# A Prospective, Multicenter Study for the Identification of Biomarker Signatures for early detection of Pulmonary Hypertension (PH)

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Primary Objectives• To identify circulating micro RNA biomarkers associated with pulmonary hypertension in blood samples.• To develop signatures for detecting patients at high risk of pulmonary hypertension to assist in the diagnosis of pulmonary…

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| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Pulmonary vascular disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON55313

**Source**
ToetsingOnline

**Brief title**
NAPUH0001 / CIPHER

### Condition

- Pulmonary vascular disorders

**Synonym**
High blood pressure in lung vessels, Pulmonary hypertension

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Janssen-Cilag

**Source(s) of monetary or material Support:** Actelion Pharmaceuticals LtD (in Nederland vertegenwoordigd door Janssen-Cilag B.V.)

## Intervention

**Keyword:** Biomarker Signatures, Early detection, Phase 0, Pulmonary hypertension

## Outcome measures

### Primary outcome

Identification of potential miRNA biomarker signatures would help in the early diagnosis of PAH. Patients at risk for PAH and CTEPH are especially likely to benefit from earlier diagnosis, as these patients often experience symptoms for years before a diagnosis is made.

Outcome: biomarker sample collection on Day 1

Time schedule of protocol, including follow-up duration: Screening period (max 60 days), Assessments on 1 day, additional assessment visit (if needed) up to 60 days after day 1.

### Secondary outcome

NAP

# Study description

### Background summary

Relevance
PH (5 main groups) is a rare pathophysiological disorder formally defined as a mean resting pulmonary artery pressure (that may involve multiple clinical conditions and can complicate several cardiovascular and respiratory diseases. Because all forms of PH are not diagnosed until the disease is severe, a non-invasive test that helps detect PH and possibly stratifies patients based on risk of PH, allowing for earlier diagnosis and intervention, is regarded as

an unmet need in the diagnosis of PH.
The proposed study is the first phase of Actelion*s development plan for biomarkers, focusing on profiling the expression levels of 100-200 (and up to 600) miRNAs in serum or plasma samples to identify miRNA biomarkers associated with PH

Scientific Rationale for Study Design
Increased or decreased levels of several circulating miRNAs have been shown to be associated with PAH and PH clinical phenotypes (Miao 2018). Increasing evidence suggests that many of these circulating miRNAs play a key role in regulating the expressions of genes that are involved in the physiological and pathological processes of PH and PAH. Some of these circulating miRNAs have been also proposed as the master regulators that coordinate and regulate multiple signaling pathways involved in the pathogenesis of PH and promote PH-associated clinical phenotypes. It is therefore possible that a miRNA biomarker signature could be developed for early detection of PH or differentiating subtypes of PH, eg, PAH and CTEPH.

**Study objective**

Primary Objectives
• To identify circulating micro RNA biomarkers associated with pulmonary hypertension in blood samples.
• To develop signatures for detecting patients at high risk of pulmonary hypertension to assist in the diagnosis of pulmonary hypertension versus non-pulmonary hypertension (as established by right heart catheterization) in patients with atypical shortness of breath.
• To estimate the sensitivity, specificity, positive predictive value, and negative predictive value of the biomarker signatures in identifying patients with pulmonary hypertension by comparing the biomarker signatures to right heart catheterization.
• To compare the sensitivity, specificity, positive predictive value, and negative predictive value of the biomarker signatures with the sensitivity, specificity, positive predictive value, and negative predictive value of transthoracic echocardiogram in identifying patients with pulmonary hypertension documented by right heart catheterization.

Secondary Objectives
• To analyze the performance of the various biomarkers in differentiating groups of pulmonary hypertension; specifically, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension and isolated pre-capillary versus post-capillary pulmonary hypertension.
• To assess the performance of the biomarker signatures in patients with pulmonary hypertension who are receiving pulmonary arterial hypertension specific drug therapies (as determined by their physician in accordance with existing standard of care) versus patients with pulmonary hypertension who are

not receiving any drug therapy, and per class of pulmonary arterial hypertension therapy.

