CONFIDENTIAL

CLINICAL STUDY PROTOCOL

A prospective, randomized, controlled trial to assess the effect of long-term oxygen therapy on 6-minute walking distance, clinical parameters and hemodynamics in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)

SOPHA

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PRINCIPAL INVESTIGATOR/ COORDINATING INVESTIGATOR (LEITER DER KLINISCHEN PRÜFUNG*) AND INVESTIGATOR

Prof. Dr. med. Ekkehard Grünig
Thoraxklinik am Universitätsklinikum Heidelberg
Zentrum für pulmonale Hypertonie
Röntgenstraße 1
69126 Heidelberg
Phone: 06221 / 396 8053
Fax: 06221 / 396 1209
ekkehard.gruenig@med.uni-heidelberg.de

* According to § 40 German Drug Law (AMG)

SPONSOR

Klinikdirektor

Roland Fank
Thoraxklinik am Universitätsklinikum Heidelberg

Röntgenstraße 1
69126 Heidelberg
Phone: 06221 / 396 2100
Fax: 06221 / 396 2102
roland.fank@med.uni-heidelberg.de

DEPUTY INVESTIGATOR

Dr. med. Benjamin Peter Egenlauf
Zentrum für pulmonale Hypertonie
Röntgenstraße 1
69126 Heidelberg
Phone: 06221 / 396 8078
Fax: 06221 / 396 1209
Benjamin.Egenlauf@med.uni-heidelberg.de

INVESTIGATOR

Dr. med. Satenik Harutyunova
Dr. med. Panagiota Xanthouli
Zentrum für pulmonale Hypertonie
Röntgenstraße 1
69126 Heidelberg
Phone: 06221 / 396 8025 und 8270
Fax: 06221 / 396 1209
Satenik.harutyunova@med.uni-heidelberg.de
Panagiota.xanthouli@med.uni-heidelberg.de

BIOMETRICIAN

Dr. Christine Fischer & MSc Nicola Benjamin
Institut für Humangenetik
INF 366, 69120 Heidelberg //
Thoraxklinik Heidelberg, Röntgenstraße 1,
69126 Heidelberg
Phone: 06221 56 5060 //06221 396 8076
Fax: 06221 56 33691 // 06221 396 1209
christine.fischer@med.uni-heidelberg.de

TRIAL COORDINATOR

Amina Salkić, LL.M.
Administratives Projektmanagement
Thoraxklinik-Heidelberg gGmbh
Röntgen Str. 1
69126 Heidelberg
Tel.: +49 (0)6221 396 2761
Fax: +49 (0)6221 396 2772
E-Mail: Amina.Salkic@med.uni-heidelberg.de

nicola.benjamin@med.uni-heidelberg.de

CLINICAL MONITOR*

Anna-Lena Gamer

Coordination Centre for Clinical Trials (KKS)
Marsilius-Arkaden – Turm West
Im Neuenheimer Feld 130.3
69120 Heidelberg
Phone: +49-6221 / 56-34323
Fax: +49-6221 / 56-33508
E-Mail: Anna-Lena.Gamer@med.uni-heidelberg.de

DATA MANAGEMENT

Evelin Deeg

Coordination Centre for Clinical Trials (KKS)
Marsilius-Arkaden – Turm West
Im Neuenheimer Feld 130.3
69120 Heidelberg
Phone: +49-6221 / 56-36215
Fax: +49-6221 / 56-33508
E-Mail: Evelin.Deeg@med.uni-heidelberg.de

STEERING COMMITTEE (SC)

Prof. Dr. med. Ekkehard Grünig
Thoraxklinik Heidelberg gGmbH am Universitätsklinikum Heidelberg
Zentrum für pulmonale Hypertonie
Röntgenstraße 1
69126 Heidelberg
Phone: 06221 / 396-8053
Fax: 06221 / 396-1209
ekkehard.gruenig@med.uni-heidelberg.de

PD Dr. Silvia Ulrich
Prof. Dr. Konrad E. Bloch
Pulmonary clinic
University Hospital of Zurich
Raemistrasse
1008091 Zurich
Phone: 0041-44 255-54362
Fax: 0041-44 255-8519
silvia.ulrich@usz.ch
Konrad.bloch@usz.ch

PARTICIPATING SITES

Thoraxklinik Heidelberg gGmbH am Universitätsklinikum Heidelberg
Zentrum für pulmonale Hypertonie
Röntgenstraße 1
69126 Heidelberg
Tel.: 06221 / 396-8053
Fax: 06221 / 396-1209

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1 Clinical study protocol synopsis

Protocol title:	A prospective, randomized, controlled trial to assess the effect of long-term oxygen therapy on 6-minute walking distance, clinical parameters and hemodynamics in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)
Acronym	SOPHA
Phase:	Phase II
Regulatory obligations:	[Pharmaceutical study under the Pharmaceutical DrugLaw (AMG); requires BfARM approval and institutional Ethical Review Board approval.]
Study location:	Heidelberg, Germany
No. of study sites:	1
Principal investigator:	Prof. Dr. Ekkehard Grünig Thoraxklinik at Heidelberg University Hospital Centre for pulmonary hypertension Röntgenstraße 1 69126 Heidelberg Phone:0049-6221 396-8053 Fax: 0049-6221 396-1209 Mail: Ekkehard.Gruenig@med.uni-heidelberg.de
Study type:	Interventional
Study design:	Investigator-Initiated-Trial (IIT) This is a prospective, randomised, controlled, parallel-group, open label monocenter (Heidelberg) study with a partial cross-over design, which investigates the effect of long term oxygen treatment in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension who present with mild or moderate hypoxemia at rest or during physical activity and therefore may require longterm oxygen therapy. Patients will be divided in a supplemental-oxygen group (primary intervention group) and no-supplemental-oxygen group (control group). Patients of the control group will be offered to participate in the interventional treatment arm after they have terminated the control period (partial cross-over; secondary intervention group). Efficacy of long term oxygen therapy will be investigated by assessing invasive and non-invasive clinical parameters at baseline and after 3 months. Efficacy parameters will be compared intra-individual

(primary and secondary intervention group) and between the intervention and the control group.

Randomization will be performed in a 1:1 ratio.

Patients will be assessed at baseline and after 3 months. Clinical assessments will comprise of medical history, WHO functional class, electrocardiogram, blood gas analysis, lung function, 6-minute walking distance, echocardiography, laboratory including NT-proBNP, invasive hemodynamics using right heart catheterization, cardiopulmonary exercise testing with stress-Doppler echocardiography and quality of life questionnaire (SF-36) at baseline and after 3 months, worsening of saturation and clinical worsening events.

Interventions

Patients will be divided in a supplemental-oxygen group and no-supplemental-oxygen group (control group)

- Patients in the supplemental-oxygen group will be prescribed >16-hour oxygen (liquid oxygen) for 12 weeks, aiming at O_2 saturation values of >90% at rest and during exercise or physical activity. Oxygen flow will be determined by titration
- Patients in the control group will not receive oxygen supply throughout the study (12 weeks), unless severe resting desaturation (SpO_2 ≤80%) or severe exercise-induced desaturation (SpO_2 <80% for ≥10 minutes) developed. If either of these conditions develop, oxygen will be prescribed and the oxygen requirement will be reassessed after 30 days.
- Patients of the control group will be offered to participate in the interventional treatment arm after they have terminated the control period (partial cross-over; secondary intervention group). Assessments of the secondary control group will be performed in analogy to the primary intervention group.

Randomization will be performed in a 1:1 ratio.

Study duration

Q1 2019- Q4 2021 *

Background

Most patients with PAH, except those with congenital heart defects and pulmonary-to-systemic shunts, have minor degrees of hypoxemia at rest and during the night (Hildebrand et al. 2012).

Current recommendations including the pneumological

guidelines for LTOT (Galiè et al. 2015) are based on evidence in patients with chronic obstructive pulmonary disease, as data for patients with PH are lacking:

- When O_2 partial pressure is repeatedly <8 kPa (<60 mmHg; alternatively, 90% of O_2 saturation), patients are advised to use O_2 to achieve a saturation of >8 kPa. (Galiè et al. 2015)
- The use of ambulatory O_2 can be considered when there is evidence of a symptomatic response or correction of exercise-induced desaturation.

In patients with COPD it has already been shown that supplemental oxygen improves dyspnea and the distance walked during a five-minute walk test compared to supplemental air (Nonoyama et al. 2007). Data regarding survival benefits due to long-term oxygen therapy in COPD is inconsistent (Medical Research Council Working Party 1981, Nocturnal Oxygen Therapy Trial Group 1980, Chaouat et al. 1999, Górecka 1997).

There are only few studies investigating the effect of oxygen supply in pulmonary hypertension, most of which merely investigate acute effects of O_2 administration. Short-term oxygen administration has been shown to reduce mean pulmonary arterial pressure, pulmonary vascular resistance and to increase cardiac output in PAH patients (Leuchte et al. 2013, Roberts et al. 2001). In one study, oxygen supply also reversed the progression of PH in patients with chronic obstructive pulmonary disease (COPD) (Weitzenblum et al. 1985).
One recent randomized-controlled trial indicates that O_2 given during cardiopulmonary exercise significantly improves maximal work rate and endurance (Ulrich et al. 2017). Furthermore, nocturnal oxygen supply for one week significantly improved 6-minute walking distance in patients with PH (Ulrich et al. 2015), sleep-associated breathing difficulties, exercise performance during the day as well as cardiac repolarisation (Schumacher et al. 2014). Patients with Eisenmenger's syndrome gain little benefit from nocturnal O_2 therapy (Sandoval et al. 2001).
Whether these positive effects of O_2 supplementation during exercise would translate into long-term improvements of exercise capacity, quality of life, hemodynamics and disease progression is not known to date. Up to now, there are no randomised studies suggesting that long-term O_2 therapy is indicated or when it should be initiated.

This will be the first study to investigate the effect of long-term oxygen treatment for ≥16h/day for 3 months compared to no oxygen supply in patients with PAH or CTEPH on 6-minute walking distance, clinical parameters, quality of life and hemodynamics. Exercise capacity, clinical parameters, quality of life and invasive hemodynamics will be measured at baseline and after 3 months (12 weeks).

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Materials & Supplies

Investigator-Initiated-Trial (IIT)

Indication of oxygen supply will be determined according to current recommendations of long term oxygen treatment in patients with pulmonary hypertension (see above). Oxygen treatment with liquid oxygen as applicable will be prescribed to patients of the intervention group. Oxygen flow will be determined by titration, aiming at O_2 saturation values of >90% at rest.

Patients in the control group will be offered prescription of oxygen supply after the end of control period (control phase), serving as secondary intervention group.

Indication

PAH patients experiencing oxygen desaturations at rest and during physical activity, when O_2 partial pressure is repeatedly <8 kPa (<60 mmHg; alternatively, 90% of O_2 saturation).

Aims and Objectives

1) To determine patient benefits from a long-term oxygen therapy (LTOT) given continuously during ≥16h/day for 12 weeks, measured by improvement of exercise performance assessed by the 6 minute walking distance (6MWD)
2) To investigate effects of oxygen treatment on QoL, measured with SF-36 questionnaire
3) To determine the hemodynamic and functional responses during long term oxygen treatment by echocardiography, stress-doppler echocardiography cardiopulmonary exercise testing and right heart catheterisation
4) To investigate the change of clinical parameters such as blood gas analysis, laboratory (NT-proBNP), WHO functional class
5) To assess time to worsening of oxygen saturation and time to clinical worsening

Sample size

N= 40 (with 20 patients randomized in each group)

The minimally important difference of 6-minute walking distance in patients with pulmonary hypertension is considered to be 33 meters, according to the literature (Mathai et al. 2012).

A recent study of Ulrich et al. has shown a 25 meter difference between nocturnal oxygen and sham-O_2 for an intervention period of one week with a concentrator device in patients with pulmonary hypertension (Ulrich et al. 2015). We assume a standard deviation of the difference of 50 meters (as seen in the data of Ulrich et al.) and a higher effect of 35 meters due to a longer intervention period and the use of oxygen supply ≥16h/day, which lies also above the threshold of minimally important difference for the 6-minute walking distance.

The primary endpoint will be analysed in a hierarchical testing strategy with:

1. Intra-individual analysis of 6MWD in the primary and secondary intervention group (difference from baseline to follow-up)

2. If (1) is significantly different, the treatment effect on 6MWD will be compared between the primary intervention group and the control group.

