study are described in E9.

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.

Prostacyclin and analogs have already been approved for PHA. However, the administration routes are not always convenient. Subcutaneous, intravenous and inhaled administrations have injection site pain and reaction, local pain and 6-9 times daily administration as disadvantage. An orally available medicinal product, such as ACT-293987, can provide a significant contribution in the treatment options for these 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

- Signed informed consent prior to initiation of any study-mandated procedure.
- Male and female patients aged from 18 years to 75 years inclusive with symptomatic PAH.
- Documented hemodynamic diagnosis of PAH.

Exclusion criteria

- Patients who have received prostacyclin (epoprostenol) or prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) within 1 month before Baseline Visit, or are scheduled to receive any of these compounds during the trial.
- Patients with moderate or severe obstructive lung disease.
- Patients with moderate or severe restrictive lung disease.
- Patients with moderate or severe hepatic impairment (Child-Pugh B and C).
- Patients with documented left ventricular dysfunction.
- Patients with severe renal insufficiency.
- Patients with BMI <18.5 Kg/m2.

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):	27-04-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Selexipag
Generic name:	-

Ethics review

Approved WMO Date:	04-06-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2011

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2009-014490-41-NL
ClinicalTrials.gov	NCT01106014
CCMO	NL30641.029.10