Document Type:	Study Protocol
Official Title:	A prospective, randomized, international, multicenter, double-arm, controlled, open-label study of Riociguat in patients with pulmonary arterial hypertension (PAH) who are on a stable dose of phosphodiesterase-5 inhibitors (PDE-5i) with or without endothelin receptor antagonist (ERA), but not at treatment goal
NCT Number:	NCT02891850
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Cover page of the integrated protocol

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

For this study, the protocol and subsequent amendments were released as follows:

- **Original protocol,** Version 1.0, dated 31 MAY 2016
- **Amendment 01**, (dated 06 OCT 2016)
  (local amendment, valid for Japan only)
- **Amendment 02**, (dated 16 NOV 2016)
  (local amendment, valid for the United Kingdom only)
- **Amendment 03**, (dated 16 NOV 2016)
  (local amendment, valid for France only)
- **Amendment 04**, (global amendment described in Section 15)
  forming integrated protocol Version 2.0, dated 6 JAN 2017

This document integrates the original protocol and its global amendment.

1. Title page - *amended*

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

Riociguat r**E**placing **P**DE-5i therapy eva**L**uated **A**gainst **C**ontinued PDE-5i th**E**rapy

REPLACE

Test drug:	BAY 63-2521/ riociguat / Adempas		
Study purpose:	To demonstrate the effectiveness of riociguat as replacement of PDE-5i therapy in PAH patients		
Clinical study phase:	4	Date:	6 JAN 2017
Registration:	2016-001067-36	Version no.:	2.0
Sponsor's study no.:	18588		
Sponsor:	Non-US territory: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA		
Sponsor's medical expert:	PPD PPD PPD Bayer SA Rua Domingos Jorge 1100 - Prédio 9301 - 2º andar 04779-900 São Paulo - SP Brasil Tel: PPD		

The study will be conducted in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: Medical Affairs Responsible (M PPD

Date: 6.2.2017 Signature:

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis – *amended*

This section was changed in Amendment 4, see Section 15.1.2.2.

Title	A prospective, randomized, international, multicenter, double-arm, controlled, open-label study of Riociguat in patients with pulmonary arterial hypertension (PAH) who are on a stable dose of phosphodiesterase-5 inhibitors (PDE-5i) with or without endothelin receptor antagonist (ERA), but not at treatment goal.
Short title	**R**iociguat r**E**placing **P**DE-5i therapy eva**L**uated **A**gainst **C**ontinued PDE-5i th**E**rapy
Acronym	REPLACE
Clinical study phase	4
Study objectives	The primary objective is to assess the proportion of patients in each treatment arm with a satisfactory clinical response as defined by a composite primary endpoint at Week 24. The secondary objective is to demonstrate safety and clinical effect at Week 24 indicated by change in 6-minute walking distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organization Functional Class (WHO FC) and clinical worsening from baseline in each treatment arm.
Test drug	Riociguat (BAY 63-2521)
Name of active ingredient	Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo [3,4 b]pyridine-3-yl]-5-pyrimidinyl (methyl)carbamate
Doses	0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg (maximum dose) 3 times daily (TID)
Route of administration	Oral
Duration of treatment	24 weeks (including initial 8 week dose adjustment period according to label).
Reference drug(s)	PDE-5i approved for treatment of PAH (tadalafil, sildenafil)
Name of active ingredients	Sildenafil: 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate Tadalafil: pyrazino[1′,2′:1,6]pyrido[3,4–b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)
Dose(s)	Sildenafil dose at least 60 mg/day Tadalafil dose range 20 to 40 mg/day at the discretion of the investigator.
Route of administration	Oral
Duration of treatment	24 weeks
Indication	PAH

Diagnosis and main criteria for inclusion /exclusion	Adult patients (18 to 75 years) with symptomatic PAH who are treated with a stable dose of a PDE-5i with or without ERA, but are not at treatment goal i.e., remaining at intermediate risk according to European Respiratory Society/European Society of Cardiology (ERS/ESC) guidelines, as indicated by their WHO FC and a 6MWD test. Patients on combination therapy with ERAs may best represent the clinical situation in which transition would be considered, whereas for most patients on PDE-5i monotherapy, combination therapy may be the next appropriate step of treatment escalation. There may however be clinical conditions where a transition to riociguat from PDE-5i monotherapy appears to be appropriate at the discretion of the treating physician. Patients with symptomatic PAH according to WHO FC III and 6MWD of 165-440 m at screening and at randomization, with a pulmonary vascular resistance (PVR) of > 400 dyn*sec*cm-5, mean pulmonary artery pressure ≥ 25 mmHg, and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg as assessed by right heart catheterization in medical history prior to screening to confirm the diagnosis. Alternatively, PCWP can be replaced by left ventricular end-diastolic pressure. PAH of the following types: idiopathic, hereditary, drug/toxin induced, and associated PAH due to connective tissue disease or congenital heart disease (patients had to have undergone surgical repair more than 1 year before enrolment), and portal hypertension with liver cirrhosis (patients with clinical relevant hepatic dysfunction are excluded). Patients who are on stable doses of a PDE-5i and ERA combination therapy or on stable PDE-5i monotherapy for at least 6 weeks prior to and at randomization (tadalafil daily dose 20 to 40 mg or sildenafil daily dose at least 60 mg). Stable is defined as no change in the type of the PDE-5i and the daily dose of PDE-5i and ERA during the 6-week period prior to and at randomization. Patients who signed informed consent and are able to follow the study instructions.
Study design	Prospective, randomized, international, multicenter, double-arm, controlled, 24-week open-label study. Patients will be randomized to remain on their current PAH-specific treatment or to replace the PDE-5i treatment with riociguat. Patients on specific combination therapy with PDE-5i and ERA need to continue taking ERA at a stable dose in both treatment arms. At Week 24 a composite endpoint of satisfactory clinical response will be assessed.