Sample size assumptions:

1) If the true treatment effect is at least an increase of 35meters in the 6-minute walking distance in the intervention group with a standard deviation of 50 meters, a sample size of 29 patients will provide a >95% power with a matched-pairs two-sided student's t-test with a significance level of 0.05 (intra-individual comparison of difference baseline to follow-up of patients from primary and secondary intervention group).
2) If the true treatment effect is at least a control group corrected increase of 50meters in the 6-minute walking distance with an equal standard deviation of 50 meters, a sample size of 17 patients in each group (total sample size n=34) will provide an 80% power with a two-sided student's t-test with a significance level of 0.05 comparing two independent means (comparison of differences baseline to follow-up between the two groups).
   The sample size of 18 patients in each group with an anticipated dropout rate of 10% leads to a final sample size of 40 (20 in each group).

The primary endpoint, 6-minute walking distance, will be compared by ANCOVA of the differences (baseline to follow-up) (1) intra-individual and (2) between the two groups with the baseline value as covariate, providing a power-advantage over the student's t-test which leads to a power of >95% and 83% or more, respectively.

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Statistical methods

Data will be pseudonymized and checked for plausibility. After database closure, data will be analysed. All data will be listed and trial summary tables will be provided with means, medians, variances and respective confidence intervals and with frequency tables.

Baseline Parameters will be described and compared between study arms and study centres.

The primary endpoint, 6-minute walking distance, will be compared by (1) matched-pairs two-sided student's t-test of primary and secondary intervention group and (2) ANCOVA of the differences (baseline to three months) between the two groups with the baseline value as covariate.

Secondary parameters at baseline and during follow-up will be compared intra-individually and between groups comparing the difference between baseline and follow-up visits. Data will be displayed by means and standard deviations, medians and variances with respective 95% confidence intervals.

p-values <0.05 will be considered as statistically significant.

Patients who withdraw from the study will be asked to complete a final examination which will be included in the data analysis.

Inclusion Criteria

Patients in both groups (n = 40) with precapillary PH, WHO class I -IV (mPAP ≥ 25 mm Hg, pulmonary arterial occlusion pressure ≤15 mm Hg), who are stable on optimized pharmacological treatment for at least six weeks and who do not suffer from other cardio-pulmonary disease will be recruited if arterial or capillary O_2 partial pressure is repeatedly (<60 mmHg; alternatively, 90% of O_2 saturation) at rest and during physical activity hypoxemia still persist (O_2 partial pressure <60 mmHg pO_2 90 %).

- men and women 18 years of age or older
- patient is diagnosed with Pulmonary Arterial Hypertension (World Health Organization (WHO) Category Group 1-3 (by the WHO Clinical classification system)), including Idiopathic (IPAH), Heritable PAH (HPAH, Familial PAH), and CTEPH, with exceptions as noted in exclusion criteria
- patient is willing and able to provide written informed consent
- patient is willing and able to comply with the protocol, including required follow-up visits
- Patient experiences oxygen desaturations below 90% (or pO_2 below 60 mmHg) at rest with oxygen desaturations below 90% (or pO_2 below 60 mmHg) during physical activity
- patient has a stable functional class of PAH with no changes of medication during the last six weeks before inclusion

Exclusion Criteria

- Patient is a female who is pregnant, nursing, or of child bearing potential and is not on a reliable form of birth control
- patient has already been treated with long-term oxygen therapy within the last 3 weeks.
- patient with pulmonary venous hypertension
- significant functional limitation in lung function tests (FEV_1>60%,TLC <60%) and CT morphological signs of pulmonary disease
- significant left heart disease, requires acute pharmacological or interventional treatment
- unstable conditions requiring pharmacological or other treatment, intensive care or relevant severe concomitant disease
- patient is enrolled, has participated within the last thirty days, or is planning to participate, in a concurrent drug and/or device study during the course of this clinical trial. Co-enrolment in

concurrent trials is only allowed with documented pre-approval from the study manager that there is not a concern that co-enrolment could confound the results of this trial.

- patient has been initiated on a new oral or parenteral PAH therapy in the last two months
- patient has had a recent (within three months) or otherwise unresolved infection requiring antibiotic treatment
- patient with a cardiac index (CI) $\leq$1.8L/min/m^2
- patient is Functional Class IV (New York Heart Association (NYHA))
- active smoking status
- patient with severe resting desaturation (repeatedly SpO_2 $\leq$85%) or severe exercise-induced desaturation (SpO_2 <80% for $\geq$10 minutes)

Individual drop out criteria

- new events such as lung embolisms
- severe left heart insufficiency as well as chronic left heart disease with signs of decompensation
- radiological signs of severe disease, interstitial lung disease (pneumonia)
- patient with severe resting desaturation (repeatedly SpO_2 $\leq$85%) or severe exercise-induced desaturation (SpO_2 <80% for $\geq$10 minutes)
- noncompliance, defined as oxygen treatment <12 hours per day for >7 days within 6 weeks (equals ~80%), assessed by patient interviews

Efficacy and safety variables

Efficacy Variables

The primary efficacy variable is the distance walked in 6 minutes in meters.

The following study procedures will be performed in every patient according to the visits schedule and analyzed as **secondary efficacy variables**.

- quality of life assessed by the SF-36 questionnaire

- Feasibility of oxygen treatment, assessed by patient consent to participate in the study (recruitment rate) and by patient compliance

- History, questionnaire evaluation, and clinical examination: Complete medical history will be obtained. Physical examination will include weight, height, blood pressure, heart rate, cardiac and pulmonary auscultation, assessments of jugular distension and peripheral oedema. WHO functional class will be assessed by specific questionnaire. Quality of life will be assessed by the short form of the medical outcome questionnaire (SF-36). Assessment of compliance via questionnaire.

- Echocardiography:
  Following parameters will be assessed: systolic pulmonary arterial pressure (sPAP, mmHg), right ventricular area (RV-area, cm^2), and right atrial area (RA-area,cm^2), tricuspid annular plane systolic excursion (TAPSE), left ventricular eccentricity index (LV-EI), RV-pump function and LV-pump function (EF).

- Stress-Doppler-echocardiography and cardiopulmonary exercise testing (spiroergometry):
  WHO protocol for incremental increase of workload (25 Watt every 2 minutes) will be used to assess cardiopulmonary response during exercise, including the following parameters:
  - sPAP,
  - RV-pump function,
  - heart rate,
  - systemic blood pressure,
  - oxygen consumption,
  - oxygen consumption/kg body weight,
  - oxygen saturation,
  - minute ventilation,
  - carbon dioxide and oxygen equivalents,
  - O_2 pulse,
  - ventilatory threshold,
  - respiratory reserve.

- Analyses of blood samples:
  Venous blood will be analysed to determine:
  - N-terminal natriuretic peptide (NT-pro BNP)
  - And additional laboratory tests that include inflammation factors, kidney, liver, blood cell count parameters
- Blood for blood gas analyses:
  - oxygen partial pressure
  - carbon dioxide partial pressure
  - oxygen saturation of the blood (SaO_2)
  - pH values
  - Bicarbonates
  - Base Excess

- Pulmonary hemodynamics by right heart catheterization:
  - cardiac index in liters per minute per square meter (of body surface area) (CI)
  - systolic pulmonary artery pressure (sPAP)
  - mean pulmonary artery pressure (mPAP)
  - diastolic pulmonary artery pressure (dPAP)
  - pulmonary artery wedge pressure (PAWP)
  - right atrial pressure (RAP)
  - pulmonary vascular resistance (PVR)
  - cardiac output and ejection fraction (CO, HZV), cardiac index (CI)

- central venous saturation, via blood gas analysis from pulmonary artery

Worsening of saturation will be determined as:

- repeated oxygen desaturation ≤85% at rest or
- severe exercise-induced desaturation (SpO_2 <80% for ≥10 minutes)

Clinical worsening will be determined as

- worsening of WHO functional class and deterioration of walking distance >15% compared to baseline
- need of iv pulmonary hypertension targeted treatment
- hospitalization due to worsening of PH

Safety variables

Patients with a serious adverse event occurring during the study treatment will be followed by the study team until the serious adverse event will have resolved to the pre-study level and/or will have been addressed according to best clinical practice. Patients withdrawing from the study prematurely will have a final physical examination.

If a patient withdraws from treatment (intervention group) or is in need of oxygen therapy (control group) and agrees to stay in the study, study related examinations will be performed and data will be obtained according to protocol.

Course of the study	**Screening phase:** Eligible patients will be asked to participate upon written informed consent. In case of agreement medical history will be taken and they will undergo screening examinations. The right heart catheterisation should not be older than 6 months before baseline and should be performed after the patient was on stable treatment for at least six weeks. In patients who have not performed a right heart catheter within the preceding 6 months, invasive hemodynamics will be measured before the beginning of the intervention. Oxygen will be prescribed and the oxygen system will be delivered to the patient. Baseline will be within 28 days after screening. **Baseline / Day 1 visit:** clinical evaluation, laboratory, blood gas analysis, SF-36 questionnaire, 6MWD, echocardiography, Stress-Doppler-echocardiography and cardiopulmonary exercise testing. **Day 1-90:** LTOT with oxygen system for 16h/day vs. no oxygen supply. Interim phone calls each month (month 1 and 2). **Month three / Day 90 visit (± 14 days):** clinical evaluation, laboratory, blood gas analysis, SF-36 questionnaire, 6MWD, echocardiography, Stress-Doppler-Echocardiography and Cardiopulmonary Exercise Testing and right heart catheterisation. Patients of the control group will be offered to participate in secondary intervention group to receive long-term oxygen treatment. (Week 12 visit will be performed again after 12 weeks, in total 24 weeks of study with control and secondary intervention phase). **Month four / Day 120 (± 14 days)** (30 days after close out): follow-up visit to assess adverse events; outpatient visit or phone call.
Excluded medication:	None
Pre-treatment period:	N/A
Duration of observation	90 days (up to 180 days in the control group with switch to secondary intervention group) + follow-up period.
Follow-up period	**30 days after close out visit** each patient performs a follow-up Visit Clinical follow-up of all SAEs until they have been resolved.
Clinic visits	Screening visit, baseline visit, month three and month four (follow-up); month six according to month three assessment in secondary intervention group and respective follow-up. Secondary intervention group will have an additional visit after 180 days (in analogy to month three visit).

Dosing regimen

Oxygen flow adaptation (titration):

Until a SpO_2 >90% or pO_2 >60mmHg is achieved

Route of administration

Inhaled (nasal) Oxygen Therapy

Timelines

01/2019 – 12/2021

Data collection	Q1 2019-Q4 2020
Data management/analysis	Q1 2021-Q3 2021
Study report/manuscript	Q4 2021

Endpoints

Primary

6-MWD, difference from baseline

Secondary

Change from baseline in hemodynamic parameters assessed by echocardiography, right-heart catheter, cardiopulmonary exercise testing and laboratory parameter as NT-proBNP at month three. Change from baseline in quality of life as assessed by SF-36.

Parameters are listed under the section “efficacy variables”.

1.1 Overview of visits and assessments (s. Diagram)

Primary intervention group						
Assessments	**Screening** -28 days **1**	**Visit 1 Baseline** Day 1 **1**	**Phone visit 1** Day 30 ± 14 days **1**	**Phone visit 2** Day 60 ± 14 days **1**	**Visit 2** Day 90 ± 14 days **1**	**Follow up (Treatment group)** Day 120 ± 14 days **1**
Informed Consent	1	-	-	-	-	-
Inclusion / exclusion criteria	1		-	-		
Evaluation of prior and concomitant medication	1	1	-	-	1	-
PAH classification, etiology, diagnosis date	1	-	-	-	-	-
WHO-FC	1	1	-	-	1	-
Vital Sign Measurements incl. Heart Rate and SpO_2	1	1	-	-	1	-
6MWD, Borg Dyspnea Score,	1	1	-	-	1	-
Height / Weight	1	1	-	-	1	-
Lung function testing (TLC; DLCO)	1	1	-	-	1	-
Blood gas analysis	1	1	-	-	1	-
RHC hemodynamics: mPAP, mRAP, PAWP, PVR, cardiac index (for initiation of trial-specific therapy: within 6 months prior or at)	1*	-	-	-	1	-
Physical examination	1	1	-	-	1	-
Hematology, Chemistry	1	1	-	-	1	-
NT-proBNP	1	1	-	-	1	-
For females only: Pregnancy test - child bearing potential - currently pregnant (Yes***/No/Unknown)	1	1	-	-	1	-
Echocardiogram , stress-doppler-echocardiography and Cardiopulmonary Exercise Testing	1	1	-	-	1	-
Quality of life (SF-36)	1	1	-	-	1	-
Adverse Events	-	-	1	1	1	1
Phone visits	-	-	1	1	-	1

