The efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed pulmonary arterial hypertension: A multi-center, double-blind, placebo-controlled, Phase 3b study

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Primary objectiveTo compare the effect on pulmonary vascular resistance (PVR) of an initial triple oral regimen (macitentan, tadalafil, selexipag) versus an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-...

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

Summary

ID

NL-OMON45816

Source
ToetsingOnline

Brief title
Triton study

Condition

- Pulmonary vascular disorders

Synonym
high blood pressure in the arteries of the lungs

Research involving

Human

Sponsors and support

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

Intervention

Keyword: PAH, pulmonary arterial hypertension

Outcome measures

Primary outcome

Primary efficacy endpoint

The primary endpoint is the ratio of Week 26 to baseline PVR.

Secondary outcome

Secondary efficacy endpoints

1. Change in N-terminal pro B-type natriuretic peptide (NT-proBNP) from

baseline to Week 26.

2. Change in 6MWD from baseline to Week 26.

3. Absence of worsening in WHO FC from baseline to Week 26.

4. Change in RHC variables other than PVR (mPAP, cardiac index, total pulmonary

resistance, mean right atrial pressure, venous oxygen saturation) from baseline

to Week 26.

5. Time from randomization to the first disease progression event up to EOMOP +

7 days (adjudicated by the Clinical Events Committee [CEC]), defined as any of

the following:

a. Death (all causes; adjudicated for PAH relationship).

b. Hospitalization for worsening PAH.

c. Initiation of prostacyclin, a prostacyclin analog, or a prostacyclin

receptor agonist for worsening PAH.

d. Clinical worsening defined as a post-baseline decrease in 6MWD by > 15% from

the highest 6MWD obtained at or after screening, accompanied by WHO FC III or

IV (both conditions confirmed at two consecutive post baseline visits separated

by 1*21 days).

Safety endpoints

* Treatment-emergent adverse events (AEs).

* AEs leading to premature discontinuation of any of the 3 study treatments.

* Treatment-emergent serious AEs.

* Treatment-emergent deaths.

* Treatment-emergent marked laboratory abnormalities.

* Change from baseline in laboratory variables.

* Change from baseline in vital signs.

Study description

Background summary

Recent guidelines for the treatment of PAH [Galiè 2013] recommended sequential combination therapy in patients with an inadequate clinical response to initial monotherapy. However, based on the recent results of the AMBITION study [Galiè 2015a], initial dual combination therapy with an ERA and a PDE-5i is emerging as a potential new standard of care in newly diagnosed PAH patients [Galiè 2015b].
To date, only one pilot study has investigated initial triple combination therapy [Sitbon 2014], showing dramatic improvements in all relevant variables such as WHO FC, 6MWD, mPAP, cardiac index, and PVR. Although the study was small (n = 18), non-controlled, and used different drugs than in the present

study (in particular, intravenous epoprostenol as the drug acting on the prostacyclin pathway), it suggests that initial triple therapy in PAH may be beneficial and safe.
With the availability of selexipag, it is possible to investigate a triple oral therapy regimen. Data from the GRIPHON trial suggest that selexipag is efficacious and safe irrespective of whether or not subjects are already receiving other PAH drugs [Selexipag IB, Selexipag IB Amendment]. In fact, the majority of the patient population in GRIPHON was prevalent and thus already being treated with an ERA and/or a PDE-5i at baseline.
The above-mentioned triple therapy data from the GRIPHON trial [Selexipag IB, Selexipag IB Amendment] and the pilot study [Sitbon 2014] provide a rationale for the present study. The purpose is to investigate whether an initial triple oral treatment regimen combining an ERA, a PDE-5i, and selexipag adds significant efficacy benefit while being safe and well tolerated, as compared to an initial dual oral treatment regimen with an ERA and a PDE-5i [Galiè 2015a].
Given the extensive and long-term controlled efficacy and safety data available with all 3 study treatments (including triple combination used in many subjects in the GRIPHON study) and the careful follow-up of subjects mandated by this protocol, the benefit/risk assessment supports the current study.

Study objective

Primary objective
To compare the effect on pulmonary vascular resistance (PVR) of an initial triple oral regimen (macitentan, tadalafil, selexipag) versus an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with pulmonary arterial hypertension (PAH).