Methodology	Patients who are not at treatment goal and at intermediate risk according to ERS/ESC guidelines will be randomized in a 1:1 ratio to remain on their current PAH-specific treatment or to replace the PDE-5i treatment with riociguat for 24 weeks. Patients need to be pretreated with a stable dose of PDE-5i +/- ERA for 6 weeks prior to and at randomization. Riociguat treatment will be started after a wash-out period of 24 hours with previous sildenafil therapy (daily dose at least 60 mg) and 48 hours after previous tadalafil therapy (daily dose 20 to 40 mg).
Type of control	A mandatory screening period of 2 weeks before randomization will be performed for all patients to ensure stability and similar starting conditions at baseline. Patients randomized to the control arm will continue to receive stable doses of tadalafil (daily dose 20 to 40 mg) or sildenafil (daily dose at least 60 mg) as well as other supportive treatments at the discretion of the investigator.
Number of patients	218 patients in total (109 per arm)

Primary variable	The primary efficacy endpoint 'satisfactory clinical response' is defined as the composite endpoint comprising the following components (independent central adjudication):
	• **2 of 3 must be fulfilled**
	  • 6MWD increase by ≥ 10% or ≥ 30 m from baseline to Week 24
	  • WHO FC I or II at Week 24
	  • NT-proBNP reduction ≥ 30% from baseline to Week 24 (NT-proBNP Week 24/baseline ratio ≤ 0.7), AND
	• **No clinical worsening** (i.e, death of any cause, hospitalization due to worsening PAH, disease progression)

Time point/frame of measurement for primary variable	Week 24

Plan for statistical analysis	All demographic variables and baseline characteristics will be summarized for all analysis sets. Medical history findings and adverse events will be coded according to the Medical Dictionary for Regulatory Activities and medications by Anatomical Therapeutic Chemical class according to the World Health Organization-Drug Dictionary. An efficacy analysis will be performed in patients valid for the Full Analysis Set (primary analysis set) and additionally in patients valid for the Per Protocol Set. Both groups (riociguat vs. active control) will be compared using a stratified Mantel-Haenzel test with a two-sided alpha level of 5%. Stratum is disease class. The null hypothesis tested for the primary endpoint of efficacy is that there is no difference in the satisfactory clinical response rates (odds ratio [OR]) when treated with riociguat compared to patients who remain on their previous therapy (i.e., H0: OR = 1). The two-sided alternative is that there is a difference (i.e., H1: OR $\neq$ 1). For statistical analysis of the primary endpoint with missing data, the last observation carried forward (LOCF) will be utilized. For composite endpoints each single component is independently replaced with the last available observation. To assess the influence of missing data, a supportive analysis without LOCF will be performed with a generalized estimating equations (GEE, binomial distribution) approach, utilizing all adequate investigations of all primary variable components at any time from including baseline up to Week 24. To assess the influence of missing values not at random, a sensitivity analysis is planned. A multiple imputation with penalty will be performed where the penalty is given by crossed improvement rates in both arms. Additionally, a tipping point analysis is planned. A multiplicity correction is not necessary for the primary endpoint because only one primary endpoint is defined. Secondary endpoints are tested hierarchically with an alpha level of 5%.

Table of contents

Table of table

Table of figures

List of abbreviations

6MWD	6 minute walking distance
AE	adverse event
ALT	alanine aminotransferase
APAH	associated PAH
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BMI	Body Mass Index
BP	blood pressure
bpm	Beats per minute
CEC	Clinical Endpoint Committee
cGMP	cyclic guanosine monophosphate
C_{max}	maximum observed concentration
cMRI	cardiac magnetic resonance imaging
CRF	case report forms
CRO	contract research organization
CTD	connective tissue disease
CTEPH	chronic thromboembolic pulmonary hypertension
CYP	cytochrome P450
DLCO	Diffusing capacity of the lung for carbon monoxide
dyn	dyn [1 dyn = 1 g*cm*s^{-2} = 10^{-5} N (Newton)]
ECG	electrocardiogram
eCRF	electronic case report form
ERA	endothelin receptor antagonist(s)
ERS	European Respiratory Society
ESC	European Society of Cardiology
EU	European Union
FAS	full analysis set
FEV_1/FVC	forced expiratory volume in one second/forced vital capacity
FPAH	familial PAH
FU	follow-up
GCP	Good Clinical Practice
GEE	generalized estimating equations
HIV	Human immunodeficiency virus
HPAH	heritable PAH
HR	heart rate
IB	Investigator's Brochure
ICF	Informed consent form
IEC	independent ethics committee
INN	international non-proprietary name
INR	international normalized ratio
IPAH	idiopathic PAH