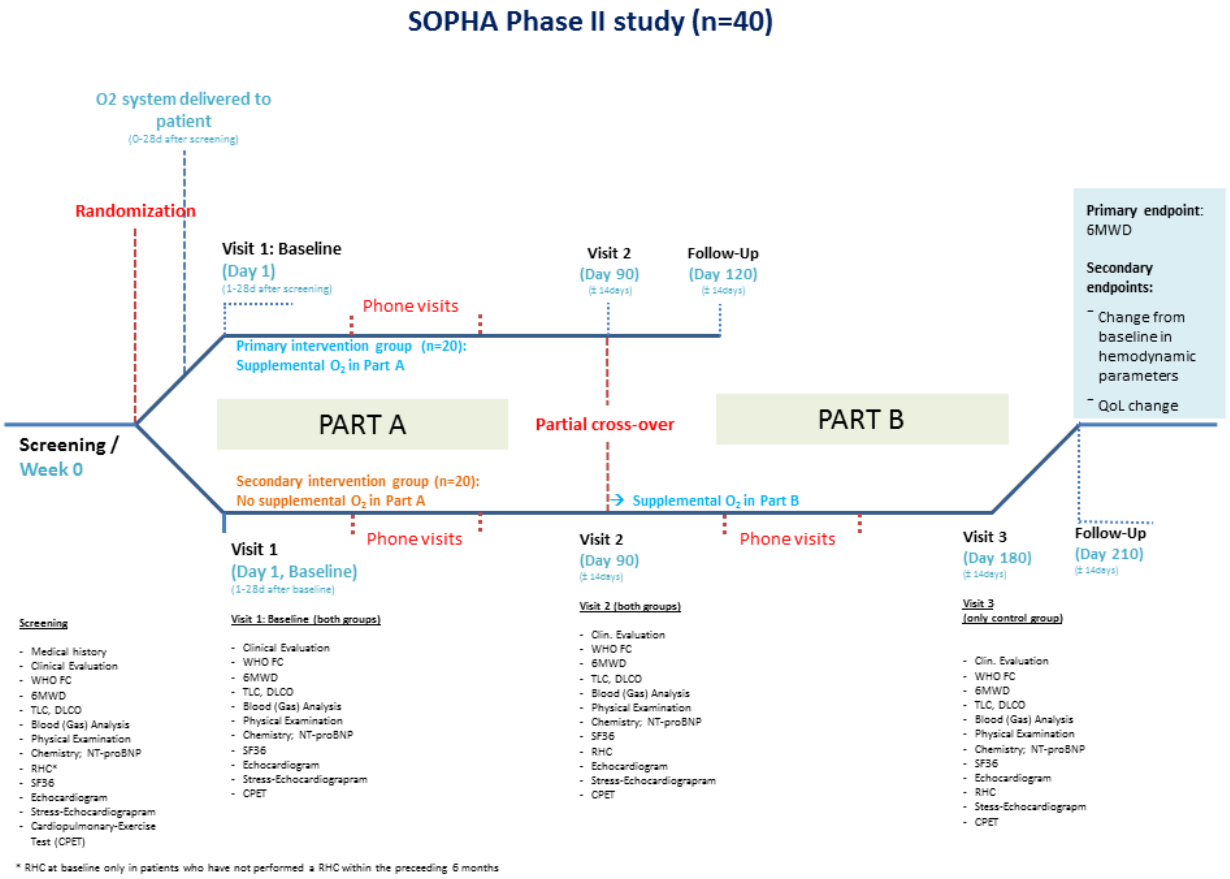
* RHC at baseline will only be performed in patients who have not performed a RHC within the preceding 6 months

Secondary intervention group (control group with crossover)

Assessments	**Screening** -28 days **1**	**Visit 1: Baseline** Day 1 **1**	**Phone visit 1** Day 30 ± 14 days **1**	**Phone visit 2** Day 60 ± 14 days **1**	**Visit 2** Day 90 ± 14 days **1**	**Phone visit 3** Day 120 ± 14 days **1**	**Phone visit 4** Day 150 ± 14 days **1**	**Visit 3** Day 180 ± 14 days **1**	**Follow up (Control group)** Day 210 ± 14 days **1**
Informed Consent	1	-	-	-	-	-	-	-	-
Inclusion / exclusion criteria	1	-	-	-	-	-	-	-	-
Evaluation of prior and concomitant medication	1	1	-	-	1	-	-	1	-
PAH classification, etiology, diagnosis date	1	-	-	-	-	-	-	-	-
WHO-FC	1	1	-	-	1	-	-	1	-
Vital Sign Measurements incl. Borg Dyspnea Score, Heart Rate and SpO_2	1	1	-	-	1	-	-	1	-
6MWD	1	1	-	-	1	-	-	1	-
Height / Weight	1	1	-	-	1	-	-	1	-
Lung function testing (TLC; DLCO)	1	1	-	-	1	-	-	1	-
Blood gas analysis	1	1	-	-	1	-	-	1	-
Stress-Doppler-Echocardiography and Cardiopulmonary Exercise Testing	-	1	-	-	1	-	-	1	-
RHC hemodynamics: mPAP, mRAP, PAWP, PVR, cardiac index (for initiation of trial-specific therapy: within 6 months prior or at)	1*	-	-	-	1	-	-	1	-
Physical examination	1	1	-	-	1	-	-	1	-
Hematology, Chemistry	1	1	-	-	1	-	-	1	-
NT-proBNP	1	1	-	-	1	-	-	1	-
For females only: Pregnancy test - child bearing potential - currently pregnant (Yes***/No/Unknown)	1	1	-	-	1	-	-	1	-
Echocardiogram	1	1	-	-	1	-	-	1	-
Quality of life (SF-36)	1	1	-	-	1	-	-	1	-
Adverse Events	-	-	1	1	1	1	1	1	1
Phone visit	-	-	1	1	-	1	1	-	1

* RHC at baseline will only be performed in patients who have not performed a RHC within the preceding 6 months

Diagram:


SOPHA Phase II study (n=40)
O2 system delivered to patient
(0-28d after screening)
Randomization
Visit 1: Baseline
(Day 1)
(1-28d after screening)
Phone visits
Visit 2
(Day 90)
(± 14days)
Follow-Up
(Day 120)
(± 14days)
Primary endpoint: 6MWD
Secondary endpoints:
- Change from baseline in hemodynamic parameters
- QoL change
Primary intervention group (n=20):
Supplemental O2 in Part A
PART A
Partial cross-over
PART B
Screening / Week 0
Secondary intervention group (n=20):
No supplemental O2 in Part A
Supplemental O2 in Part B
Phone visits
Phone visits
Visit 3
(Day 180)
(± 14days)
Follow-Up
(Day 210)
(± 14days)
Visit 1
(Day 1, Baseline)
(1-28d after baseline)
Visit 2
(Day 90)
(± 14days)
Screening
- Medical history
- Clinical Evaluation
- WHO FC
- 6MWD
- TLC, DLCO
- Blood (Gas) Analysis
- Physical Examination
- Chemistry; NT-proBNP
- RHC*
- SF36
- Echocardiogram
- Stress-Echocardiograpram
- Cardiopulmonary-Exercise Test (CPET)
Visit 1: Baseline (both groups)
- Clinical Evaluation
- WHO FC
- 6MWD
- TLC, DLCO
- Blood (Gas) Analysis
- Physical Examination
- Chemistry; NT-proBNP
- SF36
- Echocardiogram
- Stress-Echocardiograpram
- CPET
Visit 2 (both groups)
- Clin. Evaluation
- WHO FC
- 6MWD
- TLC, DLCO
- Blood (Gas) Analysis
- Physical Examination
- Chemistry; NT-proBNP
- SF36
- RHC
- Echocardiogram
- Stress-Echocardiograpram
- CPET
Visit 3 (only control group)
- Clin. Evaluation
- WHO FC
- 6MWD
- TLC, DLCO
- Blood (Gas) Analysis
- Physical Examination
- Chemistry; NT-proBNP
- SF36
- Echocardiogram
- RHC
- Stess-Echocardiograpm
- CPET
* RHC at baseline only in patients who have not performed a RHC within the preceeding 6 months

Abbreviations

6MWD	*6-Minute Walking Distance*
AE	*Adverse Event*
ANCOVA	*Analyses of Covariance*
APAH	*Associated Pulmonary Arterial Hypertension*
AMG	*German Drug Law (Deutsches Arzneimittelgesetz)*
ATS	*American Thoracic Society*
BDSG	*Bundesdatenschutzgesetz*
BfArM	*Bundesinstitut für Arzneimittel und Medizinprodukte*
BP	*Blood Pressure*
CI	*Cardiac Index*
CO	*Cardiac Output*
COPD	*Chronic Obstructive Pulmonary Disease*
CRF	*Case Report Form*
CT	*Computed Tomography*
CTCAE	*Common Terminology Criteria for Adverse Events*
CTEPH	*Chronic thromboembolic pulmonary hypertension*
CV	*Curriculum Vitae*
DBL	*Data Base Lock*
DLCO	*Diffusion limited carbon monoxide*
dPAP	*Diastolic Pulmonary Artery Pressure*
DSUR	*Development Safety Update Report*
EC	*Ethics Committee*
ECG	*Electrocardiogram*
ERS	*European Respiratory Society*
ESC	*European Society of Cardiology*
FEV_1	*Forced expiratory volume in the first second*
FPI	*First Patient In*
FSI	*First Subject In*
FVC	*Forced Vital Capacity*
GCP	*Good Clinical Practice*
GCP-V	*Good Clinical Practice Ordinance (GCP-Verordnung)*
GLDH	*Glutamate Dehydrogenase*
HDL	*High Density Lipoprotein*
HIV	*Human Immunodeficiency Virus*
HPAH	*Heritable PAH (Familial PAH)*
HR	*Heart Rate*
HZV	*Herzzeitvolumen*
ICF	*Informed Consent Form*
ICH	*International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*
IIT	*Investigator Initiated Trial*

IMP	*Investigational Medicinal Product*
INN	*International Nonproprietary Name*
IPAH	*Idiopathic Pulmonary Arterial Hypertension*
ISF	*Investigator Site File*
ISRCTN	*International Standard Randomized Controlled Trial Number*
ITT	*Intention To Treat*
LKP	*Coordinating Investigator according to AMG (Leiter der Klinischen Prüfung)*
LSI	*Last Subject In*
LSO	*Last Subject Out*
LTOT	*Long-Term Oxygen Therapy*
LV-EI	*Left Ventricular Eccentricity Index*
mPAP	*Mean Pulmonary Artery Pressure*
mRAP	*Mean Right Arterial Pressure*
NCI	*National Cancer Institute*
NT-proBNP	*N-terminal prohormone of brain natriuretic peptide*
NYHA	*New York Heart Association*
O_2	*Oxygen*
PAH	*Pulmonary Arterial Hypertension*
PAP	*Pulmonary Arterial Pressure*
PAWP	*Pulmonary Artery Wedge Pressure*
PH	*Pulmonary Hypertension*
PHAROS	*Population based Hematological Registry for Observational Studies*
pO2	*Partial Pressure of Oxygen*
PVR	*Pulmonary Vascular Resistance*
QoL	*Quality of Life*
RA(-area)	*Right Atrial (Area)*
RAP	*Right Atrial Pressure*
RHC	*Right Heart Catheterization*
RV	*Residual Volume*
RV(-area)	*Right Ventricular (Area)*
SAE	*Serious Adverse Event*
SaO_2	*Arterial Oxygen Saturation*
SpO2	*Peripheral Oxygen Saturation*
SC	*Steering Committee*
SF-36	*36-Item Short Form Survey as part of the Medical Outcome Study*
SGPT	*Serum Glutamic-Pyruvate Transaminase, also known as ALAT*
SGOT	*Serum Glutamic-Oxaloacetic Transaminase, also known as ASAT*
sPAP	*Systolic Pulmonary Artery Pressure*
SmPC/SPC	*Summary of Product Characteristics*
SUSAR	*Suspected Unexpected Serious Adverse Reaction*
SvO_2	*Venous Oxygen Saturation*

TAPSE	*Tricuspid Annular Plane Systolic Excursion*
TLC	*Total Lung Capacity*
USA	*United States of America*
WHO	*World Health Organization*
WHO-FC	*World Health Organization Functional Class*

2 Introduction

2.1 Scientific Background

Most patients with PAH, except those with congenital heart defects and pulmonary-to-systemic shunts, have minor degrees of arterial hypoxemia at rest and during the night (Hildebrand et al. 2012).

Current recommendations including the pneumological guidelines for LTOT (Galiè et al. 2015) are based on evidence in patients with chronic obstructive pulmonary disease, as data for patients with PH are lacking:

- When O_2 partial pressure is repeatedly <8 kPa (<60 mmHg; alternatively, 90% of O_2 saturation), patients are advised to use O_2 to achieve a saturation of >8 kPa. (Galiè et al. 2015)

- The use of ambulatory O_2 can be considered when there is evidence of a symptomatic response or correction of exercise-induced desaturation.

