AMBITION: A Randomised, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension

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

Summary

ID

NL-OMON39521

Source
ToetsingOnline

Brief title
AMBITION

Condition

- Pulmonary vascular disorders

Synonym
Hypertension, Pulmonary, Pulmonary Arterial Hypertension

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ambrisentan, Combination, Pulmonary Arterial Hypertension, Tadalafil

Outcome measures

Primary outcome

Time to first clinical failure of treatment.

Secondary outcome

Exersice tolerance, NT proBNP, NYHA classification, Borg dyspnoe-index, adverse

events.

Study description

Background summary

Pulmonary arterial hypertension (PAH) is a devastating, life threatening disease. A number of treatments are available but no single drug has been demonstrated to be consistently effective in treating all patients with PAH. Combining medicines with different mechanisms of action is an evolving strategy for the treatment of PAH. This approach is supported by data from several exploratory studies in PAH demonstrating the synergistic benefits of combining two or more drugs.
Ambrisentan (5 and 10 mg once daily) is an ETA-selective ERA that is approved by the FDA and EMA for the treatment of PAH (iPAH and PAH-CTD) in patients with WHO class II or III symptoms.
Tadalafil (40 mg once daily) is a PDE-5 inhibitor approved in numerous countries for the treatment of PAH (iPAH and PAH -CTD) in patients with WHO class II and III symptoms.
Because ambrisentan and tadalafil are both orally administered once a day, have different mechanisms of action targeting different intracellular pathways, and have not demonstrated any clinically relevant pharmacokinetic concerns when coadministered, an ambrisentan/tadalafil combination therapy is a rational treatment strategy for patients with PAH.
All of the larger clinical studies completed to date have evaluated combination

therapy as an add-on approach: the addition of a second PAH therapy to a subject*s monotherapy regimen. It is unknown if PAH patients may have greater improvements for sustained periods of time if combination PAH treatment is initiated as first-line therapy, rather than delaying the addition of the second therapy until the PAH status of the patient has reached a plateau or subsequently deteriorated while receiving monotherapy. The primary objective of this study is to compare the difference between two treatment strategies; first-line combination therapy (ambrisentan and tadalafil) versus first-line monotherapy (ambrisentan or tadalafil) in subjects with PAH. This will be assessed by time to the first clinical failure event.

Study objective

The primary objective of this study is to compare the two treatment strategies; first-line combination therapy (ambrisentan and tadalafil) versus first-line monotherapy (ambrisentan or tadalafil) in subjects with PAH. This will be assessed by time to the first clinical failure event.
The secondary objectives of this study are to compare the change in other clinical measures of PAH after initiating first-line combination therapy or first-line monotherapy, in subjects with PAH.
The safety and tolerability of first-line combination therapy will be compared to first-line monotherapy.
In addition, the effect of ambrisentan on exercise capacity at both peak and trough plasma concentrations will be assessed in subjects with pulmonary arterial hypertension (PAH).

Study design

Multicenter randomized double blinddouble dummy parallel group phase IV study.
Randomization (2:1:1):
1. First line combination therapy. Start with 5 mg ambrisentan and 20 mg tadalafil daily, if well tolerated increase to resp. 10 mg daily after 8 weeks and 40 mg after 4 weeks.
2. Ambrisentan monotherapy. Start with 5 mg ambrisentan fil daily, if well tolerated increase to 10 mg daily after 8 weeks .
3. Tadalafil monotherapy. Start with 20 mg tadalafil daily, if well tolerated increase to 40 mg daily after 4 weeks.
Additional randomization (1:1) for peak or trough measurements.
At least 24 weeks of treatment.
Stratification for aetiology of PAH.
Event-driven study. total study duration estimated at 3,5 years (82 events, first clinical failure). Estimated median duration per patient 2 years plus 3 months.
Approx. 614 patients.
Independent data safety monitoring board.

Intervention

Treatment with ambrisentan and/or tadalafil.

Study burden and risks

Risk: Adverse events of (combination of) study medication.
Burden: First 6 visits every 4-8 weeks and thereafter every 12 weeks. Duration 2-3 h. Final visit 4 weeks after end of treatment. Telephone call 4 weeks therafter.
Blood draw during every visit (approx. 10-55 ml/visit). Optional farmacogenetic test (10 ml of blood).
In addition: Physical examination 3x, ECG 3x, 6 min. walk test every visit, lungfunction test 1x, oxymetry 1x, pregnancy test every visit , SF-36 en Camphor questionnaires almost every visit.
Extra in comparison to regular care : more(especially 1st 6 visits) and longer visits (extra number of visits depend on condition of individual patient), more and more frequent blood tests (idem; per visit 0-40 ml extra), 6 min walk test (every visit), 2 questionnaires (almost every visit).

Contacts

Public
GlaxoSmithKline

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NL
Scientific
GlaxoSmithKline

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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 18-75 year.
* Minimal 40 kg.
* Pulmonary arterial hypertension due to
o idiopathic or heritable PAH
o in combination with connective tissue disease, drugs or toxins, HIV, congenital heart defects repaired greater than 1 year prior to screening, excl. portopulmonary hypertension and PVOD.
* Subjects must not have 3 or more left ventricular disease/dysfunction risk factors (see protocol for details)
* WHO class II or III.
* In case of HIV: stable disease (se protocol for details).
* mPAP at least 25 mmHg and PVR at least 300 dyne*sec/cm5 and PCWP or LVEDP of *15 mmHg if PVR *500 dyne*sec/cm5.
* TLC at least 60% of normal and FEV1 at least 55% of normal. Screening and baseline tests should not vary by greater than 10%.
* Distance during 6 minutes walk test 125-500 meters.
* SaO2 at least 88% (pulse oximetry).
* No trainingprogram in the past 12 weeks.
* Females of childbearing potential: 2 reliable methods of contraception (1 method if a Copper T 380A IUD or LNg 20 IUD inserted).

Exclusion criteria

* Previous PAH therapy (PDE5i, ERA, prostanoid (more than 7 days)) in the last 4 weeks.
* ERA treatment (e.g., bosentan or sitaxentan) or PDE5i treatment (e.g. Sildenafil) at any time and discontinued due to tolerance issues other than those associated with liver function abnormalities.
* Previous discontinuation of ambrisentan or tadalafil for safety or tolerability reasons.
* Intravenous inotropes in the last 2 weeks.
* Treatment with a potent inhibitor or inducer of CYP3A4.
* Calcium Channel Blockers or statins with a dose change in the last 4 weeks.
* Treatment with cyclosporine A (except for diseases of the eye).
* Any condition that was treated with nitrates in the last 12 weeks.
* Severe hepatic impairment (Child-Pugh class C with or without cirrhosis).
* Clinically significant anaemia, bleeding disorders, active peptic ulcer.

* BP more than or equal to 180/110 mmHg or less than or equal to 90/50 mmHg.
* Acute MI within the last 90 days.
* History of angina with nitrate treatment <12 weeks, nitrate use for any other condition <48h
* 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.
* History of NAION.
* Hereditary degenerative retinal disorder (e.g. retinitis pigmentosa).
* Pregnancy or breastfeeding

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):	06-01-2011
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adcirca
Generic name:	tadalafil
Registration:	Yes - NL intended use

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

Ethics review

Approved WMO Date:	02-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-10-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	16-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	31-07-2014
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; registratienummer nnb.
EudraCT	EUCTR2009-011150-17-NL
CCMO	NL32697.029.10