IRB	institutional review board
IXRS	interactive voice response system
LVEF	left ventricular ejection fraction
LOCF	last observation carried forward
LPH	living with pulmonary hypertension
MedDRA	Medical Dictionary for Regulatory Activities
mRRS	modified REVEAL Risk Score
NO	nitric oxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
OR	odds ratio
PAH	pulmonary arterial hypertension
PCA	prostacyclin analogues
PCWP	pulmonary capillary wedge pressure
PDE-5	phosphodiesterase 5
PDE-5i	phosphodiesterase 5 inhibitor
P-gp	p-glycoprotein
PH	pulmonary hypertension
PH-LVD	pulmonary hypertension due to left ventricular dysfunction
PoPH	portopulmonary PAH
PPS	per protocol set
PRA	Prostacyclin receptor agonist
PVR	pulmonary vascular resistance
QoL	Quality of Life
RHC(s)	right heart catheterization(s)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SBP	systolic blood pressure
sGC	soluble guanylate cyclase
SUSAR	suspected unexpected serious adverse reaction
TID	*ter in die* (3 times daily)
TLC	total lung capacity
ULN	upper limit of normal
V	visit
WHO-DD	World Health Organization-Drug Dictionary
WHO FC	World Health Organization Functional Class

3. Introduction - *amended*

This section was changed in Amendment 4, see Section 15.1.2.3.

Background

Riociguat (BAY 63-2521) is a direct stimulator of the soluble Guanylate Cyclase (sGC). The randomized, double-blind, placebo-controlled clinical Phase 3 study (PATENT-1) investigated the efficacy and safety of riociguat in patients with pulmonary arterial hypertension (PAH). The study met the primary endpoint (placebo-corrected change from baseline in 6-minute walking distance [6MWD] by 35.8 m) and showed statistically significant improvements in secondary endpoints, including pulmonary vascular resistance, N- terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organization Functional Class (WHO FC), clinical worsening, living with pulmonary hypertension (LPH) questionnaire, and Borg dyspnea score (1).

PAH is a devastating, life-threatening disease that is characterized by rapid progression and a high mortality (2).

Sequential combination therapy has been the most widely used clinical strategy of treatment escalation if the treatment effect reached by oral monotherapy alone is not sufficient (European Society of Cardiology [ESC]/European Respiratory Society [ERS] guidelines 2015) (3). Transition between pulmonary hypertension (PH)-specific drug therapies has not been investigated in controlled studies and treatment response in the individual patient cannot be predicted. Failure of phosphodiesterase-5 inhibitor (PDE-5i) treatment however may indicate impairment of the nitric oxide (NO)-sGC-cyclic guanosine monophosphate (cGMP) pathway (4). In contrast the treatment effect of sGC-stimulation is based on a NO-independent mode of action. Preliminary data from the open-label transition study RESPITE indicate that patients transitioned from PDE-5i to riociguat may benefit based on this principle of pathway optimization.

Rationale of the study

Oral monotherapy including PDE-5i is one recommended treatment approach for patients with PAH who are classified as WHO FC II or III (3,5). However, a significant proportion of PAH patients fail to reach or maintain treatment goals with PDE-5i monotherapy (6,7,8,9) indicating that the NO-sGC-cGMP pathway in these patients may be impaired (4). The clinical approach in patients demonstrating an insufficient clinical response on PDE-5i monotherapy is typically to add an endothelin receptor antagonist (ERA). Most PAH treatment guidelines, including ESC/ERS, suggest that sequential combination therapy is reasonable to be considered in patients with an inadequate clinical response, but the clinical evidence supporting this is weak (3,5).

An increasing body of evidence suggests that a goal directed therapy approach where a patient's treatment regimen should be re-assessed if they fail to reach certain clinical or therapeutic targets in a certain time frame may be the best approach for patients with PAH (10) as certain therapeutic targets such as WHO FC demonstrated to have prognostic implications (11,12,13). In the 2015 ESC/ERS guideline for treatment of PAH, it is stated that the overall treatment goal in patients with PAH is achieving a low risk status as defined by determinants of prognosis such as WHO FC, 6MWD, and biomarkers (NT-proBNP, imaging) reflecting right heart function.

The RESPITE study was conducted to investigate whether it is safe, feasible, and beneficial to replace PDE-5i therapy with riociguat in PAH patients demonstrating insufficient response to PDE-5 inhibition. The final data of this hypothesis-generating single arm study showed that patients failing to respond to PDE-5i could benefit from replacing a PDE-5i with riociguat by improving 6MWD, WHO FC, and NT-proBNP. The data indicate that transition of PDE-5i to riociguat may serve as a treatment strategy for PAH patients.

The rationale of the study is to confirm the potential clinical benefit of switch within the NO sGC-cGMP pathway in a randomized controlled study.

Benefit-risk assessment

Riociguat was overall considered to be safe and well tolerated in previous clinical studies at multiple doses between 1 and 2.5 mg 3 times daily (TID) in patients with PAH and other indications, e.g., chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary hypertension due to left ventricular dysfunction (PH-LVD).