In patients with COPD it has already been shown that supplemental oxygen improves dyspnea and the distance walked during a five-minute walk test compared to supplemental air (Nonoyama et al. 2007). Data regarding survival benefits due to long-term oxygen therapy in COPD is inconsistent (Medical Research Council Working Party 1981, Nocturnal Oxygen Therapy Trial Group 1980, Chaouat et al. 1999, Górecka 1997).

There are only few studies investigating the effect of oxygen supply in pulmonary hypertension, most of which merely investigate acute effects of O_2 administration. Short-term oxygen administration has been shown to reduce mean pulmonary arterial pressure, pulmonary vascular resistance and to increase cardiac output in PAH patients (Leuchte et al. 2013, Roberts et al. 2001). In one study, oxygen supply also reversed the progression of PH in patients with chronic obstructive pulmonary disease (COPD) (Weitzenblum et al. 1985).

One recent randomized-controlled trial indicates that O_2 given during cardiopulmonary exercise significantly improves maximal work rate and endurance (Ulrich et al. 2017). Furthermore, nocturnal oxygen supply for one week significantly improved 6-minute walking distance in patients with PH (Ulrich et al. 2015), sleep-associated breathing difficulties, exercise performance during the day as well as cardiac repolarisation (Schumacher et al. 2014). Patients with Eisenmenger's syndrome gain little benefit from nocturnal O_2 therapy (Sandoval et al. 2001).

Whether these positive effects of O_2 supplementation during exercise would translate into long-term improvements of exercise capacity, quality of life, hemodynamics and disease progression is not known to date. Up to now, there are no randomised studies suggesting that long-term O_2 therapy is indicated or when it should be initiated.

This will be the first study to investigate the effect of long-term oxygen treatment for ≥16h/day for 3 months compared to no oxygen supply in patients with PAH or CTEPH on 6-minute walking distance, clinical parameters, quality of life and hemodynamics. Exercise capacity, clinical parameters, quality of life and invasive hemodynamics will be measured at baseline and after 3 months (12 weeks).

2.2 Trial Rationale/ Justification

Treatment of O_2 naïve patients with PAH will be included in this investigator-initiated trial (IIT) to assess efficacy and safety of oxygen substitution. Nocturnal oxygen substitution improved the 6MWD compared to placebo in one clinical trial in PAH patients (Ulrich et al. 2015). Due to the positive results in the treatment of patients with PAH, the initiation of this proof-of-concept study is justified.

2.3 Benefit/ Risk Assessment

One recent randomized-controlled trial indicates that O_2 given during cardiopulmonary exercise significantly improves maximal work rate and endurance (Ulrich et al. 2017). Furthermore, nocturnal oxygen supply for one week significantly improved 6-minute walking distance in patients with PH (Ulrich et al. 2015), sleep-associated breathing difficulties, exercise performance during the day as well as cardiac repolarisation (Schumacher et al. 2014). Patients with Eisenmenger's syndrome gain little benefit from nocturnal O_2 therapy (Sandoval et al. 2001).

Whether these positive effects of O_2 supplementation during exercise would translate into long-term improvements of exercise capacity, quality of life, hemodynamics and disease progression is not known to date. Up to now, there are no randomised studies suggesting that long-term O_2 therapy is indicated or when it should be initiated.

2.4 Steering Committee

In order to monitor specific aspects of the current trial the following Reference Committees will be established: The clinical study will be an investigator initiated trial in the Thoraxclinic in Heidelberg specialized in the treatment of patients with PH. The Steering Committee will be responsible for coordinating the conduct of this trial. The Steering Committee will also protect the safety interests of patients in this trial by monitoring the progress and safety data of the trial.

3 Trial Objectives and Endpoints

3.1 Primary Objective and Primary Endpoint

1) To determine the benefits for PH patients from a long-term oxygen therapy (LTOT) given continuously during ≥16h/day for 12 weeks, measured by improvement of exercise performance assessed by the 6 minute walking distance (6MWD).

3.2 Secondary Objectives

1) To investigate effects of oxygen treatment on QoL, measured with SF-36 questionnaire
2) To determine the hemodynamic and functional responses during long term oxygen treatment by echocardiography, stress-doppler echocardiography cardiopulmonary exercise testing and right heart catheterisation
3) To investigate the change of clinical parameters such as blood gas analysis, laboratory (NT-proBNP), WHO functional class (WHO-FC)
4) To assess time to worsening of oxygen saturation and time to clinical worsening

4 Trial Design

Investigator-Initiated-Trial (IIT)

This is a prospective, randomised, controlled, parallel-group, open label monocenter (Heidelberg) study with a partial cross-over design, which investigates the effect of long term oxygen treatment in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension (CTEPH) who present with mild or moderate hypoxemia at rest and/or during physical activity and therefore may require longterm oxygen therapy.

Patients will be divided in a supplemental-oxygen group (primary intervention group) and no-supplemental-oxygen group (control group). Patients of the control group will be offered to participate in the interventional treatment arm after they have terminated the control period (partial cross-over; secondary intervention group).

Efficacy of long term oxygen therapy will be investigated by assessing invasive and non-invasive clinical parameters at baseline and after 3 months. Efficacy parameters will be compared intra-individually (primary and secondary intervention group) and between the intervention and the control group.

Randomization will be performed in a 1:1 ratio.

Patients will be assessed at baseline and after 3 months. Clinical assessments will comprise of medical history, WHO functional class, electrocardiogram, blood gas analysis, lung function, 6-minute walking distance, echocardiography cardiopulmonary exercise testing with stress-Doppler echocardiography, laboratory tests including NT-proBNP, invasive hemodynamics using right heart catheterization, and quality of life (questionnaire SF-36) at baseline and after 3 months, worsening of saturation and clinical worsening events.

5 Trial Duration and Schedule

5.1 Study Phases

- Screening Phase: up to 28 days before treatment start
- Treatment phase: 6 months (180 ± 7 days)
- Safety Follow-up: patient's well-being will be monitored by phone after 30 ± 7 days after last intake of study drug.

5.2 Trial Duration

The overall duration of the trial is expected to be approximately 3 years. Recruitment of subjects will start in January 2019 till December 2020.* The actual overall duration or recruitment may vary.

Total trial duration:	[3 years]
Duration of the clinical Phase:	[180 ± 7 + 30 ± 7 follow-up phase]
Beginning of the preparation Phase:	*[Q1 2019]*
FSI (First Subject In):	*[Q1 2019]*
LSI (Last Subject In):	*[Q4 2020]*
LSO (Last Subject Out):	*[Q2 2021]*
DBL (Data Base Lock):	*[Q3 2021]*
Statistical Analyses Completed:	*[Q3 2021]*
Trial Report Completed:	*[Q4 2021]*

6 Selection of Subjects

6.1 Number of Subjects

As calculated in section 10.1, 40 subjects should be enrolled in the clinical trial, 20 subjects per treatment group.

The minimally important difference of 6-minute walking distance in patients with pulmonary hypertension is considered to be 33 meters, according to the literature (Mathai et al. 2012).

A recent study of Ulrich et al. has shown a 25 meter difference between nocturnal oxygen and sham-O_2 for an intervention period of one week with a concentrator device in patients with pulmonary hypertension (Ulrich et al. 2015). We assume a standard deviation of the difference of 50 meters (as seen in the data of Ulrich et al.) and a higher effect of 35 meters due to a longer intervention period and the use of oxygen supply ≥16h/day, which lies also above the threshold of minimally important difference for the 6-minute walking distance.

The primary endpoint will be analysed in a hierarchical testing strategy with Intra-individual analysis of 6MWD in the primary and secondary intervention group (difference from baseline to follow-up).

If (1) is significantly different, the treatment effect on 6MWD will be compared between the primary intervention group and the control group.

Sample size assumptions

If the true treatment effect is at least an increase of 35 meters in the 6-minute walking distance with an equal standard deviation of 50 meters, a sample size of 29 patients will provide a >95% power with a matched-pairs two-sided student's t-test with a significance level of 0.05 (intra-individual comparison of difference baseline to follow-up in primary and secondary intervention group).

If the true treatment effect is at least a control group corrected increase of 50 meters in the 6-minute walking distance with an equal standard deviation of 50 meters, a sample size of 18 patients in each group will provide an 83% power with a two-sided student's t-test with a significance level of 0.05 comparing two independent means (comparison of differences baseline to follow-up between the two groups).

The sample size of 18 patients in each group with an anticipated dropout rate of 10% leads to a final sample size of 40 (20 in each group).

The primary endpoint, 6-minute walking distance, will be compared by ANCOVA of the differences (baseline to follow-up) (1) intra-individual and (2) between the two groups with the baseline value as covariate, providing a power-advantage over the student's t-test which leads to a power of >95% and 83% or more, respectively.

6.2 General Criteria for Subjects' Selection

It is assumed that for any patient, considered for inclusion, a regular diagnostic work up in accordance with PH guidelines (ESC/ERS Guidelines) was performed in advance.

Oxygen saturation will be validated at rest and during exercise at the screening visit. For statistical considerations see section 10.

6.3 Inclusion Criteria

Patients in both groups (n=40) with precapillary PH, WHO class I -IV (mPAP ≥ 25 mm Hg, pulmonary capillary occlusion pressure ≤15 mm Hg), who are stable on optimized pharmacological treatment for at least six weeks and who do not suffer from other cardio-pulmonary disease will be recruited if O_2 partial pressure is repeatedly (<60 mmHg; alternatively, 90% of O_2 saturation) at rest and during physical activity hypoxemia still persist (O_2 partial pressure <60 mmHg SpO2 90 %).

- men and women 18 years of age or older
- patient is diagnosed with Pulmonary Arterial Hypertension (World Health Organization (WHO) Category Group 1-3 (by the WHO Clinical classification system)), including Idiopathic (IPAH), Heritable PAH (HPAH, Familial PAH), and CTEPH, with exceptions as noted in exclusion criteria
- patient is willing and able to provide written informed consent
- patient is willing and able to comply with the protocol, including required follow-up visits
- patient experiences oxygen desaturations below 90% (or pO_2 below 60 mmHg) at rest with oxygen desaturations below 90% (or pO_2 below 60 mmHg) during physical activity
- patient has a stable functional class of PAH with no changes of medication during the last six weeks before inclusion.

6.4 Exclusion Criteria

- Female patient who is pregnant, nursing, or of child bearing potential and is not on a reliable form of birth control
- patient has already been treated with oxygen therapy within the last 3 weeks
- patient with pulmonary venous hypertension
- significant functional limitation in lung function tests (FEV_1>60%, TLC <60%) and CT morphological signs of pulmonary disease
- significant left heart disease, requires acute pharmacological or interventional treatment
- unstable conditions requiring pharmacological or other treatment, intensive care or relevant severe concomitant disease

- patient is enrolled, has participated within the last thirty days, or is planning to participate, in a concurrent drug and/or device study during the course of this clinical trial. Co-enrolment in concurrent trials is only allowed with documented pre-approval from the study manager that there is not a concern that co-enrolment could confound the results of this trial.
- patient has been initiated on a new oral or parenteral PAH therapy in the last two months
- patient has had a recent (within three months) or otherwise unresolved infection requiring antibiotic treatment
- patient with a cardiac index (CI) $\leq$1.8L/min/m^2
- patient is Functional Class IV (New York Heart Association (NYHA))
- active smoking status
- patient with severe resting desaturation (repeatedly SpO_2 $\leq$85%) or severe exercise-induced desaturation before enrolment (SpO_2 <80% for $\geq$10 minutes)

6.5 Criteria for Removal or Withdrawal

6.5.1 Withdrawal of Subjects

A subject will be withdrawn from the trial treatment for the following reasons:

- at their own request or at request of the legal representative
- if, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being
- occurrence of a severe serious adverse event (SAE) caused by the IMP
- occurrence of an adverse event (AE) which makes the continuation of the study undesirable
- new events such as lung embolisms
- severe left heart insufficiency as well as chronic left heart disease with signs of decompensation
- radiological signs of severe interstitial lung disease (pneumonia)
- patient with severe resting desaturation (repeatedly SpO_2 $\leq$85%) and/or severe exercise-induced desaturation (SpO_2 <80% for $\geq$10 minutes)
- noncompliance, defined as oxygen treatment <12 hours per day for >7 days within 6 weeks (equals ~80%), assessed by patient interviews

The Coordinating investigator decides about withdrawal of subjects from trial treatment in case of occurrence of criteria mentioned above. Any decision to continue with the study treatment despite occurrence of any of the withdrawal criteria has to be justified in written form in the Case Record Form (CRF) and in the subject's medical records.

