A prospective, randomized, international, multicenter, double-arm, controlled, open label study of Riociguat in patients with pulmonary arterial hypertension (PAH) who are on a stable dose of phosphodiesterase-5 inhibitors (PDE-5i) with or without endothelin receptor antagonist (ERA), but not at treatment goal.

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Ethical review	Approved WMO
Status	Completed
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON45410

Source
ToetsingOnline

Brief title
REPLACE

Condition

- Cardiac arrhythmias

Synonym
high blood pressure in the pulmonary arteries, pulmonary arterial hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: farmaceutische industrie (BAYER).

Intervention

Keyword: open label, pulmonary arterial hypertension, randomized, Riociguat

Outcome measures

Primary outcome

The primary efficacy endpoint *satisfactory clinical response* is defined as

the composite endpoint comprising the following components (independent central

adjudication):

* 2 of 3 must be fulfilled

* 6MWD increase by * 10% or * 30 m from baseline to Week 24

* WHO FC I or II at Week 24

* NT-proBNP reduction * 30% from baseline to Week 24 (NT-proBNP Week

24/baseline ratio * 0.7), AND

* No clinical worsening (i.e, death of any cause, hospitalization due to

worsening PAH, disease progression)

Secondary outcome

not applicable

Study description

Background summary

Riociguat (BAY 63-2521) is a direct stimulator of the soluble Guanylate Cyclase (sGC). The randomized, double-blind, placebo-controlled clinical Phase 3 study (PATENT-1) investigated the efficacy and safety of riociguat in patients with pulmonary arterial hypertension (PAH). The study met the primary endpoint (placebo-corrected change from baseline in 6-minute walking distance [6MWD] by 35.8 m) and showed statistically significant improvements in secondary endpoints, including pulmonary vascular resistance, N- terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organization Functional Class (WHO FC), clinical worsening, living with pulmonary hypertension (LPH) questionnaire, and Borg dyspnea score (1).
PAH is a devastating, life-threatening disease that is characterized by rapid progression and a high mortality (2).
Sequential combination therapy has been the most widely used clinical strategy of treatment escalation if the treatment effect reached by oral monotherapy alone is not sufficient (European Society of Cardiology [ESC]/European Respiratory Society [ERS] guidelines 2015) (3). Transition between pulmonary hypertension (PH)-specific drug therapies has not been investigated in controlled studies and treatment response in the individual patient cannot be predicted. Failure of phosphodiesterase-5 inhibitor (PDE-5i) treatment however may indicate impairment of the nitric oxide (NO)-sGC-cyclic guanosine monophosphate (cGMP) pathway (4). In contrast the treatment effect of sGC-stimulation is based on a NO-independent mode of action. Preliminary data from the open-label transition study RESPITE indicate that patients transitioned from PDE-5i to riociguat may benefit based on this principle of pathway optimization.

Study objective

The primary objective is to assess the proportion of patients in each treatment arm with a satisfactory clinical response as defined by a composite primary endpoint at Week 24.

The secondary objective is to demonstrate safety and clinical effect at Week 24 indicated by change in 6-minute walking distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organization Functional Class (WHO FC) and clinical worsening from baseline in each treatment arm.

Study design

Prospective, randomized, international, multicenter, double-arm, controlled, 24-week open-label study.

Patients will be randomized to remain on their current PAH-specific treatment or to replace the PDE-5i treatment with riociguat.
Patients on specific combination therapy with PDE-5i and ERA need to continue taking ERA at a stable dose in both treatment arms.
At Week 24 a composite endpoint of satisfactory clinical response will be assessed.

Intervention

Patients who are not at treatment goal and at intermediate risk according to ERS/ESC guidelines will be randomized in a 1:1 ratio to remain on their current PAH-specific treatment or to replace the PDE-5i treatment with riociguat for 24 weeks.

Patients need to be pretreated with a stable dose of PDE-5i +/- ERA for 6 weeks prior to and at randomization.