Beneficial effects of riociguat with regard to exercise capacity, cardiopulmonary hemodynamics, and symptoms while being overall safe and well tolerated have been demonstrated recently in PAH as well as CTEPH in two independent clinical Phase 3 studies, the PATENT-1 and CHEST-1, as well as the long-term extension studies thereof.

The safety analysis of the clinical studies showed that most adverse drug effects were non-serious in nature, mainly linked to the mechanisms of action of riociguat, and with a low number of permanent treatment discontinuation.

Epistaxis and hemoptysis are known events for the underlying disease with a high proportion of patients taking anti-coagulants. However, the observation of few serious and life-threatening/fatal cases of hemoptysis and pulmonary hemorrhage poses a potential risk since these events may also occur under riociguat treatment.

Recently, results of a study on efficacy and safety of riociguat in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) showed an increased risk of mortality and serious adverse events among patients who received riociguat compared to those who received placebo, and an absence of apparent clinical benefit. The study was terminated early upon the advice of its data monitoring committee (DMC). It was concluded that the benefit risk balance of riociguat in patients with PH-IIP is negative. Riociguat is contraindicated in patients with PH-IIP.

The REPLACE study (18588) will only include patients with subtypes of Pulmonary Arterial Hypertension (PAH), Dana Point Group 1 (14). Patients with all other types of PH/ Dana Point Groups are excluded, also comprising patients with PH-IIP, according to the protocol.

The overall benefit-risk balance of riociguat is considered positive if used in adherence to this clinical study protocol and in accordance with the recommendations and guidance given in the Investigator's Brochure (IB).

Primary hypothesis

Replacement of PDE-5i by riociguat in patients who are not at treatment goal but on a stable dose of PDE-5i +/- ERA will lead to a significantly higher rate of satisfactory clinical response compared to patients who remain on PDE-5i +/- ERA because of the optimization of the NO-sGC-cGMP pathway provided by riociguat and its NO-independent mechanism of action.

Stable is defined as no change in the type of the PDE-5i and the daily dose of PDE-5i and ERA during the 6-week period prior to and at randomization.

Secondary hypothesis

In the group comparison, transition to riociguat will significantly improve 6MWD, NT-proBNP, WHO FC, and will have a reduction in clinical worsening at Week 24 compared to continuation of PDE-5i +/- ERA therapy.

4. Study objectives

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

The secondary objective is to demonstrate safety and clinical effect at Week 24 indicated by change in 6MWD, NT-proBNP, WHO FC and clinical worsening from baseline in each treatment arm.

5. Study design - *amended*

This section was changed in Amendment 4, see Section 15.1.2.4.

Design overview

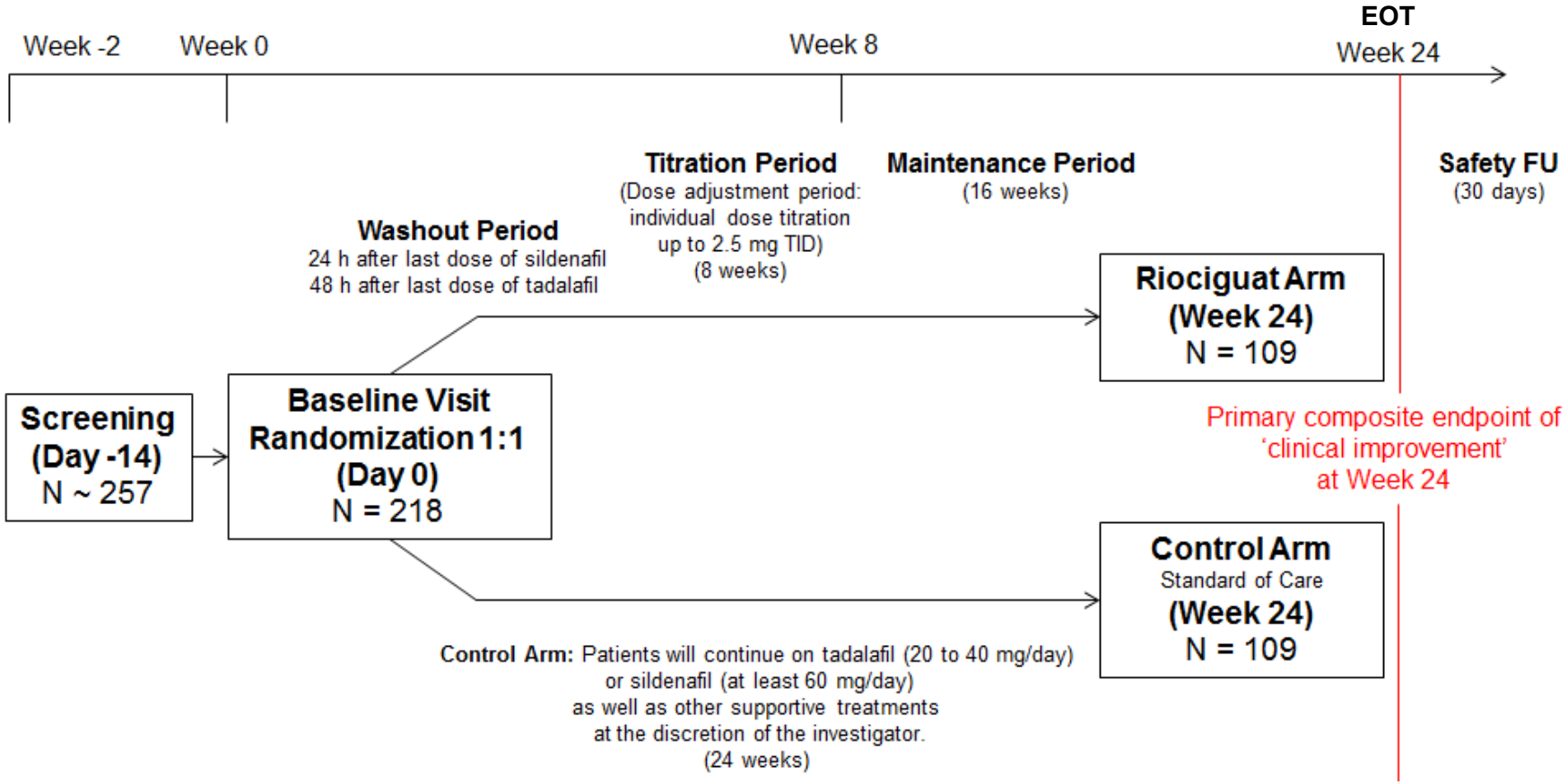
This is a prospective, randomized, international, multicenter, double-arm, 24-week, controlled, open-label study of riociguat in patients with PAH who are on a stable dose of PDE-5i +/- ERA, but not at treatment goal. The decision for a randomized but not blinded study design was made in agreement with the advisory committee for feasibility reasons. As riociguat is available as an approved treatment in the majority of countries, recruitment was not considered feasible into a blinded Phase 4 study. Moreover, the open-label, randomized design with a fixed duration of 24 weeks and the composite endpoint of satisfactory clinical response is considered a pragmatic alternative to allow for meaningful results with reasonable effort and within a reasonable time frame.