Exploratory Objectives
• To assess the performance of the biomarker signatures for discriminating non-pulmonary hypertension (mean pulmonary artery pressure <=20 mmHg), vs patients with 20 mmHg < mean pulmonary artery pressure <25 mmHg vs patients with mean pulmonary artery pressure >=25 mmHg.
• To assess the performance of the biomarker signatures in patients with various subgroups of pulmonary arterial hypertension, including but not limited to, heritable forms of pulmonary arterial hypertension and patients with systemic diseases.

• To assess the performance of biomarker signatures in Functional Class II patients versus

## Study design

This is a prospective, multicenter study to discover, design and develop blood biomarker signatures in patients with PH. A diagram of the study design is provided in Figure 1. The study population will include prevalent (previously diagnosed) and incident (newly diagnosed) patients who have undergone right heart catheterization (RHC) grouped according to the following subgroups: prevalent non-PH (RHC within 6 months), or incident non PH (RHC within 6 weeks), or incident PH (RHC within 6 weeks), or prevalent PH without or with pulmonary arterial hypertension (PAH) therapy (RHC within 18 months). This will provide adequate samples for biomarker signature discovery and validation of the signature*s performance. The number of participants enrolled in each group will ensure representation of the main PH groups of interest, ie, PAH and chronic thromboembolic pulmonary hypertension (CTEPH).
At the time of enrollment in the study, blood samples will be taken and a transthoracic echocardiogram (TTE) will be performed for each participant. All TTE will be centrally read in a blinded manner. TTE readings will be used to compare the diagnostic performance of the biomarker signature(s) to the current best practice for non-invasive diagnosis of PH.
No genetic/genomic testing is planned in this protocol, however, blood samples containing white blood cells will be collected to enable future analysis using the most appropriate genomic analysis platform to allow for genomic research, as necessary where local regulations permit. Participation in the genomic research is optional.

## Study burden and risks

NAP

# Contacts

**Public**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Male or female.
2. Age >=18 years of age inclusive.
3. Having undergone an RHC within 18 months (prevalent PH patients) or 6 months (prevalent non-PH patients) or have undergone or planned RHC within 6 weeks (incident patients). The results of the incident RHC (incident patients) or the most recent RHC (prevalent patients) will be used to classify the participant in one of the study population categories.
4. Medically stable on the basis of physical examination, medical history and vital signs performed at screening. Any abnormalities must be consistent with the underlying illness in the study population and this determination must be recorded in the participant*s source documents and initialed by the investigator.

5. Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
6. Must provide informed consent (or their legally-acceptable representative must sign) if he or she agrees to provide an optional (DNA) sample for research (where local regulations permit). Refusal to give consent for the optional (DNA) research sample does not exclude a participant from participation in the study.

### Exclusion criteria

1. Participants requiring renal dialysis.
2. History of lung or heart transplant (waiting list status or consideration of enlisting is allowed).
3. Severe left ventricular dysfunction: Left ventricular ejection function <35%.
4. Ongoing contagious respiratory disease.
5. Participants that have previously contributed blood samples for biomarker analysis in the Actelion retrospective study of biomarkers for PH.
6. Participants unable to have at least 2 tubes of 10 mL blood drawn (i.e., one 10 mL plasma tube and one 10 mL serum tube).
7. For incident patients: treatment with any PAH specific drug prior to collection of biomarker samples.

## Study design

### Design

**Study type:** Observational invasive

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Diagnostic |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 14-04-2021 |
| Enrollment: | 30 |
| Type: | Actual |

# Ethics review

Approved WMO
Date: 04-03-2021

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 |
|---|---|
| ClinicalTrials.gov | NCT04193046 |
| CCMO | NL74376.029.20 |

# Study results

Date completed: 14-12-2021

Results posted: 13-08-2024

**First publication**
22-12-2022

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

**Internal documents**
File