Riociguat treatment will be started after a wash-out period of 24 hours with previous sildenafil therapy (daily dose at least 60 mg) and 48 hours after previous tadalafil therapy (daily dose 20 to 40 mg).

Study burden and risks

The treatment duration is 24 weeks for an individual

Most of the undesirable effects of Riociguat are caused by its pharmacological mode of action on smooth muscle cells, mainly the relaxation of blood vessels. The effect of Riociguat on smooth muscle cells may also lead to gastrointestinal (stomach and intestine) symptoms.
The following undesirable effects of the compound have been observed in clinical trials with patients treated for PAH (pulmonary arterial hypertension):
* Very common greater than or equal to 10%: headache, dizziness (feeling light-headed), dyspepsia (indigestion), peripheral edema (swelling of limbs), nausea, diarrhea, and vomiting.
* Common greater than or equal to 1% to less than 10%: hypotension (low blood pressure), anemia (reduction of red blood cells), palpitations (feeling of heart racing), gastrointestinal and abdominal pains, abdominal distension (bloating), , constipation, dysphagia (difficulty swallowing), gastroesophageal reflux (heartburn), gastritis (inflammation in lining of the stomach) and gastroenteritis, nasal congestion (difficulty breathing through your nose), epistaxis (nose bleed), and hemoptysis (coughing up blood).
* Uncommon greater than or equal to 0.1% to less than 1%: pulmonary hemorrhage (bleeding from the lungs). Serious bleedings from the lung * in few cases with fatal outcome (death) * have been observed in clinical trials in patients with PAH treated with Riociguat. In patients with pulmonary hypertension, there is

an increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy (blood thinners). The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with Riociguat, especially in the presence of risk factors, such as recent episodes of serious hemoptysis (coughing up blood) including those managed by bronchial arterial embolization (a procedure used to treat severe hemoptysis).

If the patient have a history or active state of serious hemoptysis / pulmonary hemorrhage or have undergone interventional treatment to stop bleeding from vessels to the lung (Bronchial Arterial Embolization), he/she will not be able to participate in this study.
If during the study bleeding from the lung occurs, the patient must inform the study doctor immediately, he/she will discuss with the patient the potential harm (risk) of further staying on Riociguat in the study, against the potential benefits.
Gastrointestinal motility disorders (such as indigestion, nausea and vomiting), especially of the upper gastrointestinal tract were more frequently seen in Riociguat treated patients and were expected from Riociguat*s mode of action (the way in which the drug interacts and produces a medical effect). The vast majority of patients could continue treatment as side effects were mostly non-serious and treated with medication.
Due to its pharmacological mode of action (the way in which the drug interacts and produces a medical effect), an uncovering of an existing pulmonary veno-occlusive disease (the vein form of primary pulmonary hypertension) is possible. PVOD (pulmonary veno-occlusive disease) is a very rare condition that is difficult to diagnose. It is a rare form of pulmonary hypertension caused by blockage of the small veins in the lungs. As a result, oxygen rich blood cannot pass through the lung and cannot reach the left heart. Because Riociguat improves the blood flow through the lung arteries, Riociguat can cause a weakening of the clinical status of PVOD patients, indicated by pulmonary congestion and subsequent pulmonary edema (i.e. accumulation of water within the lung causing difficult breathing).
Given the severity of the underlying disease this effect may be life-threatening. Clinical symptoms of a PVOD may occur weeks to months after start of treatment with Riociguat. If this occurs administration of Riociguat has to be stopped immediately.

Recently, a study with Riociguat was terminated due to an imbalance in mortality (death) and in serious adverse events in patients with increased pressure in pulmonary circulation associated with scarring of the lungs, of unknown cause (idiopathic interstitial pneumonia). BAYER AG, the Sponsor of the current trial that patient are participating in, has analyzed the available data, which has also been reviewed by independent data monitoring committees and health authorities. It was determined that there is no evidence that this new information has any impact on the benefits or risks to you for the current

trial.