Any patient removed from the study due to an AE or SAE will be monitored up until no more signs and symptoms are verifiable or the subject is on stable condition. The patient, either willingly withdrawn from the study or due to premature termination, will be asked thoroughly to complete all examinations scheduled for the final trial day, and these will be performed as far as possible and documented.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

In case of withdrawal of a subject at his/ her own request, the reason should be asked for as extensively as possible and documented.

All efforts will be made to follow up the subject.

A subject may/ will be withdrawn from <u>all trial related procedures</u> (including follow-up visits) for the following reasons:

- at his/her own request or at request of his/her legal representative
- non-adherence to the trial-related requirements, which may (have) influence(d) the validity of the trial data

In case of clinical worsening / deterioration of patients in the control group, an early termination visit may be performed and patients may be offered to take part in the interventional treatment arm in order to receive long-term oxygen treatment ahead of schedule.

6.5.2 Replacement of Subjects

Per treatment arm, 20 subjects will be enrolled and included into the intention to treat (ITT) and safety analysis (SA). Subjects who terminate the study prematurely will not be replaced as a 20% drop-out rate is included in this sample size calculation.

6.5.3 Premature Closure of the Clinical Trial

The trial can be prematurely closed or suspended by the Coordinating Investigator in case if new serious risks for subjects become known. The Ethics Committee (EC) and the competent regulatory authorities must then be informed. Furthermore, the Ethics Committee(s) and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (completed, partially completed, and blank CRF, randomization envelopes, IMP, etc.) must be returned to and/or kept within the files of the Coordinating Investigator.

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial centres and investigators.

6.6 Prior and Concomitant Illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and will be documented on the appropriate pages of the CRF as medical history. Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

6.7 Prior and Concomitant Treatments

Relevant additional treatments administered to the subjects on entry to the trial or at any time during the trial are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

In case of clinical worsening and if clinically indicated additional PAH-targeted rescue medication will be initiated at the discretion of the investigators. Participants will not be included if scheduled to receive another investigational drug during the course of this study.

7 Investigational Medicinal Product

7.1 General Information about the Investigational Medicinal Product

7.1.1 Oxygen (O_2)

Investigational medicinal product: Oxygen medicAL

International Nonproprietary Name (INN): Oxygen

ATC code: V03AN01

Pharmaceutical formulation: $O_2 \geq 99.5$ Vol. %; other components $H_2O \leq 67$ parts per million by volume (ppmv), $CO_2 \leq 300$ ppmv, $CO \leq 5$ ppmv

Route of administration: nasal

Time and frequency of administration: long-term oxygen therapy (LTOT) given continuously during ≥16h/day for 12 weeks

Dosage: titration

Storage conditions: no special storage conditions required

Marketing authorization holder: different marketing authorization holders will be available, as oxygen will be prescribed according to marketing approval in Germany /(e.g. VitalAire, Linde, Vivisol, …).

Devices: liquid oxygen may be applied via different devices, such as Freelox, Liberator, Stroller, Spirit, Helios, Inogen One

7.2 Therapeutic Effects

Most patients with PAH, except those with congenital heart defects and pulmonary-to-systemic shunts, have minor degrees of hypoxemia at rest and during the night (Hildebrand et al. 2012).

Current recommendations including the pneumological guidelines for LTOT (Galiè et al. 2015) are based on evidence in patients with chronic obstructive pulmonary disease, as data for patients with PH are lacking:

- When O_2 partial pressure is repeatedly <8 kPa (<60 mmHg; alternatively, 90% of O_2 saturation), patients are advised to use O_2 to achieve a saturation of >8 kPa. (Galiè et al. 2015)
- The use of ambulatory O_2 can be considered when there is evidence of a symptomatic response or correction of exercise-induced desaturation.

In patients with COPD it has already been shown that supplemental oxygen improves dyspnea and the distance walked during a five-minute walk test compared to supplemental air (Nonoyama et al. 2007). Data regarding survival benefits due to long-term oxygen therapy in COPD is inconsistent (Medical Research Council Working Party 1981, Nocturnal Oxygen Therapy Trial Group 1980, Chaouat et al. 1999, Górecka 1997).

There are only few studies investigating the effect of oxygen supply in pulmonary hypertension, most of which merely investigate acute effects of O_2 administration. Short-term oxygen administration has been shown to reduce mean pulmonary arterial pressure, pulmonary vascular resistance and to increase cardiac output in PAH patients (Leuchte et al. 2013, Roberts et al. 2001). In one study, oxygen supply also reversed the progression of PH in patients with chronic obstructive pulmonary disease (COPD) (Weitzenblum et al. 1985).

One recent randomized-controlled trial indicates that O_2 given during cardiopulmonary exercise significantly improves maximal work rate and endurance (Ulrich et al. 2017). Furthermore, nocturnal oxygen supply for one week significantly improved 6-minute walking distance in

patients with PH (Ulrich et al. 2015), sleep-associated breathing difficulties, exercise performance during the day as well as cardiac repolarisation (Schumacher et al. 2014). Patients with Eisenmenger's syndrome gain little benefit from nocturnal O_2 therapy (Sandoval et al. 2001).

Whether these positive effects of O_2 supplementation during exercise would translate into long-term improvements of exercise capacity, quality of life, hemodynamics and disease progression is not known to date. Up to now, there are no randomised studies suggesting that long-term O_2 therapy is indicated or when it should be initiated.

7.3 Known Side Effects

People exposed to high concentrations of oxygen for long periods of time are at risk for oxygen toxicity. These include ventilator patients, premature infants and people receiving hyperbaric oxygen treatment (Collopy et al. 2012). For this reason, it is recommended that when oxygen therapy is warranted, the lowest effective dose be given (Jenkinson et al. 1993).

Possible side effects of oxygen treatment are drying out of the mucous membranes in case of inappropriate application, coughing and increased dyspnea in case of oversupply. Patients with a serious adverse event occurring during the study treatment will be followed by the study team until the serious adverse event will have resolved to the pre-study level and/or will have been addressed according to best clinical practice. Patients withdrawing from the study prematurely will have a final physical examination.

7.4 Dosage Schedule, Titration and Administration

Study medication will be oxygen (O_2) in diverse concentrations, titrated until a SaO_2>90% or pO_2 >60 mmHg is achieved, for 20 patients vs. no supplemental O_2 for 20 patients over 90 ± 7 days. Patients of the control group will be offered to participate in the interventional treatment arm after they have terminated the control period (partial cross-over; secondary intervention group). After the end of the study it is up to the judgment of the investigator to prescribe oxygen to all patients who might benefit from the treatment. This decision will be based on the physician's and the patient's estimation taking into account the observed individual treatment effect, progression of disease, patient view and any comments from the Ethics Committee, if applicable. Patient care and monitoring will be performed in the patients' specialized centers.

Titration

Oxygen flow adaptation (titration): Until a SpO_2 >90% or pO_2 >60mmHg is achieved

Administration

Oxygen therapy will be administered inhaled (nasal).

7.5 Treatment Assignment

Patients who have signed the consent form will be given a unique screening number including centre number (e.g. 01, 02…) and patient ID (001, 002, …). Screening number will ascend, starting with 001, 002, etc. If the patient is eligible for the prospective drug trial, a 1:1 randomization will be performed into oxygen and no-supplemental oxygen group and a consecutive randomization number will be allocated to the patient. The oxygen supplier will provide the oxygen to the patients in the intervention group in a concentration based on the initial titration performed during baseline. The trial medication will be administered to subjects only after confirming their eligibility after the initial screening. Subjects withdrawn from the trial retain their identification codes (e.g. randomization number, if already given). New subjects must always be allotted a new identification code.

7.6 Randomization

PAH patients experiencing oxygen desaturations at rest and during physical activity, when O_2 partial pressure is repeatedly <8 kPa (<60 mmHg; alternatively, 90% of O_2 saturation). Patients will be divided in a supplemental-oxygen group (primary intervention group) and no-supplemental-oxygen group (control group). Patients of the control group will be offered to participate in the interventional treatment arm after they have terminated the control period (partial cross-over; secondary intervention group). Randomization will be performed in a 1:1 ratio. Randomization to one of the groups will be performed by block randomization. Randomization lists will be created by the data management using a computer to generate random numbers.

7.7 Labelling and Supply

Indication of oxygen supply will be determined according to current recommendations of long term oxygen treatment in patients with pulmonary hypertension. Oxygen treatment with liquid oxygen as applicable will be prescribed to patients of the intervention group. Oxygen flow will be determined by titration, aiming at O_2 saturation values of >90% at rest.

Patients in the control group will be offered prescription of oxygen supply after the end of the control period (control phase), serving as secondary intervention group.

7.8 Supplies and Accountability

Oxygen treatment with liquid oxygen as applicable will be prescribed to patients of the intervention group.

7.9 Compliance

Oxygen will be prescirbed to the subjects by the investigator. Compliance will be assessed by daily measurements of oxygen saturation at home. Furthermore, the patients will receive a patient diary recording oxygen saturation and time points. The patient diary will be checked for compliance at each study visit. Noncompliance will be defined as oxygen treatment <12 hours per day for >7 days within 6 weeks (equals ~80%), assessed by patient interviews.

8 Trial Methods

8.1 Overview of visits and assessments

Primary intervention group						
Assessments	**Screening** -28 days **1**	**Visit 1 Baseline** Day 1 **1**	**Phone visit 1** Day 30 ± 14 days **1**	**Phone visit 2** Day 60 ± 14 days **1**	**Visit 2** Day 90 ± 14 days **1**	**Follow up (Treatment group)** Day 120 ± 14 days **1**
Informed Consent	1	-	-	-	-	-
Inclusion / exclusion criteria	1		-	-		
Evaluation of prior and concomitant medication	1	1	-	-	1	-
PAH classification, etiology, diagnosis date,	1	-	-	-	-	-
WHO FC	1	1	-	-	1	-
Vital Sign Measurements incl. Borg Dyspnea Score, Heart Rate and SpO_2	1	1	-	-	1	-
6MWD (for initiation of a new PAH-specific therapy: within 3 months prior or at)	1	1	-	-	1	-
Height / Weight	1	1	-	-	1	-
Lung function testing (TLC; DLCO)	1	1	-	-	1	-
Blood gas analysis	1	1	-	-	1	-
RHC hemodynamics: mPAP, mRAP, PAWP, PVR, cardiac index (for initiation of trial-specific therapy: within 6 months prior or at)	1*	-	-	-	1	-
Physical examination	1	1	-	-	1	-
Hematology, Chemistry	1	1	-	-	1	-
NT-proBNP	1	1	-	-	1	-
For females only: Pregnancy test - child bearing potential - currently pregnant (Yes***/No/Unknown)	1	1	-	-	1	-
Echocardiogram, Stress-Echo, Cardiopulmonary exercise test	1	1	-	-	1	-
Quality of life (SF-36)	1	1	-	-	1	-
Adverse Events	-	1	1	1	1	1
Phone visits	-	-	1	1	-	1

* RHC at baseline will only be performed in patients who have not performed a RHC within the preceding 6 months

Secondary intervention group (control group with crossover)

Assessments	**Screening** -28 days **1**	**Visit 1: Baseline** Day 1 **1**	**Phone visit 1** Day 30 ± 14 days **1**	**Phone visit 2** Day 60 ± 14 days **1**	**Visit 2** Day 90 ± 14 days **1**	**Phone visit 3** Day 120 ± 14 days **1**	**Phone visit 4** Day 150 ± 14 days **1**	**Visit 3** Day 180 ± 14 days **1**	**Follow up (Control group)** Day 210 ± 14 days **1**
Informed Consent	1	-	-	-	-	-	-	-	-
Inclusion / exclusion criteria	1	-	-	-	-	-	-	-	-
Evaluation of prior and concomitant medication	1	1	-	-	1	-	-	1	-
PAH classification, etiology, diagnosis date,	1	-	-	-	-	-	-	-	-
WHO FC	1	1	-	-	1	-	-	1	-
Vital Sign Measurements incl. Borg Dyspnea Score, Heart Rate and SpO_2	1	1	-	-	1	-	-	1	-
6MWD (for initiation of a new PAH-specific therapy: within 3 months prior or at)	1	1	-	-	1	-	-	1	-
Height / Weight	1	1	-	-	1	-	-	1	-
Lung function testing (TLC; DLCO)	1	1	-	-	1	-	-	1	-
Blood gas analysis	1	1	-	-	1	-	-	1	-
RHC hemodynamics: mPAP, mRAP, PAWP, PVR, cardiac index (for initiation of trial-specific therapy: within 6 months prior or at)	1*	-	-	-	1	-	-	1	-
Physical examination	1	1	-	-	1	-	-	1	-
Hematology, Chemistry	1	1	-	-	1	-	-	1	-
NT-proBNP	1	1	-	-	1	-	-	1	-
For females only: Pregnancy test - child bearing potential - currently pregnant (Yes***/No/Unknown)	1	1	-	-	1	-	-	1	-
Echocardiogram, stress-echocardiography, cardio-pulmonary exercise test	1	1	-	-	1	-	-	1	-
Quality of life (SF-36)	1	1	-	-	1	-	-	1	-
Adverse Events	-	1	1	1	1	1	1	1	1
Phone visit	-	-	1	1	-	1	1	-	1

* RHC at baseline will only be performed in patients who have not performed a RHC within the preceding 6 months

8.2 Assessments

8.2.1 Physical examination and demographic data

The physical examination comprises measurement of body weight and height (height will be measured only once) and a routine internal medical examination. Physical examinations will be performed to ensure suitability according to the inclusion and exclusion criteria and to document the health status before and following treatment with the IMPs.

