AMB115811: A randomised, multicentre, double-blind, placebo-controlled study of ambrisentan in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH)

Published: 14-08-2013
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Primary: to assess the efficacy of ambrisentan 5mg after treatment period of 16 weeks, in subjects with inoperable CTEPH. Secondary: safety and tolerability.

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

Summary

ID

NL-OMON40399

Source
ToetsingOnline

Brief title
AMB115811

Condition

- Pulmonary vascular disorders

Synonym
chronic thromboembolic pulmonary hypertension, CTEPH

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline BV
Source(s) of monetary or material Support: GlaxoSmithKline BV

Intervention

Keyword: ambrisentan, hypertension, pulmonary, thromboembolic

Outcome measures

Primary outcome

Change from baseline in 6 min walk test measured at week 16.

Secondary outcome

Adverse events, PVR, WHO functional class, Borg CR10 scale, clinical worsening

of CTEPH, other haemodynamics, NT-proBNP, SF-36 questionnaire.

Study description

Background summary

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition characterized by thrombus organization, stenosis of pulmonary artery, and subsequent vascular remodeling in small unobstructed vessels, resulting in increased pulmonary vascular resistance, progressive pulmonary hypertension (PH) and right heart failure. CTEPH is associated with considerable morbidity and mortality.
The preferred treatment for CTEPH is surgical disobliteration of the arteries by pulmonary endarterectomy. The perioperative mortality is 5 to 10%. There are significant improvements in hemodynamics. However for some patients surgery is not an option. Management of these patients was previously supportive. Disease-modifying therapies used in other forms of pulmonary arterial hypertension have been utilized. There are no licensed treatments for CTEPH. Ambrisentan is a selective endotheline receptor antagonist licensed for the treatment of WHO FC II and III PH. Given that the histopathologic changes seen in CTEPH, the evidence that endotheline-1 levels are raised, and the clinical evidence (mainly uncontrolled) that a number of licensed PH treatments show efficacy in CTEPH, it is hypothesised that ambrisentan may provide benefit to patients with inoperable CTEPH.

Study objective

Primary: to assess the efficacy of ambrisentan 5mg after treatment period of 16 weeks, in subjects with inoperable CTEPH.
Secondary: safety and tolerability.

Study design

Phase III, randomised, double-blind placebo controlled parallel group study.
Randomization (1:1) to
* ambrisentan 5 mg daily
* placebo.
160 subjects.
16 weeks of therapy. Following the End of Study visit all subjects will have the option of entering a long-term Open Label Extension (AMB116457) at the end of the Double-Blind treatment phase, until product is licensed and commercially available for CTEPH.
Independent Data Monitoring Committee.

Intervention

Treatment with ambrisentan or placebo.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: 7 visits in 24 weeks.
Blood draws every visit (5-10 ml/occasion). Optional pharmacogenetic research (6 ml blood). Urine test 3x. Pregnancy test every visit.
Physical examination 3x, ECG 2x, 6 minute walk test every visit, echocardiography 1x, right heart catheterization 2x, oximetry every visit, SF-36 questionnaire 2x.

Contacts

Public
GlaxoSmithKline BV

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Age 18-80 year.
* Inoperable CTEPH (see protocol page 19 for details).
* mPAP > 25 mmHg, PVR > 400 dynes.sec/cm5 and PCWP or LVEDP < 15 mmHg.
* Distance during 6 minutes walk test 150-475 meters.
* WHO class II or III.
* SaO2 at least 92% (pulse oximetry).
* Anticoagulation for a minimum of 3 months.
* Females of childbearing potential: 2 reliable methods of contraception.

Exclusion criteria

* Previous PAH therapy (PDE5i, ERA, prostanoid (more than 7 days)) in the last 12 weeks.
* Any previous ERA treatment discontinued due to tolerance issues other than those associated with liver function abnormalities.
* Previous endarteriectomy or balloon pulmonary angioplasty.
* Intravenous inotropes in the last 2 weeks.
* Calcium Channel Blockers or statins with a dose change in the last 4 weeks.
* Enrolled in an exercise training program for cardiopulmonary rehabilitation in the last 12 weeks or plans to enrol during the first 16 weeks of the study (see protocol page 21 for details).
* BP > 180/110 mmHg or < 90/50 mmHg.
* Acute MI within the last 90 days.
* Clinically significant aortic or mitral valve disease; pericardial constriction; restrictive or

congestive cardiomyopathy; life-threatening cardiac arrhythmias; significant left ventricular dysfunction; left ventricular outflow obstruction; symptomatic coronary artery disease; autonomic hypotension; fluid depletion.
* FEV1<70% of predicted.
* MBI *35.
* General exclusion criteria, see protocol page 22.
* Pregnancy or breastfeeding

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):	17-03-2014
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Volibris
Generic name:	ambrisentan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	14-08-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2015
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	EUCTR2012-001646-18-NL

Register	ID
CCMO	NL45327.029.13
Other	www.clinicaltrials.gov; registratienummer n.n.b.