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

Patients who fulfill the following inclusion criteria are eligible to enter the study:
1. Male and female patients aged 18 to 75 years.
2. Patients with symptomatic PAH with a pulmonary vascular resistance (PVR) > 400 dyn*sec*cm-5, mean pulmonary artery pressure * 25 mmHg, and pulmonary capillary wedge pressure (PCWP) * 15 mmHg as assessed by the most recent right heart catheterization (RHC) from medical history prior to screening to confirm the diagnosis. Alternatively, PCWP can be replaced by left ventricular end-diastolic pressure (* 15 mmHg).
* PAH of the following types:
* a. Idiopathic

* b. Hereditary
* c. Drug and toxin induced PAH
* d. Associated with PAH due to:
* Connective tissue disease (CTD)
* Congenital heart disease, but only if the patient underwent surgical repair more than one year before enrolment
* Portal hypertension with liver cirrhosis (Note: patients with clinical relevant hepatic dysfunction are excluded; see exclusions related to disorders in organ function)
3. Patients who are on stable doses of a PDE 5i and ERA combination therapy or on stable PDE 5i monotherapy 6 weeks prior to and at randomization but not at treatment goal (tadalafil 20 to 40 mg once daily or sildenafil at least 60 mg daily dose).
4. WHO FC III at screening and at randomization.
5. 6MWD test between 165 m and 440 m at screening and at randomization.
6. Stable dose of diuretics, if used, for at least 30 days prior to and at randomization.
7. Patients who are able to understand and follow instructions and who are able to participate in the study for the entire study.
8. Women of childbearing potential must agree to use adequate contraception when sexually active. Adequate contraception is defined as any combination of at least 2 effective methods of birth control, of which at least 1 is a physical barrier (e.g. condom with hormonal contraception like implants or combined oral contraceptives, condom with intrauterine devices). This applies beginning with signing of the informed consent form until 30 (+5) days after the last administration of study drug.
9. Patients must have given their written informed consent to participate in the study after having received adequate previous information and prior to any study-specific procedures.

Exclusion criteria

Patients who fulfill any of the exclusion criteria are not eligible to enter the study:
1. Participation in another interventional clinical study within 30 days prior to screening.
2. Previous randomization to treatment during this study (no re-randomization).
3. Previous treatment with riociguat.
4. Pregnant women (i.e., positive serum ß-human-chorionic-gonadotropin test or other signs of pregnancy), or breast feeding women, or women with childbearing potential not using a combination of 2 effective contraception methods (as laid out in inclusion criterion no. 8) throughout the study.
5. Patients with a medical disorder, condition, or history of such that would impair the patient*s ability to participate or complete this study, in the opinion of the investigator.
6. Patients with substance abuse (e.g., alcohol or drug abuse) within the previous 3 months prior to and at randomization.
7. Patients with underlying medical disorders with an anticipated life expectancy below 2 years (e.g., active cancer disease with localized and/or metastasized tumor mass).
8. Patients with a history of severe allergies or multiple drug allergies.
9. Patients with hypersensitivity to the investigational drug or any of the excipients.
10. Patients unable to perform a valid 6MWD test (e.g., orthopedic disease, peripheral artery occlusive disease, which affects the patient*s ability to walk). Note: Patients, who require