A mandatory screening period of 2 weeks before randomization will be performed for all patients to ensure stability and similar starting conditions at baseline.

Eligible PAH patients will be randomized in a 1:1 ratio to remain on their current PAH-specific treatment (the control arm) or to replace the PDE-5i treatment with riociguat (the riociguat arm).

Patients on specific combination therapy with PDE-5i and ERA need to continue taking ERA at a stable dose in both treatment arms.
At Week 24, a composite endpoint of satisfactory clinical response will be assessed.
An overview of the study design is shown in Figure 5–1.

Figure 5–1: Study Design Overview



Abbreviations: EOT = End of Treatment; FU = Follow-up; N = number of patients; TID = three times daily.

Patients in both treatment arms follow the same visit schedule (see also Section 16.1).

At the discretion of the investigators and if applicable (e.g., short distance to study center) the home visits may also be performed at the study center.

For riociguat the initial home visits (H1-3) and V2 include the dose titration period, followed by the maintenance period with the established individual dose.

Treatment period (Duration: 24 weeks)

Patients randomized to the **control arm** at the baseline visit (Week 0) will continue on their current PAH-specific treatment for 24 weeks.

Patients randomized to the **riociguat arm**, will have a **wash-out period** before starting the titration period of riociguat:

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

Titration period (Riociguat arm, duration: 8 weeks)

The dose titration will be performed with the aid of an interactive voice response system (IXRS). The investigator decision regarding study medication must be clearly documented in the source documents prior to contacting IXRS.

The starting dose will be 1 mg riociguat TID. The individual riociguat dose will be titrated every 2 weeks according to the patient's well-being and peripheral systolic blood pressure (SBP) measured at trough, preferably before intake of the next morning dose. At each titration visit for the riociguat arm (Weeks 2, 4, and 6), the investigator needs to decide, based on the patient's SBP, whether the study medication dose should be modified.

The respective decision (increase, maintain, or decrease dose) must be entered in the IXRS that will automatically allocate the right dose in accordance with the respective individual titration scheme. Afterwards, the investigator will be informed by the system which dosage needs to be dispensed to the patient for the next titration period (starts preferably with the morning dose). Blood pressure measurements and communication with the center for dose decision will be facilitated by experienced study nurses.

The investigators will apply the following blood pressure (BP) based titration rules for their dose decision and should follow the local riociguat label for detailed information as follows:

> Dosage should be increased in 2-week intervals by 0.5 mg increments to a maximum of 2.5 mg three times daily, if SBP is ≥95 mmHg and the patient has no signs or symptoms of hypotension. If SBP falls below 95 mmHg, dosage should be maintained provided the patient does not show any signs or symptoms of hypotension. If at any time during the up-titration phase systolic blood pressure decreases below 95 mmHg, and the patient shows signs or symptoms of hypotension, the current dose should be decreased by 0.5 mg tid.

General Note: While dose up-titration can only occur at the scheduled visits, a dose decrease can be performed at any time based on the patient's SBP and well-being. In case of intended dose decrease which can be done independently from any planned study visit, the investigator will contact the IXRS and request a dose adjustment. This visit is to be declared as an unscheduled visit.

In general, if the investigator requests an increase or decrease in the riociguat dose via the IXRS, the subsequent dose modification will not exceed plus/minus 0.5 mg.