Secondary objectives
To compare an initial triple oral regimen (macitentan, tadalafil, selexipag) with an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH, with respect to cardio-pulmonary hemodynamics (other than PVR), exercise capacity, disease severity, disease progression events, safety, and tolerability.

Exploratory objectives
To compare an initial triple oral regimen (macitentan, tadalafil, selexipag) with an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH, with respect to additional disease severity endpoints.

Study design

This is a prospective, multi-center, double-blind, randomized, placebo controlled, parallel group, Phase 3b, efficacy and safety study comparing a

triple oral regimen (macitentan, tadalafil, selexipag) with a dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH.

Intervention

Investigational treatment
* Macitentan, open-label, oral tablet, 10 mg once daily (preferably always in the morning or always in the evening; to be recorded in the electronic Case Report Form [eCRF]).
* Tadalafil, open-label, oral tablet, 20 mg one or two tablets once daily (preferably always in the morning or always in the evening; to be recorded in the eCRF).
* Selexipag oral tablet, 200 µg, one to eight tablets twice daily (in the morning and in the evening).

Comparator treatment
* Macitentan, open-label, oral tablet, 10 mg once daily (preferably always in the morning or always in the evening; to be recorded in the eCRF).
* Tadalafil, open-label, oral tablet, 20 mg one or two tablets once daily (preferably always in the morning or always in the evening; to be recorded in the eCRF).
* Matching placebo to selexipag oral tablet, 200 µg, one to eight tablets twice daily (in the morning and in the evening).

Study burden and risks

There will be several visits done to the clinic or by telephone:
- screening visit
- visit Day 1
- visit or phone call at Day 8
- visit Day 15
- thereafter; monthly visits and blood draws for at least 6 months.
- For women who are able to get pregnant, there will be monthly verficication of blood or urin until 1 month after the last study medication is taken to confirm that she is not pregnant.
- weekly phone calls starting on Day 1 and every week for 7 weeks.
- visit week 12
- visit week 26
- visit month 12, 18, 24, etc. (every 6 months).
- end of main observation period; 6 months after last patient was enrolled.
- end of treatment period; 4 months after the end of main observation period.
-end of study visit or Phone call: 5 months after the end of main observation period.
- unscheduled visits if needed and tests are done as medically required.

Foreseeable risks and discomforts due to study related procedures:
* There is a slight risk of pain or bruising and infection when blood is drawn for laboratory blood tests.
* Right heart catheterization involves placing a thin, flexible tube into a vein in the arm, neck or groin which then follows the blood stream inside the heart into the main lung artery, where it can be used to measure the lung artery pressures. X-ray is used to follow the tube. The procedure is typically more uncomfortable than painful and will usually be done while the subject is awake, because the physician needs his/her cooperation. Right heart catheterization may be associated with side effects. Minor local side effects include bruising or hematoma, swelling and infection. Sometimes subjects may have an irritating sensation in the chest, less frequently this is felt as pain and is usually not harmful. Side effects that are seen rarely include heart rhythm abnormalities, low blood pressure, bleeding, general infection, collapsed lung, or clotting of the blood, sometimes followed by an obstruction of an artery. As with any procedure involving the heart, complications can sometimes, although rarely, be fatal. The study doctor will discuss the risks of the right heart catheterization with the subjects.

Risks Associated with the product:
Macitentan:
* The most common side effects reported to date with macitentan are nasopharyngitis, pharyngitis and other signs and symptoms of inflammation of the throat and nasal passages, bronchitis (inflammation of the airways), headache, low blood pressure, urinary tract infection, influenza (flu) and anemia (low hemoglobin). In order to closely follow your hemoglobin level during treatment with macitentan, your doctor will arrange for regular blood tests. If the results of these tests are abnormal, your doctor may ask you to have your blood retested within 10 days and may consider interrupting or stopping the study medication. Additional testing may also be performed in order to better and further evaluate cases of anemia or low hemoglobin levels.