8.2.2 Hemodynamic parameters

Hemodynamic parameters will be determined by right heart catheterization according to current guidelines (Opitz et al. 2011). The right heart catheterization (RHC) will be performed at baseline only in patients who have not performed a RHC within the preceeding 6 months during Visit 2 and end of the study only to the control group.

Directly, invasive measured parameters are: right atrial pressure, mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PAWP), cardiac output (CO), cardiac index (CI), and venous oxygen saturation (SvO_2). During the right heart catheterization, a continuous ECG will be performed. The values will be based on two to three measurements at one time point. Hemodynamics will be measured at rest and during exercise with a supine bicycle ergometer (all parameters except right atrial pressure, which will be measured at rest and optionally during exercise).

Directly non-invasive measured parameters: heart rate, blood pressure

Methodology: Swan-Ganz catheterization and thermodilution methodology

Pulmonary hemodynamics by right heart catheterization:

- cardiac index in liters per minute per square meter (of body surface area) /(CI)
- systolic pulmonary artery pressure (sPAP)
- mean pulmonary artery pressure (mPAP)
- diastolic pulmonary artery pressure (dPAP)
- pulmonary artery wedge pressure (PAWP)
- right atrial pressure (RAP)
- pulmonary vascular resistance (PVR)
- cardiac output and ejection fraction (CO, HZV), cardiac index (CI)
- central venous saturation via blood gas analysis from pulmonary artery

8.2.3 Echocardiography and Stress Doppler Echocardiography with cardiopulmonary exercise testing

Echocardiography will be performed according to current guidelines (Rudski et al. 2010).

Following parameters will be assessed: systolic pulmonary arterial pressure (sPAP, mmHg), right ventricular area (RV-area, cm^2), and right atrial area (RA-area,cm^2), tricuspid annular plane systolic excursion (TAPSE), left ventricular eccentricity index (LV-EI), RV-pump function and LV- pump fuction (EF).

WHO protocol for incremental increase of workload (25 Watt every 2 minutes) will be used to assess cardiopulmonary response during exercise, including the following parameters:

- sPAP,
- RV-pump function,
- heart rate,
- systemic blood pressure,
- oxygen consumption,
- oxygen consumption/kg body weight,
- oxygen saturation,
- minute ventilation,
- carbon dioxide and oxygen equivalents,
- O_2 pulse,
- ventilatory threshold,
- respiratory reserve.

8.2.4 Determination of WHO functional class

Functional assessment of pulmonary hypertension will be performed according to the WHO-Functional Class, i.e. the Evian Symposium, 1998, modified New York Heart Association (NYHA) Classification:

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea of fatigue, chest pain or near syncope.

Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

8.2.5 Lung function tests and blood gas analysis

Lung function test: Body plethysmography (preferred method) including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), total lung capacity (TLC), diffusion-limited carbon monoxide (DLCO), residual volume), normally accounting for about 25% of TLC.

Blood gas analysis: capillary or arterial blood gas analysis; partial pressure of oxygen and carbon dioxide, oxygen saturation (SpO_2), pH values, bicarbonates, base excess.

If the patient receives oxygen the amount will be recorded in the CRF in liters/minute.

8.2.6 6-minute walking distance and Borg dyspnea Score (CR 10)

Both tests will be performed according to ATS guidelines (ATS 2002). The patient is asked to walk along a prescribed path as far as possible during a 6 minute interval of time. The patient may walk at whatever pace he/she feels comfortable with the goal of walking the most distance he/she feels possible. If the patient feels the need to rest, he/she may do this. Blood pressure, heart rate and oxygen saturation will be measured before and after the test. The test will be performed two times at each time point: one test will be performed without oxygen; one test will be performed with oxygen supply (for all tests with the same amount of oxygen for each patient, which will be determined at baseline by titration). In between tests, the patient should rest for at least 30 minutes to prevent from interacting effects of oxygen and/or exhaustion.

The Borg Scale (Breathlessness Scale) is commonly used to measure shortness of breath of patients or in sports medicine. In this study, the Borg Scale will be applied to record dyspnea immediately following the 6-minute walk test.

The Borg Scale comprises the following parameters according to the ATS guidelines (ATS 2002):

0	Nothing at All
0.5	Very very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat Moderate
5	Severe
6	
7	Very Severe
8	
9	Very very severe (almost maximal)
10	Maximal

8.2.7 Quality of Life (QoL)

QoL will be assessed using the SF 36-questionnaire (see Appendix) that will be handed out to the patients. Scoring will be carried out according to the test manual.

The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale, i.e. a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The eight sections are: vitality; physical functioning; bodily pain; general health perceptions; physical role functioning; emotional role functioning; social role functioning; mental health.

8.2.8 Vital signs

Blood pressure, heart rate and oxygen saturation will be measured after the patient has been at rest for at least 5 minutes.

Blood pressure (BP; systolic and diastolic) will be measured by means of a standard manual or an automatic blood pressure measuring device (cuff method). Nevertheless, the same method should be used during the entire study period (the type of device has to be recorded into the CRF). The same upper arm will be used for each measurement of blood pressure, preferably the left arm.

Heart rate (HR) and oxygen saturation (SaO_2) will be measured by pulse oximetry.

8.2.9 Electrocardiography

A 12-lead electrocardiogram (ECG) will be performed. For deriving the 12-lead ECGs the patients should always be in supine position. The 12-lead ECGs should be derived after a resting period of at least 10 minutes. The investigator will review the ECGs for potential AEs.

A continuous 3-lead ECG monitoring will be applied during right heart catheterization.

8.2.10 Clinical laboratory investigations

Clinical laboratory investigations will comprise:

Biomarkers	NT-proBNP
Additional	laboratory tests that usually include inflammation factors, kidney, liver, blood cell count parameters

All laboratory assessments will be determined locally on-site.

8.3 Study Phases and Visits

8.3.1 Screening Phase

Eligible patients will be asked to participate upon written informed consent. In case of agreement medical history will be taken and they will undergo screening examinations.

The right heart catheterisation should not be older than 6 months before baseline and should be performed after the patient was on stable treatment for at least six weeks. In patients who have not performed a right heart catheter within the preceding 6 months, invasive hemodynamics will be measured before the beginning of the intervention. Oxygen will be prescribed and the oxygen system will be delivered to the patient. Baseline will be within 28 days after screening.

Screening visit, baseline visit, month three and month four (follow-up); month six according to month three assessment in secondary intervention group and respective follow-up.

Secondary intervention group will have an additional visit after 180 days (in analogy to month three visit).

8.3.2 Visit 1 Baseline / Randomization [DAY 1]

Baseline visit may be performed according to the hospital's routine practice as in-hospital stay. **Baseline / Day 1 visit 1:** During the visit clinical evaluation, laboratory, blood gas analysis, SF-36 questionnaire, 6MWD, echocardiography, Stress-Doppler-echocardiography and cardio-pulmonary exercise testing will be assessed and concomitant medications and diseases/clinical symptoms recorded. After the explanation of intake and titration, oxygen or no supplemental oxygen will be handed out. The treatment diary will be handed to the patients. Patient's eligibility to participate in the IIT will be confirmed. Subsequently, patients will be randomized to either treatment arm with oxygen or the no supplemental O_2 arm.

8.3.3 DAY 1-90 (3 Months)

Oxygen vs. no oxygen supply for at least 16 hours a day will be performed. Interim phone calls each month (month 1 and 2) and assessment of adverse events.

8.3.4 Month three / Day 90 visit 2 (± 7 days)

Clinical evaluation, laboratory, blood gas analysis, SF-36 questionnaire, 6MWD, echocardiography, stress-echocardiography, cardiopulmonary exercise test, right heart catheterization and adverse events will be assessed. Patients of the control group will be offered to participate in secondary intervention group to receive long-term oxygen treatment. (week 12 visit will be performed again after 12 weeks, in total 24 weeks of study with control and secondary intervention phase).

8.3.5 Month four / Day 120 (± 7 days) (30 days after close out)

The follow-up visit to assess adverse events will then take place in terms of an outpatient visit or phone call.

8.3.6 Termination Visit

In case the decision has been made to stop the study prematurely, a termination visit should be performed at the respective point in time or as soon as possible after stop of medication. In general, the same safety and efficacy relevant measurements should be performed as at the last Visit, especially the hemodynamic measurements. In case of clinical worsening / deterioration of patients in the control group, an early termination visit may be performed and patients may be offered to take part in the interventional treatment arm in order to receive long-term oxygen treatment ahead of schedule.

8.3.7 Pre-treatment period and duration of observation and follow-up

There will be non-pre-treatment period. The duration of the observation will be 90 days (up to 180 days in the control group with switch to secondary intervention group) + follow-up period. The follow-up period will be 30 days after close out visit each patient performs a follow-up Visit Clinical follow-up of all SAEs until they have been resolved.

8.4 Methods of Data Collection

Data will be entered on a paper-based CRF by the center's study nurses. The CRFs will be collected by the clinical monitor and forwarded to data management. All data will be entered into one database by the data management followed by data cleaning (e.g. range checks), queries and preparation for data analysis.

8.4.1 Efficacy Parameters

The primary efficacy variable is the distance walked in 6 minutes in meters.

8.4.2 Safety Parameters

Safety variables include and will be determined:

1. Electrocardiogram (ECG)
2. Vital signs: Blood pressure (BP), heart rate/pulse (HR)
3. Hemodynamics: Cardiac Output, venous oxygen saturation (during RHC)
4. Echocardiography
5. Clinical laboratory investigations
6. Concomitant medication
7. Concomitant diseases
8. Adverse events

8.5 Plan for Treatment of Care after the Trial

After 6 months of supplementation, oxygen therapy may be prescribed to all patients who might benefit from the treatment. This decision will be based on the physician's and the patient's estimation. Patient care and monitoring will be performed in the patients' specialized centers.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

According to Good Clinical Practice GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the IMP.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Significant changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening (change in nature, severity or frequency) of medical conditions/ diseases existing before clinical trial start
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.
- Events related or possibly related to concomitant medications

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

AEs are classified as "non-serious" or "serious".

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the subject was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe)
- Requires subject hospitalization or prolongation of existing hospitalization (unless the admission results in a stay of less than 12 hours or the admission is pre-planned or the admission is not associated with an adverse event)
- Results in persistent or significant disability/ incapacity or
- Is a congenital anomaly/ birth defect.
- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious (e.g. treatment at home for allergic bronchospasm).

The following events don't need to be reported as an SAE:

- Planned hospitalization due to scheduled elective catheterization (e.g. reevaluation for Eurotranplant listing), scheduled hospitalization for further diagnostics or therapeutic measures.

9.1.3 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the applicable "Summary of Product Characteristics" (SmPC) or scientific literature. Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute 'unexpected' events.

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to IMP and 'unexpected', i.e. the nature and/ or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs). The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

In case, either the investigator who primarily reported the SAE or the second assessor classify the SAE as 'suspected' (i.e. either related or *probably* or *possibly related* to the IMP *or not assessable*) and the SAE is unexpected it will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee, the competent higher federal authority, i.e. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), and to all participating investigators.

