Prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension

Published: 20-02-2014
Last updated: 20-04-2024

Primary objective* To evaluate the effect of macitentan 10 mg on pulmonary vascular resistance (PVR) at rest in comparison with placebo in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).Secondary objectives* To...

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

Summary

ID

NL-OMON41516

Source
ToetsingOnline

Brief title
MERIT-1:

Condition

- Pulmonary vascular disorders
- Embolism and thrombosis

Synonym

PAH high blood pressure in the lungs

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Inoperable chronic thromboembolic pulmonary hypertension, Macitentan

Outcome measures

Primary outcome

Efficacy

Primary endpoint

* PVR at rest at Week 16 expressed as percent of baseline PVR at rest.

Secondary endpoints

* Change from baseline to Week 24 in exercise capacity, as measured by the 6MWD.

* Change from baseline to Week 24 in Borg dyspnea index collected at the end of

the 6MWT.

* Proportion of subjects with worsening in WHO FC from baseline to Week 24.

Additional efficacy endpoints are described in the protocol.

For the efficacy endpoints, the baseline value is the last valid assessment

obtained prior to randomization.

Tolerability and safety

* Treatment-emergent AEs up to 30 days after study drug discontinuation.

* AEs leading to premature discontinuation of study drug.

* Treatment-emergent SAEs up to 30 days after study drug discontinuation.

* Treatment-emergent marked laboratory abnormalities up to 30 days after study drug discontinuation.

* Change in laboratory variables from baseline to all assessed timepoints during the study.

* Change in vital signs (arterial blood pressure, heart rate) and body weight from baseline to all assessed timepoints during the study.

Except when otherwise specified, the baseline value is the last valid assessment obtained prior to randomization.

Pharmacokinetic/pharmacodynamic endpoints

Pharmacokinetic (PK) endpoints

* Trough concentrations of macitentan and its metabolite ACT-132577 in plasma at Week 16 and Week 24, or at EOT in case of premature study drug discontinuation.

Secondary outcome

Secondary endpoints

* Change from baseline to Week 24 in exercise capacity, as measured by the 6MWD.

* Change from baseline to Week 24 in Borg dyspnea index collected at the end of the 6MWT.

* Proportion of subjects with worsening in WHO FC from baseline to Week 24.

Additional efficacy endpoints are described in the protocol.

For the efficacy endpoints, the baseline value is the last valid assessment

obtained prior to randomization.

Study description

Background summary

Chronic thromboembolic pulmonary hypertension (CTEPH), one of the leading causes of severe pulmonary hypertension (PH), develops from the obstruction of pulmonary artery branches following episodes of pulmonary embolism (PE) with incomplete thrombus resolution, formation of fibrosis and remodeling of pulmonary blood vessels. Consequently, pulmonary vascular resistance (PVR) is increased, leading to PH and progressive right heart failure [Jenkins 2012]. CTEPH belongs to the WHO Group 4 [Simonneau 2009].

Pulmonary endarterectomy (PEA) is the gold standard treatment for CTEPH and represents a potentially curative option in eligible patients [Jamieson 2003]. However, many patients with CTEPH are considered non-operable due to predominantly distal thromboembolic pathology, or concomitant small-vessel arteriopathy. Therefore, there is a high need for medical treatments for CTEPH patients who are inoperable.

Histopathologic studies of vascular changes in CTEPH have identified vascular lesions similar to those seen in idiopathic PAH (iPAH) [Galiè 2006]. There is also evidence that in particular CTEPH subjects with a predominantly distal, PAH-like arteriopathy might benefit from vasodilating pharmacotherapy.[Jaïs 2008].

As in PAH, ET-mediated vascular remodeling has been demonstrated in animal models of CTEPH, and increased ET levels and ETB receptor expression have been observed in CTEPH patients [Jaïs 2008].
For these reasons, ERA appears to be a potential treatment option for inoperable CTEPH

Macitentan (ACT-064992) is an orally active, non-peptide, potent dual endothelin (ET) ETA and ETB receptor antagonist (ERA) in clinical development. Endothelin receptor antagonists are being developed for a variety of diseases associated with the deleterious effects of ET, particularly in the pulmonary and cardiovascular fields.

This study aims to investigate the effect in the CTEPH population of macitentan, an ERA that demonstrated higher potency than bosentan in nonclinical in vivo studies [Macitentan IB].