* Abnormal liver function (elevation of liver enzymes) has been associated with other drugs of the same class of medication (endothelin receptor antagonists), to which macitentan belongs. In order to closely follow your liver function during treatment with macitentan, your doctor will arrange for regular blood tests. If the results of these tests are abnormal, your doctor may decide to stop or interrupt macitentan study medication and will ask you to have your liver values tested at least weekly until liver enzyme values come back to normal. If you notice yellowing of the skin or eyes (jaundice), or if you have fever, vomiting or nausea, stomach pain, dark urine, itching, unusual tiredness, or loss of appetite, contact your study doctor without delay because this may be related to abnormal liver function.

* Other potential side effects that have been associated with this class of medication and may be observed also with macitentan include swelling of the

legs and ankles or other signs of fluid retention. If you notice any swelling of the legs or ankles, an unusual weight increase after you started taking macitentan study medication, or if you experience worsening of your heart failure symptoms (e.g., shortness of breath, etc.), please contact your study doctor without delay.

* Reduced sperm counts have been observed in some men taking a medicine similar to macitentan, an effect which might impair the fertility (ability to father a child).

* Potential side effects associated with macitentan may also include low counts of platelets or of white blood cells.

* Hypersensitivity reactions (e.g. swelling of the face or tongue, rash, itching) have been observed with macitentan.

Tadalafil:
* Very common side effects reported for tadalafil include headache, cold, infection of the upper and lower airways, getting red or hot in the face, nausea, upset stomach, muscle pain, back pain, and pain in extremity.

* Common side effects reported for tadalafil include hypersensitivity reactions, fainting, migraine, blurred vision, feeling that your heart is racing, low blood pressure, nose bleeding, vomiting, flowing back of stomach content in your food pipe, rash, increased uterine bleeding, fluid retention in your face, and chest pain.

* Uncommon side effects reported for tadalafil include seizures, passing memory loss, ringing in the ears, sudden cardiac death, fast heart rate, increased blood pressure, hives, increased sweating, blood in urine, erection that lasts more than 4 hours, bleeding from the penis, and blood in the ejaculate.

* For the following side effects the frequency could not be estimated from the available data: swelling below the surface of the skin (most often around eyes and lips), stroke, decreased or loss of vision in one or both eyes, sudden hearing loss, heartache, irregular beating of your heart, heart attack, Stevens-Johnson-Syndrome (painful blistering of the skin due to an allergic drug reaction), widespread scaling of the skin, and prolonged erection.

Selexipag:
* The most common side effect reported to date with selexipag is headache.

* You may also notice one or more of the following side effects: diarrhea, nausea, pain in the jaw, vomiting, pain in extremity, muscle pain, getting red or hot in the face, joint pain, and skin rash.

* Other less common side effects that you might notice include anemia,

decreased blood pressure, abdominal pain, and decreased appetite.

* Some cases of hyperthyroidism (abnormally increased function of the thyroid gland) have been observed with selexipag. If your doctor deems it medically justified some additional examination may be requested to assess your thyroid function.

Contacts

Public
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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed informed consent prior to any study-mandated procedure.
2. Male or female * 18 and * 75 years of age at screening.
3. Initial PAH diagnosis < 6 months prior to Day 1.
4. RHC performed between Day *28 and Day 1 (RHC data obtained at the study site within

this time frame, but before the study, i.e., before signed informed consent, are acceptable), meeting all the following criteria:
* Mean pulmonary artery pressure (mPAP) * 25 mmHg.
* Pulmonary artery wedge pressure or left ventricular end-diastolic pressure * 15 mmHg.
* PVR * 480 dyn*sec/cm5 (* 6 Wood Units).
* Negative vasoreactivity test mandatory in idiopathic PAH (at this or a previous RHC).
5. Symptomatic PAH belonging to one of the following subgroups:
* Idiopathic.
* Heritable.
* Drug or toxin induced.
* Associated with one of the following:
- Connective tissue disease.
- HIV infection.
- Congenital heart disease with simple systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) * 1 year after surgical repair.
6. 6-minute walk distance (6MWD) * 50 m at screening.
7. Women of childbearing potential must:
* Have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at the Day 1 visit, and
* Agree to perform monthly pregnancy tests up to EOS, and
* Agree to use reliable contraception from screening up to 1 month following discontinuation of the last study treatment. Reliable contraception must be started at least 11 days prior to Day 1.