It is allowed in case of riociguat side effects to suspend a foreseen up-titration step and to maintain the dose (this should be entered into the IXRS).

During the titration period, a request of an increase of riociguat dose is only possible at the planned titration visits at Weeks 2, 4, and 6. The dose reached at the end of the titration period at Week 8 is considered the patient's optimal dose based on SBP and well-being.

Maintenance period (Riociguat arm, duration: 16 weeks)

Riociguat should be continued at the optimal dose as determined at the end of the titration period (Week 8) throughout the maintenance period.

Visits (for both arms) will take place at Week 16 and Week 24. The IXRS will automatically allocate the right riociguat dose at each visit.

Dose reductions or discontinuation of riociguat for safety reasons are allowed at any time. Increases or re-increases in 0.5 mg steps (maximum dose 2.5 mg) are possible at the investigator's discretion weighing the benefit with potential risks implied, e.g., hypotension.

Smoking status is assessed regularly during the study as plasma concentrations of riociguat in smokers are reduced compared to non-smokers, and dose adjustment may be necessary in patients who start or stop smoking during treatment with riociguat.

General Note: In case of intended dose adjustments, the investigator will contact the IXRS, which can be done independently from any planned study visit, and request a dose adjustment. This visit is to be declared as an unscheduled visit.

Premature discontinuation of study treatment

In case of premature discontinuation of study treatment, the process detailed in Section 6.3.1.1 should be followed.

Visit 4 / End of Treatment (EOT) (Week 24 ± 4 days)

All patients randomized to either treatment arm should perform Visit 4 / EOT. This is the last visit of the maintenance period, when all relevant efficacy and safety measurements will be performed.

Safety Follow-Up (FU) visit (30 days ± 5 days after last intake of study treatment)

A safety FU visit is to be performed 30 days (± 5 days) after the planned end of study treatment OR 30 days (± 5 days) after premature discontinuation of study treatment.

Primary endpoint (at Week 24)

The primary composite endpoint is to assess the proportion of patients in each treatment arm with a satisfactory clinical response at Week 24 defined as improvement in "2 of 3" (see Section 10.3.2.1).

Justification of the design

Riociguat was considered safe and well tolerated in previous clinical studies at multiple doses between 1.0 and 2.5 mg TID in patients with PAH. This study will be conducted to assess the effectiveness of replacing PDE-5i therapy with riociguat compared with maintaining PDE-5i therapy in PAH patients who are on a stable dose of PDE-5i +/- ERA, but not at treatment goal.

While it may appear inappropriate to randomize patients who are not "at treatment goal" to the control arm, where their current PAH-specific treatment regimen will just be continued, in the absence of a clear definition of treatment response, the definition for this study is inspired by the ESC/ ERS table for risk assessment (15) and based on 6MWD and WHO FC only. Other parameters of prognostic relevance including pulmonary hemodynamics may well be in the range of low risk/ at treatment goal according to guidelines. It can be assumed that a large number of patients on mono-or combination therapy with PAH-targeted drugs are in a stable clinical situation, but do not reach WHO FC I/II or a 6MWD > 440 m. Clinical stability at randomization will be ensured by requirements such as stable doses of PAH-therapy and diuretics, and the mandatory 14-day screening period. By this, the study design intends to represent the real-life clinical situation of PAH patients, in which close follow-up of prognostically relevant parameters is required for the decision on a next step of treatment escalation. As there will be rater-blinded assessments and central adjudication, but no blinding of the study treatment arms, the investigator will at any time be able to decide about any necessary treatment escalation. Thus, even treatment of a patient randomized to the control or maintenance arm will stringently follow treatment guidelines.

End of Study

The end of the study as a whole will be reached as soon as the last safety FU visit of the last patient according to the above definition has been reached in all participating countries (European Union [EU] and non-EU).

Primary completion

Primary completion will be upon reaching the primary endpoint at 24 weeks of treatment.

6. Study population

The patient population that best reflects the clinical situation for transition is patients on ERA-combination therapy, as for most patients on PDE-5i monotherapy combination therapy may be the next appropriate step of treatment escalation. There may however be clinical conditions where a transition to riociguat from PDE-5i monotherapy appears to be appropriate at the discretion of the treating physician.

6.1 Inclusion criteria - *amended*

This section was changed in Amendment 4, see Section 15.1.2.5.

Patients who fulfill the following inclusion criteria are eligible to enter the study:

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

- PAH of the following types:
    - a. Idiopathic
    - b. Hereditary
    - c. Drug and toxin induced PAH
    - d. Associated with PAH due to:
        - Connective tissue disease (CTD)
        - Congenital heart disease, but only if the patient underwent surgical repair more than one year before enrolment
        - Portal hypertension with liver cirrhosis (Note: patients with clinical relevant hepatic dysfunction are excluded; see exclusions related to disorders in organ function)

3. Patients who are on stable doses of a PDE-5i and ERA combination therapy or on stable PDE-5i monotherapy 6 weeks prior to and at randomization but not at treatment goal (tadalafil 20 to 40 mg once daily or sildenafil at least 60 mg daily dose).
4. WHO FC III at screening and at randomization.
5. 6MWD test between 165 m and 440 m at screening and at randomization.
6. Stable dose of diuretics, if used, for at least 30 days prior to and at randomization.
7. Patients who are able to understand and follow instructions and who are able to participate in the study for the entire study.

