# Bosentan in Exercise Induced Pulmonary Arterial Hypertension in Congenital Heart Disease

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Identify congenital heart disease patients with exercise-induced pulmonary arterial hypertension. Analyze changes in pulmonary arterial pressures at peak exercise in patients with exercise induced pulmonary arterial hypertension before and after…

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Congenital cardiac disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON40031

**Source**
ToetsingOnline

**Brief title**
BICYCLE trial

### Condition

- Congenital cardiac disorders
- Vascular hypertensive disorders

**Synonym**
Exercise induced pulmonary arterial hypertension, increased pulmonary pressure during exercise

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum

**Source(s) of monetary or material Support:** ICIN-KNAW

## Intervention

**Keyword:** Aerobic capacity, Congenital heart disease, Exercise capacity, Pulmonary arterial hypertension

## Outcome measures

### Primary outcome

To determine:

• change in mean pulmonary arterial pressure (mPAP) at peak exercise

o measured by means of transthoracic echocardiography at 3 and 6 months

followup: mPAP = 0.6 x systolic PAP.

o peak exercise is defined as 80% of maximum calculated heart rate: peak

exercise=0.8*(220-age)

### Secondary outcome

To determine:

• Cardiopulmonary exercise capacity (i.e. peak oxygen consumption, VE/VCO2

ratio, O2 pulse)

• Pulmonary hemodynamics (i.e. systolic pulmonary arterial pressure, pulmonary

vascular resistance, pressure-flow relationships during and at peak exercise)

• Right ventricular function (i.e. TAPSE, TEI index, TDI-S, right ventricular

dimensions)

• Laboratory parameters (i.e. NT-pro BNP, troponin T)

• NYHA functional class

• Quality of life (assessed by TAAQOL-CHD, SF-36 and Minnesota CHD-HF

questionnaire)

• Demographics (age, gender, marital status, work, income); assessed by

demographic questionnaire.

# Study description

### Background summary

Pulmonary arterial hypertension (PAH) can be a rapidly progressive disorder and is associated with a high mortality rate, despite medical intervention. With the availability of effective therapy, early disease detection is an important strategic objective to improve treatment outcomes. Resting echocardiography is currently the recommended screening modality for high-risk population groups. However, it is clear that abnormalities in resting hemodynamics (and symptoms) are late sequelae of the pathobiological processes that begin in the distal pulmonary arteries. Exercise stress may unmask early pulmonary vascular dysfunction, however the definition, clinical significance, and natural history of *exercise PAH* remain undefined. However, based on clinical experience and literature the prevalence is estimated at ~ 20%.Treatment with endothelin receptor blockers has shown a beneficial influence on the clinical performance in patients with exercise induced PAH due to systemic sclerosis and primary pulmonary hypertension. Whether endothelin receptor blockers decrease pulmonary pressures and improve clinical outcome in patients with exercise induced pulmonary arterial hypertension due to congenital heart disease is unknown.

### Study objective

Identify congenital heart disease patients with exercise-induced pulmonary arterial hypertension. Analyze changes in pulmonary arterial pressures at peak exercise in patients with exercise induced pulmonary arterial hypertension before and after treatment with bosentan, compared to placebo.

### Study design

Randomized placebo controlled trial with a study period of 26 weeks.

### Intervention

After randomization one group (n=20) receives a 125 mg tablet of Bosentan twice daily for 6 months. The other group (n=20) receives placebo for 6 months.

### Study burden and risks

All investigations, blood analysis excepted, are non-invasive and free of risk.
The burden for the patients mainly consists of the time that is consumed by the investigations, namely: history taking + physical examination (15 min); Quality-of-Life- score (15 min); demographic questionnaire (5min); laboratory tests (electrolytes, creatinine, urea, albumin and neurohormones, troponin T) (5min); 12 lead electrocardiogram (10 min); exercise echocardiography (45 min); cardiovascular exercise testing (30 min).
The trial medication has a potential risk of liver damage, which will be monitored regularly by laboratory testing of liver transaminases.

## 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

In order to be eligible to participate in this study, a subject must meet all of the following

criteria:
- adult (>18 years) and mentally competent
- Open or closed septal defect (ASD I/II, VSD, AVSD)
- Open or closed systemic-to-pulmonary shunt (PDA)
- Negative pregnancy test
- Presence of X-PAH, including one of the following criteria, at peak exercise.
* mPAP > 34 mmHg with CO <= 10 l/min
* mPAP > 40 mmHg with CO <= 15 l/min
* mPAP > 45 mmHg with CO <= 20 l/min
* mPAP > 50 mmHg with CO <= 30 l/min
* PVR (slope pressure/flow plot) of > 2.5 mmHg/l/min during exercise

## Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Incapable of giving informed consent
- Pregnancy or lactation (a pregnancy test is offered to every female patient within fertile age)
- Women of child-bearing age who are sexually active without practising reliable methods of contraception. The use of oral contraceptives only, is not considered reliable.
- Substance abuse (alcohol, medicines, drugs)
- Subjects who are not able to perform cardiopulmonary exercise testing
- Any cardiac operation <6 months before inclusion
- PAH of any aetiology other than the one specified in the inclusion criteria
- Left ventricular ejection fraction < 30%
- Significant impairment of renal function (GFR < 30 ml/min/1.73m2)
- Moderate to severe liver disease: Child Pugh class B or C
- Raised plasma transaminases level > three times upper normal limit
- Arterial hypotension (systolic blood pressure < 85mmHg)
- Anaemia (Hb < 10g/L, or <6.21 mmol/L)
- Significant valvular disease, other than tricuspid or pulmonary regurgitation
- Chronic lung disease or total lung capacity < 80% predicted value
- History of significant pulmonary embolism
- Other relevant diseases (HIV infection, Hep B/C infection)
- Subjects with known intolerance to bosentan or their constituents
- Prohibited medication: any medication listed below which has not been discontinued at least 30 days prior to inclusion
o Unspecified or other significant medication (glybenclamide or immunosuppression)
o PAH therapy (endothelin receptor antagonists, PDE-5 inhibitors, prostanoids)
o Medication which is not compatible with bosentan or interferes with its metabolism (inhibitors or inducers of CYP2C9, CYP3A4) or medication which may interfere with bosentan treatment according to the investigator

# Study design

## Design

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|---|---|
| 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): | 14-06-2013 |
| Enrollment: | 40 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Tracleer |
| Generic name: | Bosentan |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

| | |
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| Date: | 20-03-2013 |
| Application type: | First submission |
| 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 | EUCTR2012-004067-41-NL |
| CCMO | NL42568.018.12 |