Randomized, double blind, placebo controlled, parallel group, multi-center study to evaluate the hemodynamic effects of Riociguat (BAY 63-2521) as well as safety and kinetics in patients with pulmonary hypertension associated with left ventricular systolic dysfunction

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The primary objective of this study is to : Assess the hemodynamic profile of Riociguat in patients with symptomatic pulmonary hypertension associated with left ventricular systolic dysfunction The secondary objectives of this study are to : -...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON36280

Source
ToetsingOnline

Brief title
LEPHT

Condition

- Heart failures
- Pulmonary vascular disorders

Synonym

Pulmonary hypertension in combination with left heart failure/ increased blood pressure

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer HealthCare AG

Intervention

Keyword: Pulmonary hypertension

Outcome measures

Primary outcome

The primary efficacy variable is the change form baseline of PAPmean at rest

measured by RHC after 16 weeks.

Secondary outcome

E.G.

- Change from baseline in venous oxygen saturation (SvO2) measured by RHC

- Change from baseline in PVR, SVR, TPG and PCWP, all measured by RHC

- Change from baseline in TAPSE, PAPsyst and LVEF, E/A, E/E*, E wave

deceleration time all measured by echocardiography

- Change from Baseline in WHO class

- Change from baseline in 6MWD and in Borg CR 10 scale (measured at the end of

the 6MWD Test)

- Change from baseline in QoL Scores (MLHF, EQ-5D)

- Change from baseline in cardiac biomarkers NT-pro BNP, Troponin T

- Change from baseline in exploratory biomarkers ADMA and osteopontin

For the complete list see section 8.3.2. of the protocol

Study description

Background summary

Mortality in patients with a reduced left ventricular ejection fraction due to ischemic heart disease or dilatative cardiomyopathy is high. If accompanied by pulmonary hypertension (PH) morbidity and mortality rise excessively. While there is a high medical need for a drug unloading left and right ventricle evenly, there is currently no approved drug for this indication (WHO PH Group II). Preliminary trials with Riociguat showed favorable hemodynamic effects in patients with pulmonary hypertension, including patients with left ventricular systolic dysfunction without major safety concerns. Thus, Riociguat is assumed to hold great promise for treatment of patients with pulmonary hypertension in combination with left ventricular systolic dysfunction on top of the standard heart failure therapy.

Study objective

The primary objective of this study is to :
Assess the hemodynamic profile of Riociguat in patients with symptomatic pulmonary hypertension associated with left ventricular systolic dysfunction

The secondary objectives of this study are to :
- Assess safety, tolerability and pharmacokinetic profile of Riociguat in patients with symptomatic pulmonary hypertension associated with left ventricular systolic dysfunction
- To explore doses of Riociguat
- To assess potential endpoints for a phase III trial

Study design

Randomized, double blind, placebo controlled, parallel group, multi-center

Intervention

There will be a 4 treatment arms, all with a 3 times a day (TID) regimen :
* Riociguat up to 2 mg TID (Tit 0.5 * 1.0 * 2.0 mg) (50 patients)
* Riociguat up to 1 mg TID (Tit 0.5 * 1.0 mg) (25 patients)
* Riociguat up to 0.5 mg TID (fixed dose) (25 patients)

* Placebo
TID
(50 patients)

The trial cabn be divided in the flowwing phases:
1. Pre-treatment period of up to 4 weeks
2. Main study phase: 16 weken
a. Titration phase: 8 weeks
b. Treatment phase: 8 weeks
3. Safety Follow Up phase: 30 days

There will be an optional open-label tong-term extension phase after 16 weeks for all patients who tolerated study medication well.

Study burden and risks

Main study; if patients complete the entire trial:
- Max 8 hospitals visits
- Study medication TID
- Possible adverse events of the study medication
- Longfunctiontest (1x, this assay only has to be perfomed if the results of a previous examination are older then 90 days)
- WHO functional class (3x)
- 6 MWD (3x)
- Borg CR 10 Scale (3x)
- RHC (2x)
- Echocardiography (2x)
- CPET (2x)
- Pregnancy test, if applicable (3x)
- Physical examination(4x)
- Blood pressure(11x)
- Hart rate (11x)
- ECG (8x)
- Lab (8x)
- EQ-5D questionnaire(2x)
- MLHF questionnaire (2x)
- Cardiac biomarkers (3x)
- Pharmacokinetics (10x)
- Pharmacogenetics (1x)

Contacts

Public
Bayer

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NL
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* 18 to 80 years of age at the time of informed consent
(The lower age limit may be higher if legally required in participating countries.)
* Male and female subjects with symptomatic PH-sLVD (group 2 / 2.1 of Dana Point Classification and World Health Organization [WHO] class II-IV) due to ischemic heart disease or dilated cardiomyopathy (DCM). Transplant candidates can be included.
(Other groups of pulmonary hypertension, especially CTEPH, must have been ruled out according to accepted diagnostic procedures and guidelines, see section 5.1.2 Exclusion criteria.)
PH-sLVD is defined as:
* LVEF * 40%, diagnosed by echocardiography, radionuclide ventriculography or left heart catheter (LHC) exam within 30 days before randomization, or in the baseline echocardiography (NOTE: the definition of PH-sLVD was changed in amendment 3 see section 13.2.1.2)
* PAPmean * 25 mmHg at rest, measured by right heart catheter (RHC)
* Subjects must be pre treated and individually maximally titrated with optimized CHF therapy according to European Society of Cardiology (ESC) (9), American College of Cardiology/American Heart Association (ACC/AHA) (10) or Japanese Circulation Society (11) guidelines with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor

blockers (ARBs), beta blockers and mineralocorticoid receptor (MR) antagonists as clinically indicated. The dose regimen must have been stable for > 30 days prior to randomization. Diuretic therapy must have been stable for * 1 week before performing baseline RHC.
* RHC results for the definite diagnosis of PH not older than 1 week at Visit 1. RHC must have been performed in the participating centre under standardized conditions (refer to the study specific right heart catheterization manual).
* Left heart catheter results available any time prior to randomization to judge if left-heart disease is caused by ischemic heart disease or dilated cardiomyopathy
* A negative stress test must have been performed < 1 year prior to randomization according to guidelines (stress electrocardiography [ECG], stress echocardiography, stress scintigraphy) to exclude overt or silent ischemia.
* Women are eligible if not of childbearing potential, defined as:
* postmenopausal women (i.e. last menstrual bleeding at least 2 years before randomization)
* women with bilateral tubal ligation
* women with bilateral ovariectomy
* women with hysterectomy
or, if of childbearing potential, women are eligible if
* a serological pregnancy test is negative at the pre study visit, and
* the woman uses a combination of condoms and a safe and highly effective contraception method (hormonal contraception with implants or combined oral contraceptives, certain intrauterine devices) for the duration of the study.
* Subject is able to understand and follow instructions and is able to participate in the study for the entire period
* Written informed consent.

Exclusion criteria

* PH in groups other than group 2.1 according to Dana Point classification (2). In particular, CTEPH must have been ruled out according to accepted diagnostic procedures and guidelines.
* Cardiac decompensation, either with hospitalization or visit to the emergency department, * 30 days prior to randomization
* Resynchronization therapy initiated * 90 days prior to randomization
* Need of intravenous (IV) diuretics * 30 days prior to randomization
* Treatment with IV inotropes or IV vasodilators * 30 days prior to randomization
* Chronic treatment with endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors or prostanoids * 30 days prior to randomization, or with nitrates * 7 days prior to randomization (PDE5 inhibitors * 7 days prior to randomization if indicated for erectile dysfunction)
* Subjects who medically require treatment with drugs that are not in line with the in or exclusion criteria of this study or that are prohibited concomitant medications (see section 6.9) for this study
* Bronchial asthma or chronic obstructive pulmonary disease (COPD) with forced expiratory volume in one second (FEV1) < 60% of predicted
* Restrictive lung disease with total lung capacity (TLC) < 60% of predicted

* Subjects on O2 therapy
* Severe congenital abnormalities of the lungs, thorax or diaphragm
* Clinically relevant hepatic dysfunction indicated by either:
* aspartate aminotransferase (AST) * 3 times the upper limit of normal (ULN)
* Child Pugh stage B and C in cirrhotic patients.
* Severe renal impairment (glomerular filtration rate [GFR] < 30 mL/min calculated by Modification of Diet in Renal Disease [MDRD] formula)
* Uncontrolled arterial hypertension (systolic blood pressure [SBP] > 180 mmHg or diastolic blood pressure [DBP] > 110 mmHg)
* SBP < 100 mmHg at baseline or clinical signs or symptoms of hypotension (Note: Limit changed and additional text added in amendment 3 see section 13.2.1.3)
* Myocardial disease other than ischemic or dilatative, such as infiltrative myocardial disease (i.e. amyloidosis, hypertrophic cardiomyopathy)
* Severe aortic or mitral stenosis, or any such stenosis with indication for surgery
* Coronary artery disease with angina of Canadian Cardiovascular Society (CCS) class III or IV or requiring nitrates, unstable angina, or acute myocardial infarction less than 90 days prior to randomization
* Reperfusion procedure (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) less than 90 days prior to randomization, or less than 3 weeks in case of a negative stress test effect after PCI
* Stroke with persistent neurological deficit or known hemodynamically relevant symptomatic carotid artery stenosis
* Subjects positive for human immunodeficiency virus (HIV)
* Resting heart rate (HR) while awake of < 50 beats per minute (BPM) or > 105 BPM (in case of atrial fibrillation > 110 BPM)
* Investigational treatment in another clinical trial during the preceding 30 days
* Subjects with a medical disorder, condition, or history thereof that in the opinion of the investigator would impair the subject*s ability to participate or complete the 4 month main study
* Subjects with underlying medical disorders with an anticipated life expectancy below 2 years not due to cardiac conditions (e.g. active cancer disease with localized and/or metastasized tumor mass)
* Subjects with a history of multiple drug allergies
* Subjects with hypersensitivity to the investigational drug or any of the excipients
* Previous assignment to treatment during this study.

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):	12-09-2010
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	Riociguat

Ethics review

Approved WMO Date:	12-02-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2010
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2010
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:	07-07-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2016
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
EudraCT	EUCTR2009-015878-35-NL
ClinicalTrials.gov	NCT01065454
CCMO	NL30714.029.10