8. Women of childbearing potential must agree to use adequate contraception when sexually active. Adequate contraception is defined as any combination of at least 2 effective methods of birth control, of which at least 1 is a physical barrier (e.g. condom with hormonal contraception like implants or combined oral contraceptives, condom with intrauterine devices). This applies beginning with signing of the informed consent form until 30 (+5) days after the last administration of study drug.
9. Patients must have given their written informed consent to participate in the study after having received adequate previous information and prior to any study-specific procedures.

6.2 Exclusion criteria - *amended*

This section was changed in Amendment 4, see Section 15.1.2.6.

Patients who fulfill any of the exclusion criteria are not eligible to enter the study:

1. Participation in another interventional clinical study within 30 days prior to screening.
2. Previous randomization to treatment during this study (no re-randomization).
3. Previous treatment with riociguat.
4. Pregnant women (i.e., positive serum ß-human-chorionic-gonadotropin test or other signs of pregnancy), or breast feeding women, or women with childbearing potential not using a combination of 2 effective contraception methods (as laid out in inclusion criterion no. 8) throughout the study.
5. Patients with a medical disorder, condition, or history of such that would impair the patient's ability to participate or complete this study, in the opinion of the investigator.
6. Patients with substance abuse (e.g., alcohol or drug abuse) within the previous 3 months prior to and at randomization.
7. Patients with underlying medical disorders with an anticipated life expectancy below 2 years (e.g., active cancer disease with localized and/or metastasized tumor mass).
8. Patients with a history of severe allergies or multiple drug allergies.
9. Patients with hypersensitivity to the investigational drug or any of the excipients.
10. Patients unable to perform a valid 6MWD test (e.g., orthopedic disease, peripheral artery occlusive disease, which affects the patient's ability to walk). Note: Patients, who require walking aids, may be included if in the opinion of the investigator the walking distance is not impaired. Patients with a variance of more than 15% between the screening and the randomization (i.e., baseline) 6MWD test.
11. Participation at a supportive physical training program, defined as a structured exercise and rehabilitation program supervised by a physician and/or a physiotherapist within 12 weeks prior to screening. Participants enrolled in an exercise program for pulmonary rehabilitation > 12 weeks prior to screening may enter the study if they

agree to maintain their current level of rehabilitation during the screening and the 24 weeks of the study.

12. Excluded medication/treatment:
    a. Patients who are screened for possible participation in the study must not be withdrawn from treatments which are medically required. If such treatments are not in-line with the entry criteria of this study, the patient must not be enrolled. Concomitant use with riociguat of the following specific medications for treatment of PAH is not allowed at any time during the study:
        - PDE-5i (e.g., sildenafil, tadalafil or vardenafil) must not be co-administered with riociguat
        - Non-specific PDE-inhibitors (e.g., dipyridamole, theophylline)
        - NO donors (e.g., nitrates, amyl nitrite)
    b. Prostacyclin analogues (PCA) and prostacyclin-receptor agonists (PRA) by any administration route within 30 days prior to and at randomization (except for vasoreactivity testing).
13. Exclusion criteria related to pulmonary disease:
    a. All types of PH (including PH-IIP) except subtypes of Dana Point Group I specified in the inclusion criteria.
    b. Evidence of clinically significant restrictive or obstructive parenchymal lung diseases in the judgment of the investigator (e.g., based on a clean computed tomography lung scan).
    c. Severe congenital abnormalities of the lungs, thorax, and diaphragm.
    d. Severe restrictive lung disease (total lung capacity [TLC] < 60%).
    e. Moderate obstructive lung disease (forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] < 50%).
    f. Confirmed obstructive sleep apnea
    g. Severe diffusion impairment (diffusing capacity of the lung for carbon monoxide < 30% predicted).
    h. History or active state of serious hemoptysis/pulmonary hemorrhage including those managed by bronchial artery embolization.
14. Exclusion criterion related to hypoxia (pulse oximeter at rest):
    a. Peripheral capillary oxygen saturation (SpO_2) < 88% despite supplemental oxygen therapy (≤ 4 L/min) at rest.
15. Cardiovascular exclusion criteria:
    a. Uncontrolled arterial hypertension (SBP > 180 mmHg and/or diastolic BP > 110 mmHg).

b. SBP < 95 mmHg prior to and at randomization.

c. Resting heart rate in the awake patient < 50 bpm or > 105 bpm.

d. Permanent atrial fibrillation and new onset of atrial fibrillation within the last 3 months prior to screening.

e. Left ventricular systolic dysfunction by echocardiography (left ventricular ejection fraction [LVEF] < 40%, Simpson's methodology).

f. Hypertrophic obstructive cardiomyopathy.

g. Severe proven or suspected coronary artery disease (patients with Canadian Cardiovascular Society Angina Classification class 2 to 4, and/or requiring nitrates, and/or acute coronary syndrome, or coronary interventions (PCI, CABG) within the last 3 months prior to and at randomization).