9.1.5 Grading of AEs

The **grading** of an AE should be assessed by the investigator according to the 5-grade scale defined in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 established by the National Cancer Institute (NCI) of the United States of America (USA) as follows:

Grade 1: mild AE, temporary event which is tolerated well by the subject

Grade 2: moderate AE; event which results in discomfort for the subject and impairs his/ her normal activity

Grade 3: severe AE; event which results in substantial impairment of normal activities of subject

Grade 4: life-threatening AE or AE causing disablement

Grade 5: death related to AE

9.1.6 Relationship and outcome of AEs, action taken

The investigator will evaluate each AE that occurred after administration of the IMP regarding the **coherency** with the administration of the investigational medicinal product possibly:

related: There is a reasonable possibility that the event may have been caused by IMP. A certain event has a **strong temporal relationship** and an alternative cause is unlikely.

probable: An AE that has a reasonable possibility that the event is likely to have been caused by IMP. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.

possible: An AE that has a reasonable possibility that the event may have been caused by IMP. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.

unlikely: Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication

appear to explain the reported adverse event.

not related: An AE that does not follow a reasonable temporal sequence related to IMP and is likely to have been produced by the subject's clinical state, other modes of therapy or other known etiology.

not assessable: There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

The **outcome** of an AE at the time of the last observation will be classified as:

Recovered/ resolved	all signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation
Recovering/ resolving	the intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution
Not recovered/ not resolved	signs and symptoms of an AE are mostly unchanged at the time of the last interrogation
Recovered/ resolved with sequel	actual signs and symptoms of an AE disappeared but there are sequels related to the AE
Fatal	resulting in death. If there is more than one adverse event only the adverse event leading to death (possibly related) will be characterized as 'fatal'
Unknown	the outcome is unknown or implausible and the information cannot be supplemented or verified

The **action taken** with the IMP will be assigned to one of the following categories:

'Dose not changed': no change in the dose of IMP.

'Dose reduced': reduction in the dose of IMP.

'Dose increased': increase in the dose of IMP.

'Drug withdrawn': discontinuation of IMP.

'Unknown': the information is unknown or implausible and it cannot be supplemented or verified.

'Not applicable': the question is implausible (e.g. the subject is dead).

The term 'Countermeasures' refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. The following categories will be used to categorize the countermeasures to adverse events:

None: no action taken

Drug treatment: newly-prescribed medication or change in dose of a medication

Others: other countermeasures, e.g. an operative procedure

9.2 Period of Observation and Documentation

All AEs reported by the subject or detected by the investigator, will be collected during the trial and must be documented on the appropriate pages of the CRF. AEs must also be documented in the subject's medical records.

In this trial, all AEs that occur after first administration of the IMP up to the last visit (i.e. follow-up visit) will be documented on the pages provided in the CRF. AEs will be assessed by the investigator using no-leading questions or observed during any visit during the whole study. The patient should be motivated to report any AEs by phone to the investigator occurring in between study visits. All subjects who have AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition.

Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

9.3 Reporting of Serious Adverse Events by the Investigator

All SAEs must be reported by the investigator to the responsible Safety Officer within 24 hours after the SAE becomes known using the "Serious Adverse Event" form. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, information regarding onset, end date, severity, outcome and action taken with the IMP, an assessment of the causal relationship between the event and the trial medication.

The reporting will be performed by faxing a completed 'SAE Form' to the KKS Heidelberg,
Fax number: 06221-56-33725

At the time of the initial report, the investigator will fill in a SAE form comprising the following information:

- Patient/subject demographics
- Start and end date of treatment with the IMP
- Nature of the AE including date of onset, severity and treatment (including hospitalization)
- Action taken with respect to the IMP

- Relationship to the IMP in the opinion of the investigator
- Relevant concomitant drug therapy, relevant medical history, relevant test and diagnostic procedures
- Outcome (clinical state at time of current observation)
- Recovery date (if available)
- In the case of death, the cause and post-mortem findings (if available).

Any requested supporting documentation (e.g. ECG, laboratory results, autopsy report) should be sent to the same address stated above. The original SAE-reports and all other reports will be kept by the investigator.

9.4 Expedited Reporting

SUSARs are to be reported to the ethics committee, competent higher federal authority (BfArM), and to all participating investigators within regulative defined timelines, i.e. they are subject to an expedited reporting.

All SAE will be subject to a second assessment by a designated person, who will be independent from the reporting investigator and the trial sponsor. The designated person for the present trial, referred to as second assessor is: Dr. Christian Nagel.

The assessor will fill out a 'Narrative Second Assessment Form' for each SAE containing at least the following information: i) Assessment of relationship between SAE and IMP; ii) Assessment of expectedness of SAE (derived from SmPC); iii) Assessment of relationship between SAE and underlying disease iv) Statement if the benefit/ risk assessment for the trial did change as a result of the SAE.

The expedited reporting (to competent authority, responsible ethics committee and investigators) will be carried out by the responsible Safety Officer at KKS Heidelberg.

Details concerning the SAE management including the reporting of SUSARs will be described in the separate document "Safety Manual".

9.5 Emergency Treatment

During and following a subject's participation in the trial, the investigator should ensure that adequate medical care is provided to a subject for any AE including clinically significant laboratory values. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

In case of clinical worsening and if clinically indicated additional PAH-targeted rescue medication will be initiated.

10 Statistical Procedures

10.1 Sample Size Calculation

In this randomized study patients with confirmed PAH will be randomized into two groups: one group receiving oxygen and without oxygen supplementation.

The minimally important difference of 6-minute walking distance in patients with pulmonary hypertension is considered to be 33 meters, according to the literature (Mathai et al. 2012).

A recent study of Ulrich et al. has shown a 25 meter difference between nocturnal oxygen and sham-O_2 for an intervention period of one week with a concentrator device in patients with pulmonary hypertension (Ulrich et al. 2015). We assume a standard deviation of the difference of 50 meters (as seen in the data of Ulrich et al.) and a higher effect of 35 meters due to a longer intervention period and the use of oxygen supply ≥16h/day, which lies also above the threshold of minimally important difference for the 6-minute walking distance.

The primary endpoint will be analysed in a hierarchical testing strategy. The main comparison will be the difference in a) intra-individual treatment effect and b) between oxygen arm and no oxygen. The primary endpoint will be the intra-individual analysis of 6MWD in the primary and secondary intervention group (difference from baseline to follow-up). If the primary endpoint is significantly different, the treatment effect on 6MWD will be compared between the primary intervention group and the control group. In order to cover a possible 20% drop-out rate, we will include 20 patients in each group N= 40 patients in total.

The sample size was calculated by means of a two-sided two-sample t-test. Primary efficacy analysis will be performed by an ANCOVA model including baseline scores as covariate, thereby yielding a power advantage over the standard t-test used for sample size calculation. The calculated sample size will thus provide 90% power or more.

Sample size assumptions

1. If the true treatment effect is at least an increase of 35 meters in the 6-minute walking distance with an equal standard deviation of 50 meters, a sample size of 29 patients will provide a >95% power with a matched-pairs two-sided student's t-test with a significance level of 0.05 (intra-individual comparison of difference baseline to follow-up in primary and secondary intervention group).

2. If the true treatment effect is at least a control group corrected increase of 50 meters in the 6-minute walking distance with an equal standard deviation of 50 meters, a sample size of 18 patients in each group will provide a 83% power with a two-sided student's t-test with a significance level of 0.05 comparing two independent means (comparison of differences baseline to follow-up between the two groups).

   The sample size of 18 patients in each group with an anticipated dropout rate of 10% leads to a final sample size of 40 (20 in each group).

The sample size was calculated by means of a two-sided two-sample t-test. Primary efficacy analysis will be performed by an ANCOVA model including baseline scores as covariate, thereby yielding a power advantage over the standard t-test used for sample size calculation. The calculated sample size will thus provide 90% power or more. The primary endpoint, 6-minute walking distance, will be compared by ANCOVA of the differences (baseline to follow-up) (1) intra-individual and (2) between the two groups with the baseline value as covariate, providing a power-advantage over the student's t-test which leads to a power of >95% and 83% or more, respectively.

10.2 Analysis Variables

Primary Outcome:

The primary endpoint will be analysed in a hierarchical testing strategy with

1. Intra-individual analysis of 6MWD in the primary and secondary intervention group (difference from baseline to follow-up)
2. If (1) is significantly different, the treatment effect on 6MWD will be compared between the primary intervention group and the control group.

Secondary Outcome Variables:

The following study procedures will be performed in every patient according to the visits schedule and analyzed as secondary efficacy variables. The methods for analysis will be the same as for the primary endpoint. Parameters/assessments comprise

- quality of life assessed by the SF-36 questionnaire (two main summation scores, eight subscales)

- Feasibility of oxygen treatment, assessed by patient consent to participate in the study (recruitment rate) and by patient compliance

- History, questionnaire evaluation, and clinical examination:
  Complete medical history will be obtained. Physical examination will include weight, height, blood pressure, heart rate, cardiac and pulmonary auscultation, assessments of jugular distension and peripheral oedema. WHO functional class will be assessed by specific questionnaire. Quality of life will be assessed by the short form of the medical outcome questionnaire (SF-36). Assessment of compliance via questionnaire.

- Echocardiography:
  Following parameters will be assessed: systolic pulmonary arterial pressure (sPAP, mmHg), right ventricular area (RV-area, cm^2), and right atrial area (RA-area,cm^2), tricuspid annular plane systolic excursion (TAPSE), left ventricular eccentricity index (LV-EI), RV-pump function

- Stress-Doppler-echocardiography and cardiopulmonary exercise testing (spiroergometry):
  WHO protocol for incremental increase of workload (25 Watt every 2 minutes) will be used to assess cardiopulmonary response during exercise, including the following parameters:
  - sPAP,
  - RV-pump function,
  - heart rate,
  - systemic blood pressure,
  - oxygen consumption,
  - oxygen consumption/kg body weight,
  - oxygen saturation,
  - minute ventilation,
  - carbon dioxide and oxygen equivalents,
  - O_2 pulse,
  - ventilatory threshold,
  - respiratory reserve.

- Analyses of blood samples:
  Venous blood will be analysed to determine:
  - N-terminal natriuretic peptide (NT-pro BNP)

- And additional laboratory tests that usually include inflammation factors, kidney, liver, blood cell count parameters

- Capillary blood for blood gas analyses:
  - oxygen partial pressure
  - carbon dioxide partial pressure
  - oxygen saturation of the blood(SaO_2)
  - pH values
  - Bicarbonates
  - Base Excess

- Pulmonary hemodynamics by right heart catheterization:
  - cardiac index in liters per minute per square meter (of body surface area) /(CI)
  - systolic pulmonary artery pressure (sPAP)
  - mean pulmonary artery pressure (mPAP)
  - diastolic pulmonary artery pressure (dPAP)
  - pulmonary artery wedge pressure (PAWP)
  - right atrial pressure (RAP)
  - pulmonary vascular resistance (PVR)
  - cardiac output and ejection fraction (CO, HZV), cardiac index (CI)
  - central venous saturation, via blood gas analysis from pulmonary artery

10.3 Definition of Trial Population to be analysed

All patients randomized and treated will be valid for the intention-to-treat analysis population. A randomized patient is valid for the intention-to-treat, if he/she had at least one day of oxygen administration.

Major protocol deviations are:

1. Patients who do not meet the inclusion criteria
2. Administration of study medication not according to protocol (e.g. compliance less than 80% or greater than 120%)

The above specifications of the analysis populations are in accordance with the recommendations given in the ICH-E9 Guideline “Note for guidance on statistical principles for clinical trials”.

10.4 Statistical Methods

10.4.1 General

Descriptive statistics

All data (demographic and other baseline characteristics, continuous data at each visit and their change to baseline) will be listed and trial summary tables will be provided.

Descriptive statistics will be displayed by treatment with and without oxygen supplementation corrected for the active treatment group, including the usual location and scale statistics (mean, median, standard deviation, standard error, first and third quartiles, minimum and maximum) and 95% confidence limits of mean and median.

Frequency tables for qualitative data will be provided.

Hypotheses and statistical interference

Hypothesis 1

Null-Hypothesis (H_0): The mean of the primary endpoint of the treatment group is the same at baseline and after 3 months.

Alternative hypothesis (H_1): The mean of the primary endpoint after 3 months differs from the distribution at baseline in the active group.

If not mentioned otherwise, all statistical tests will be performed with a type I two-sided error rate of $\alpha = 0.05$

Efficacy analysis

The primary efficacy analysis will be performed in patients valid for intention-to-treat analysis. The per-protocol analysis will be supportive.

Primary endpoint

The evaluation of the primary efficacy endpoint will be the change from baseline to 6 months in the 6-minutes walking distance in meters. The primary analysis set will be intention to treat set.

Cases of missing values, where the patient withdraws or dies will be described and compared to the per-protocol set.

The main comparison will be the difference in treatment effect between O_2 arm and no O_2 supply arm. 95% confidence intervals of treatment difference will also be calculated. The primary comparison will be an ANCOVA model including baseline scores as covariate.

The above approach assumes 6-minute walking distance will be approximately normally distributed.

Secondary efficacy variables will be formally tested for statistical significance of a difference between the oxygen supplementation and no oxygen supplementation arm.