walking aids, may be included if in the opinion of the investigator the walking distance is not impaired. Patients with a variance of more than 15% between the screening and the randomization (i.e., baseline) 6MWD test.
11. Participation at a supportive physical training program, defined as a structured exercise and rehabilitation program supervised by a physician and/or a physiotherapist within 12 weeks prior to screening. Participants enrolled in an exercise program for pulmonary rehabilitation > 12 weeks prior to screening may enter the study if they agree to maintain their current level of rehabilitation during the screening and the 24 weeks of the study.
12. Excluded medication/treatment:
a. Patients who are screened for possible participation in the study must not be withdrawn from treatments which are medically required. If such treatments are not in-line with the entry criteria of this study, the patient must not be enrolled. Concomitant use with riociguat of the following specific medications for treatment of PAH is not allowed at any time during the study:
* PDE 5i (e.g., sildenafil, tadalafil or vardenafil) must not be co-administered with riociguat
* Non-specific PDE-inhibitors (e.g., dipyridamole, theophylline)
* NO donors (e.g., nitrates, amyl nitrite)
b. Prostacyclin analogues (PCA) and prostacyclin-receptor agonists (PRA) by any administration route within 30 days prior to and at randomization (except for vasoreactivity testing).
13. Exclusion criteria related to pulmonary disease:
a. All types of PH (including PH-IIP) except subtypes of Dana Point Group I specified in the inclusion criteria.
b. Evidence of clinically significant restrictive or obstructive parenchymal lung diseases in the judgment of the investigator (e.g., based on a clean computed tomography lung scan).
c. Severe congenital abnormalities of the lungs, thorax, and diaphragm.
d. Severe restrictive lung disease (total lung capacity [TLC] < 60%).
e. Moderate obstructive lung disease (forced expiratory volume in one second/forced vital capacity [FEV1/FVC] < 50%).
f. Confirmed obstructive sleep apnea
g. Severe diffusion impairment (diffusing capacity of the lung for carbon monoxide < 30% predicted).
h. History or active state of serious hemoptysis/pulmonary hemorrhage including those managed by bronchial artery embolization.
14. Exclusion criterion related to hypoxia (pulse oximeter at rest):
a. Peripheral capillary oxygen saturation (SpO2) < 88% despite supplemental oxygen therapy (* 4 L/min) at rest.
15. Cardiovascular exclusion criteria:
a. Uncontrolled arterial hypertension (SBP > 180 mmHg and/or diastolic BP > 110 mmHg).
b. SBP < 95 mmHg prior to and at randomization.
c. Resting heart rate in the awake patient < 50 bpm or > 105 bpm.
d. Permanent atrial fibrillation and new onset of atrial fibrillation within the last 3 months prior to screening.
e. Left ventricular systolic dysfunction by echocardiography (left ventricular ejection fraction [LVEF] < 40%, Simpson*s methodology).
f. Hypertrophic obstructive cardiomyopathy.
g. Severe proven or suspected coronary artery disease (patients with Canadian

Cardiovascular Society Angina Classification class 2 to 4, and/or requiring nitrates, and/or acute coronary syndrome, or coronary interventions (PCI, CABG) within the last 3 months prior to and at randomization).
h. Clinical evidence of symptomatic atherosclerotic disease (e.g., peripheral artery disease with reduced walking distance, history of stroke with persistent neurological deficit etc.).
i. History of stroke within 3 months prior to and at randomization.
j. Congenital or acquired valvular or myocardial disease if clinically significant apart from tricuspid valvular insufficiency due to PAH.
k. Three or more of the following left ventricular disease/ dysfunction risk factors:
* Body Mass Index (BMI) * 30
* History of Essential Hypertension
* Diabetes mellitus of any type
* History of significant Coronary Disease
16. Exclusion criteria related to disorders in organ function:
a. Clinical relevant hepatic dysfunction indicated by:
* Bilirubin > 2 times upper limit of normal (ULN), and/or
* Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times ULN
b. Signs of severe hepatic insufficiency (Child Pugh C), and/or
c. Renal insufficiency (glomerular filtration rate < 30 mL/min (calculated based on the Cockcroft formula or Modification of Diet in Renal Disease formula).
17. Other exclusion criteria:
a. Other co-morbidities impairing exercise capacity.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-10-2017

Enrollment:	5
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:	ADEMPAS
Generic name:	RIOCIGUAT
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	REVATIO
Generic name:	Sildenafil
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-12-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2018
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	EUCTR2016-001067-36-NL
CCMO	NL58930.029.16

Study results

Date completed:	29-03-2019
Results posted:	23-12-2020

First publication
23-11-2020