Exclusion criteria

1. Any PAH-specific drug therapy (e.g., any endothelin receptor antagonist [ERA], phosphodiesterase-5 inhibitor (PDE-5i), soluble guanylate cyclase stimulator, prostacyclin, prostacyclin analog, or prostacyclin receptor agonist) at any time prior to Day 1 (single-dose administration for vasoreactivity testing is permitted; previous iloprost used intermittently for the treatment of digital ulcers or Raynaud*s phenomenon is permitted if stopped > 6 months prior to Day 1).
2. Cardio-pulmonary rehabilitation program based on exercise (planned, or started * 12 weeks prior to Day 1).
3. Body mass index (BMI) > 40 kg/m2 at screening.
4. Presence of three or more of the following risk factors for heart failure with preserved ejection fraction at screening:
* BMI > 30 kg/m2.
* Diabetes mellitus of any type.
* Essential hypertension.
* Coronary artery disease, i.e., any of the following:
- History of stable angina or
- More than 50% stenosis in a coronary artery (by coronary angiography) or
- History of myocardial infarction or
- History of or planned coronary artery bypass grafting and/or coronary artery stenting.

5. Acute myocardial infarction * 12 weeks prior to screening.
6. Stroke * 12 weeks prior to screening.
7. Known permanent atrial fibrillation.
8. Systolic blood pressure < 90 mmHg at screening or Day 1.
9. Ongoing or planned treatment with organic nitrates and/or doxazosin.
10. Presence of one or more of the following signs of relevant lung disease at any time up to screening:
* Diffusing capacity of the lung for carbon monoxide (DLCO) < 40% of predicted (eligible only if no or mild interstitial lung disease on computed tomography).
* Forced vital capacity (FVC) < 60% of predicted.
* Forced expiratory volume in one second (FEV1) < 60% of predicted.
11. Known or suspected pulmonary veno-occlusive disease.
12. Documented severe hepatic impairment (with or without cirrhosis) according to National Cancer Institute organ dysfunction working group criteria, defined as total bilirubin > 3 × upper limit of the normal range (ULN) accompanied by aspartate aminotransferase (AST) > ULN (assessed by central laboratory at screening); and/or Child-Pugh Class C.
13. Serum AST and/or alanine aminotransferase (ALT) > 3 × ULN (assessed by central laboratory at screening).
14. Severe renal impairment (estimated creatinine clearance * 30 mL/min/1.73 m2) assessed by central laboratory at screening.
15. Ongoing or planned dialysis.
16. Hemoglobin < 100 g/L assessed by central laboratory at screening.
17. Known or suspected uncontrolled thyroid disease (hypo- or hyperthyroidism).
18. Loss of vision in one or both eyes because of non-arteritic ischemic optic neuropathy.
19. Treatment with strong inducers of cytochrome P450 3A4 (CYP3A4) (e.g., carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John*s wort) * 28 days prior to Day 1.
20. Treatment with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) * 28 days prior to Day 1.
21. Treatment with another investigational drug (planned, or taken * 12 weeks prior to Day 1).
22. Hypersensitivity to any of the 3 study treatments or any excipient of their formulations (lactose, magnesium stearate, microcrystalline cellulose, hydroxypropyl cellulose, povidone, corn starch, sodium starch glycolate type A, polyvinyl alcohol, polysorbate 80, titanium dioxide, talc, xanthan gum, lecithin from soya, croscarmellose sodium, hypromellose, sodium laurylsulfate, triacetin, iron oxide yellow, iron oxide red, iron oxide black, d-mannitol, propylene glycol, carnauba wax).
23. Pregnancy, breastfeeding, or intention to become pregnant during the study.
24. Concomitant life-threatening disease with a life expectancy < 12 months.
25. Alcohol abuse.
26. Any factor or condition likely to affect protocol compliance of the subject, as judged by the investigator.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-11-2017
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adcirca
Generic name:	Tadalalfil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Selexipag
Product type:	Medicine
Brand name:	Opsumit
Generic name:	Macitentan
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-03-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date: 22-02-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 28-02-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 26-04-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 18-05-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 01-08-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 20-09-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 17-01-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 25-02-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 09-04-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2020
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	EUCTR2015-003438-28-NL
ClinicalTrials.gov	NCT02558231
CCMO	NL54928.029.15

Study results

Date completed:	23-01-2020
Results posted:	16-04-2021

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File