Secondary efficacy analysis comprises quality of life (SF-36 questionnaire), feasibility of oxygen treatment assessed by patient consent to participate in the study, history, questionnaire evaluation, and clinical examination, echocardiography, stress-doppler-echocardiography and cardiopulmonary exercise testing, laboratory parameters, capillary blood for blood gas analyses, pulmonary hemodynamics by RHC. WHO functional class is supposed either to remain the same, to improve by one or two categories, or to deteriorate by one category in most cases. A change score (baseline minus end of study) will be calculated, which could go from -3 (class 4 at baseline and class 1 at end of study) to +3 (class 1 at baseline and class 4 at end of study). This will be analyzed using the Wilcoxon test.

Safety analysis

The safety analysis will be performed in the population valid for safety. All tabulations will be descriptive only. Tables will be produced for drug-related treatment-emergent adverse events and serious adverse events.

Mortality in the 6 month period of the study will be summarized descriptively. Any deaths in the study period will be listed, with day of death relative to start and stop of study drug and cause of death. Vital signs will be summarized by visit and treatment group.

Biometric analysis will be defined in the statistical analysis plan which has to be authorized before data base lock by the biometrician and the Coordinating Investigator.

11 Data Management

11.1 Data Collection

A paper-based case report form (CRF) will be used in this study. All entries made in the CRF must be verifiable against source documents. The source data parameter to be verified and the identification of the source document must be documented.

All findings including clinical and laboratory data will be documented in the subject's medical record and in the CRF. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data. Any errors should have a single line drawn through them so that the original entry remains legible. The correct data should be entered at the site with the investigator's signature, date and reason for change to confirm the correctness of entries in the CRF. Self-explanatory corrections need not to be justified.

The correctness of entries in CRF will be confirmed by dated signature of the responsible investigator. The original CRF will be transferred to the data management; one copy will be kept by the investigator.

11.2 Data Handling

After first check for plausibility by eye, all data will be entered in a database as recorded in the CRF. After completion of data entry, checks for plausibility, consistency, and completeness of the data will be performed. Based on these checks, queries will be produced combined with the queries generated by visual control.

All missing data or inconsistencies will be reported back to the center and clarified by the responsible investigator. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

11.3 Storage and Archiving of Data

According to the §13 (10) of the German GCP-Ordinance all important trial documents (e.g. CRF) will be archived for at least 10 years after the trial termination.

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including subject identification list and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP E6(R2) and to local law or regulations.

12 Ethical and Legal Aspects

12.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

12.2 Subject Information and Informed Consent

Before being admitted to the clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The subject must give consent in writing. The signed Informed Consent Form will be filed by the investigator.

A copy of the signed informed consent document must be given to the subject. The documents must be in a language understandable to the subject and must specify who informed the subject.

The subjects will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

12.3 Confidentiality

The data obtained in the course of the trial will be treated pursuant to the General Data Protection Regulation (GDPR) (EU) 2016/679 and relevant national.

During the clinical trial, subjects will be identified solely by means of their initials, year of birth, and an individual identification code (subject number, randomization number). Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of EU and national data legislation will be fulfilled in its entirety.

The subject consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors).

According to relevant European and national provisions authorized persons (clinical monitors, auditors, inspectors) may inspect the subject-related data collected during the trial .

The investigator will maintain a subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

Subjects who did not consent to circulate their pseudonymized data will not be included into the trial.

12.4 Responsibilities of the Investigator

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.

The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.5 Approval of Trial Protocol and Amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) as well as to the competent higher federal authority (BfArM). A written favorable vote of the EC and an (implicit) approval by the competent higher federal authority are a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made

and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

Before the first subject is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes (see §10, (1) of German GCP-Regulation-V) will be submitted to EC and the competent higher federal authority in writing as protocol amendments. They have to be approved by the EC and the competent higher federal authority.

The investigator will keep a record of all communication with the EC and the regulatory authorities.

12.6 Continuous Information to Independent Ethics Committee

Pursuant to the German Drug Law (AMG) and the GCP Ordinance, the EC and the competent higher federal authority will be informed of all suspected unexpected serious adverse reactions (SUSARs). Both institutions will be informed in case the risk/ benefit assessment did change or any others new and significant hazards for subjects' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year – Development Safety Update Report (DSUR).

The EC and the regulatory authorities must be informed of the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase, i.e. after last subject out (LSO).

12.7 Notification of Regulatory Authorities

The local regulatory authorities responsible for each particular investigator will be informed before the beginning, during and at the end of the trial according to the applicable regulations. Each investigator is obliged to notify his/ her local regulatory authority.

12.8 Registration of the Trial

Prior to the beginning of the clinical phase (FPI) the coordinating/ principal investigator will register the trial at Current Controlled Trials (http://www.controlled-trials.com/) [or http://www.clinicaltrials.gov]. Thus the trial will be given a unique International Standard Randomized Controlled Trial Number ISRCTN, which is a prerequisite for a publication in a peer-review paper.

12.9 Insurance

According to § 40 AMG, the Sponsor has to subscribe to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with

applicable law and professional standards. This clinical trial's participants are insured according to the German Medicinal Products Act (AMG).*

Insurance company:	HDI Gerling Industrie Versicherung AG
Telephonnumber:	0511-645-0
Fax:	0511-645-4545
Insurance certificate (Versicherungsscheinnummer)	5701031003018

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The subject is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the subject.

The insurance company has to be informed about all amendments that could affect subjects' safety.

13 Quality Assurance

13.1 Monitoring

Monitoring will be done by personal visits from a clinical monitor in order to comply with GCP guidelines. The center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects.

The monitor will review the entries into the CRFs on the basis of source documents. This will include on-site checking of the CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. The investigator must allow the monitor to verify all essential documents including source documents and must provide support at all times to the monitor.

By frequent communications (letters, telephone, fax), the site monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.

13.2 Inspections/ Audits

Regulatory authorities may request access to all source documents, CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities.

14 Agreements

14.1 Financing of the Trial

The trial will be financed using funds of OMT/VitalAire.

This funding source had no role in the design of this study and will not have any role during analyses, interpretation of the data, or decision to submit results.

14.2 Financial Disclosure

Before the start of the trial, the investigator will disclose any proprietary or financial interests he or she might hold in the sponsors/ a funding company, in the investigational product(s) or any commercial organization being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement, whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

14.3 Reports

The Biometrician will prepare the biometrical report. The final trial report will be prepared by the biometrician and the Steering Committee members.

14.4 Publication

All information concerning the trial is confidential before publication, which will be performed by the steering committee members of the trial.

15 Signatures

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal product
- The moral, ethical, and scientific principles governing clinical research as set out in the applicable version of Declaration of Helsinki and the principles of GCP.

The investigator will be supplied with details of any significant or new finding including AEs relating to treatment with the investigational medicinal product.

Date: _____ Signature:_____

Name (block letters): Roland Fank
Function: Sponsor

Date: _____ Signature:_____

Name (block letters): Prof. Dr. med. Ekkehard Grünig
Function: Coordinating Investigator/ Investigator according to §40 AMG

Date: _____ Signature:_____

Name (block letters): Nicola Benjamin
Function: Biometrician

16 Declaration of Investigator

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enroll the first subject only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all subjects.

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described. I will provide a Curriculum Vitae (CV) before trial start. I agree that the CV may be submitted to the responsible regulatory authorities.

Date _____ Signature:_____

Name (block letters): Prof. Dr. med. Ekkehard Grünig

Function: Investigator

Trial Center (address): Röntgenstr. 1
69126 Heidelberg
Germany

18 References

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19 Appendices

Declaration of Helsinki (applicable Version)*

SF-36 (German version “Fragebogen zum Gesundheitszustand“)

Patient diary*

FRAGEBOGEN ZUM GESUNDHEITSZUSTAND

In diesem Fragebogen geht es um Ihre Beurteilung Ihres Gesundheitszustandes in den letzten 4 Wochen. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

Bitte beantworten Sie jede der folgenden Fragen, in dem Sie bei den Antwortmöglichkeiten die Zahl ankreuzen, die am besten auf Sie zutrifft.

1. Wie würden Sie Ihren Gesundheitszustand in den letzten 4 Wochen im Allgemeinen beschreiben?
(Bitte kreuzen Sie nur eine Zahl an)

Ausgezeichnet 1

Sehr gut 2

Gut 3

Weniger gut 4

Schlecht 5

2. Im Vergleich zum Jahr davor, wie würden Sie Ihren Gesundheitszustand vor einem Jahr beschreiben.
(Bitte kreuzen Sie nur eine Zahl an)

Derzeit viel besser als vor einem Jahr 1

Derzeit etwas besser als vor einem Jahr 2

Etwa so wie vor einem Jahr 3

Derzeit etwas schlechter als vor einem Jahr 4

Derzeit viel schlechter als vor einem Jahr 5

3. Im Folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. Sind sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt? Wenn ja, wie stark?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

TÄTIGKEITEN	Ja, stark eingeschränkt	Ja, etwas eingeschränkt	Nein, überhaupt nicht eingeschränkt
a. anstrengende Tätigkeiten, z.B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben	1	2	3
b. mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, Staub saugen, kegeln, Golf spielen	1	2	3
c. Einkaufstaschen heben oder tragen	1	2	3
d. mehrer Treppenabsätze steigen	1	2	3
e. einen Treppenabsatz steigen	1	2	3
f. sich beugen, knien, bücken	1	2	3
g. mehr als 1 Kilometer zu Fuß gehen	1	2	3
h. mehrere Straßenkreuzungen weit zu Fuß gehen	1	2	3
i. eine Straßenkreuzung weit zu Fuß gehen	1	2	3
j. sich baden oder anziehen	1	2	3

4.Hatten Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

SCHWIERIGKEITEN		JA	NEIN
a.	Ich konnte nicht so lange wie üblich tätig sein	1	2
b.	Ich habe weniger geschafft als ich wollte	1	2
c.	Ich konnte nur bestimmte Dinge tun	1	2
d.	Ich hatte Schwierigkeiten bei der Ausführung (z.B. ich musste mich besonders anstrengen)	1	2

5. Hatten Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten)?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

SCHWIERIGKEITEN		JA	NEIN
a.	Ich konnte nicht so lange wie üblich tätig sein	1	2
b.	Ich habe weniger geschafft als ich wollte	1	2
c.	Ich konnte nicht so sorgfältig wie üblich arbeiten	1	2

6. Wie sehr haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre normalen Kontakte zu Familienangehörigen, Freunden, Nachbarn oder zum Bekanntenkreis beeinträchtigt

(Bitte kreuzen Sie nur eine Zahl an)

Überhaupt nicht 1

Etwas 2

Mäßig 3

Ziemlich 4

Sehr 5

7. Wie stark waren Ihre Schmerzen in den vergangenen 4 Wochen?

(Bitte kreuzen Sie nur eine Zahl an)

Ich hatte keine Schmerzen 1

Sehr leicht 2

Leicht 3

Mäßig 4

Stark 5

Sehr stark 6

8. Inwieweit haben die Schmerzen Sie in den vergangenen 4 Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert

(Bitte kreuzen Sie nur eine Zahl an)

Überhaupt nicht 1

Ein bisschen 2

Mäßig 3

Ziemlich 4

Sehr 5

9. In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen gegangen ist. (Bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht). Wie oft waren Sie in den vergangenen 4 Wochen....

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

Befinden	immer	Mei-stens	Ziemlich oft	Manch-mal	Selten	Nie
a. ...voller Schwung?	1	2	3	4	5	6
b. ...sehr nervös?	1	2	3	4	5	6
c. ...so niedergeschlagen, daß Sie nichts aufheitern konnte?	1	2	3	4	5	6
d. ...so ruhig und gelassen?	1	2	3	4	5	6

e. ...voller Energie?	1	2	3	4	5	6
f. ...entmutigt und traurig?	1	2	3	4	5	6
g. ...erschöpft?	1	2	3	4	5	6
h. ...glücklich?	1	2	3	4	5	6
i. ...müde?	1	2	3	4	5	6

10. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?

(Bitte kreuzen Sie nur eine Zahl an)

Immer 1

Meistens 2

Manchmal 3

Selten 4

Nie 5

11. Inwieweit trifft jede der folgenden Aussagen auf Sie zu?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

AUSSAGEN	Trifft ganz zu	Trifft weitge-hend zu	Weiß nicht	Trifft weitge-hend nicht zu	Trifft über-haupt nicht zu
a. Ich scheine etwas leichter als andere krank zu werden	1	2	3	4	5
b. Ich bin genauso gesund wie alle anderen, die ich kenne	1	2	3	4	5
c. Ich erwarte, daß meine Gesundheit nachlässt	1	2	3	4	5
d. Ich erfreue mich ausgezeichneter Gesundheit	1	2	3	4	5

Patient diary

Datum	Stunden mit Sauerstoff		Bemerkungen
Monat:_____	Tagsüber	Nachts	
1			
2			
3			
4			
5			
6			
7			
8			
9			
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12			
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