Study objective

Primary objective
* To evaluate the effect of macitentan 10 mg on pulmonary vascular resistance (PVR) at rest in comparison with placebo in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

Secondary objectives
* To evaluate the effects of macitentan 10 mg in comparison with placebo on:
* Exercise capacity
* Dyspnea (assessed by the Borg dyspnea index)
* WHO functional class (FC)
* To evaluate the safety and tolerability of macitentan 10 mg in this subject population.

Study design

This study is designed as a prospective, randomized, placebo controlled, double-blind, multi-center, parallel-group, Phase 2 study.

Subjects will receive macitentan or placebo for 24 weeks. Previous experience with ERAs, including bosentan, has shown that a duration of 16 weeks is sufficient to observe significant placebo-adjusted treatment effects on hemodynamic variables [Galiè 2006]. However exercise capacity increases gradually in this population, and does not immediately follow the hemodynamic improvement. Therefore, a treatment duration of 24 weeks has been chosen for this study.

In studies involving hemodynamics and exercise capacity, measurement variability and placebo effect are of sufficient magnitude to justify the inclusion of a placebo control group [Wright 2009]. A placebo-controlled study is considered ethically acceptable due to the eligibility criteria restricting enrollment to stable CTEPH subjects and the duration of treatment which is relatively short (i.e., 24 weeks).

Intervention

Study drugs include macitentan in the dosage of 10mg or placebo

Study burden and risks

Assessments performed at screening are:
Physical examination (including vital signs, weight, height)
Right heart catheterization (if not performed within 8 weeks prior to screening visit)
Pulmonary function test (if not performed within 1 year prior to screening visit)
Determination of WHO functional class

Ventilation/perfusion scan (if not performed within 1 year prior to screening)
At least one of the following tests ((if not performed within 1 year prior to screening)
- Computed Tomography Pulmonary Angiogram
- Magnetic resonance angiography
- Pulmonary Angiography
6 minute walk test, borg dyspnea index evaluation, heart rate (2 in total)
PAH-Sympact questionnaire (to be completed at home by the patient)
Complete laboratory tests (for which blood is drawn from the patient)

Physical examinations, 6mwt/borg dyspnea/HR, complete laboratory test and determination of WHO class are repeated at each visit, RHC at visit 4,
PAH-sympact questionnaire at visit 3 and visit 4,
The EQ-5D questionnaire needs to be completed at visit 2,3,4 and 5
Blood for biomarkertest is drawn at visit 2,3,4 and 5
Blood for PK sampling is drawn at visit 4 and 5.

Adverse events of macitentan are listed in the Investigator*s Brochure. For possible complications regarding the heart catheterization please refer to E9 of this ABR form.

The conduct of this trial can be justified as 10-50% of the CTEPH patients are non-operable (Pulmonary endarterectomy is the standard therapy) due to predominantly distal thromboembolic pathology, or concomitant small-vessel arteriopathy. Therefore, there is a high need for medical treatments for CTEPH patients who are inoperable.

Contacts

Public
Actelion Registration Ltd.

Boulevard de la Madeleine 21
Paris 75001
FR
Scientific
Actelion Registration Ltd.

Boulevard de la Madeleine 21
Paris 75001
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female * 18 and * 80 years of age.;- Subject with CTEPH (WHO Group 4) judged as inoperable due to the localization of the obstruction being surgically inaccessible (i.e., distal disease).

Exclusion criteria

- Previous pulmonary endarterectomy.
- Recurrent thromboembolism despite sufficient oral anticoagulants.
- Symptomatic acute pulmonary embolism in the 6-month period prior to randomization.
- Known moderate-to-severe restrictive lung disease (i.e., TLC < 60% of predicted value) or obstructive lung disease (i.e., FEV1 < 70% of predicted, with FEV1/FVC < 65%) or known significant chronic lung disease diagnosed by chest imaging (e.g., interstitial lung disease, emphysema).
- Acute or chronic conditions (other than dyspnea) that limit the ability to comply with study requirements in the 3-month period prior to Screening visit or during the Screening period.

Study design

Design

Study phase:	2
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):	20-08-2014
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opsumit
Generic name:	Macitentan

Ethics review

Approved WMO Date:	20-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2016
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
Other	clinicaltrials.gov (NCT02021292)and CCMO register
EudraCT	EUCTR2013-002950-56-NL
CCMO	NL46965.029.14