h. Clinical evidence of symptomatic atherosclerotic disease (e.g., peripheral artery disease with reduced walking distance, history of stroke with persistent neurological deficit etc.).

i. History of stroke within 3 months prior to and at randomization.

j. Congenital or acquired valvular or myocardial disease if clinically significant apart from tricuspid valvular insufficiency due to PAH.

k. Three or more of the following left ventricular disease/ dysfunction risk factors:

- Body Mass Index (BMI) ≥ 30
- History of Essential Hypertension
- Diabetes mellitus of any type
- History of significant Coronary Disease

16. Exclusion criteria related to disorders in organ function:

a. Clinical relevant hepatic dysfunction indicated by:

- Bilirubin > 2 times upper limit of normal (ULN), and/or
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times ULN

b. Signs of severe hepatic insufficiency (Child Pugh C), and/or

c. Renal insufficiency (glomerular filtration rate < 30 mL/min (calculated based on the Cockcroft formula or Modification of Diet in Renal Disease formula).

17. Other exclusion criteria:

a. Other co-morbidities impairing exercise capacity.

6.3 Withdrawal of patients from study

6.3.1 Withdrawal – *amended*

This section was changed in Amendment 4, see Section 15.1.2.7.

6.3.1.1 Discontinuation of study treatment - *amended*

Study treatment (riociguat or control) discontinuation for any reason does not represent withdrawal from the study and should not result in withdrawal of the patient from the study. Please see definitions for premature discontinuation from the study in Section 6.3.1.2.

Patients who prematurely discontinue from the study treatment will still be followed up for collection of safety and efficacy data at Visit 4 / EOT at Week 24 (± 4 days) and should also perform the safety FU visit at 30 days (± 5 days) after the last intake of study drug. Note that the safety FU visit may occur before Visit 4 / EOT if premature discontinuation from treatment occurs early during the study.

In all cases, the reason for study treatment discontinuation must be recorded in the electronic case report form (eCRF) and in the patient's medical records.

Patients may decide to withdraw their consent to participate in the study and to no longer attend study visits and take the study treatment (if not already discontinued); they may object to generation and processing of post-study treatment discontinuation data. Patient decision will be recorded in the eCRF. Patients who withdraw from the study will have the vital status (alive or dead) reported in the eCRF at Visit 4 / EOT. The contact can be by visit, phone or e-mail, and also by family members. Every effort should be made to contact the patient by telephone at the times the study visits were scheduled for the remaining duration of the study, to determine if any of the primary, secondary, or other endpoints have been reached. All attempts to retrieve information about the patients should be documented in the patient's records. In addition to withdrawing their consent for attending the study visits, patients may also object to releasing any other information regarding their health status. For this, the patient must sign a corresponding declaration of objection; alternatively, the patient's oral objection may be documented in the source data. In such cases, every effort should be made to obtain vital status (alive or dead) information through consultation of public databases, wherever allowed by local regulations.

Criteria for withdrawal from study treatment

Patients *must* be withdrawn from study treatment if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study treatment would be harmful to the patient's well-being.

- Occurrence of adverse events (AEs) or intercurrent diseases which the investigator judges unacceptable for continuation of participation in the study.
- Occurrence of adverse drug reactions, which have from the investigator's point of view, a negative impact on the patient's individual risk-benefit ratio. (Investigators are obliged to reassess the patient's individual risk-benefit ratio on a continuous basis. Factors like anticipated treatment effect, progression of underlying disease, occurrence of side effects and alternative treatment options have to be considered).
- In case a patient is diagnosed with pulmonary veno-occlusive disease (PVOD) while on treatment with study drug, the administration of riociguat has to be stopped immediately
- Pertinent non-compliance with the conditions for the study or instructions by the investigator
- In case of pregnancy or breast feeding
- Participation in another clinical study
- Patient does not tolerate the lowest possible riociguat dose (0.5 mg TID)

Patients *may* be withdrawn from the study treatment if any of the following occurs:

- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance, safety concerns).

Although not preferred, patients may interrupt their intake of study treatment due to reasonable circumstances/reasons at any time (e.g., hospitalization in a remote hospital without study treatment access, safety reasons, side effects). If an interruption lasts longer than 14 days in a row, it is at the discretion of the investigator to discontinue the study participation, and the eCRF of the early termination visit must be completed.

In case of treatment interruptions for 3 days or more, treatment should be restarted at 1 mg TID for 2 weeks, and continued with the dose titration regimen as shown in Figure 7–1.

6.3.1.2 Discontinuation of study - *amended*

Depending on the time point of withdrawal, a withdrawn patient is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A patient who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure".

Re-screening of a "screening failure" is allowed; thus, participation of an initial "screening failure" patient at a later time point, provided he/she meets all selection criteria upon re-screening, is acceptable. Re-screening should be limited to situations preventing the patient from safely completing the study procedures (e.g., acute infections or diseases affecting the

patient`s ability to complete the 6MWD test, acute dysregulations of blood pressure). Re-screening due to fluctuating data around the upper or lower limit of reference, in order to achieve a value within the normal range, is not allowed.

The investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. Also, for re-screening, the patient has to re-sign the informed consent form (ICF), even if it was not changed after the patient's previous screening.

Dropout

A patient who discontinues study participation prematurely for any reason after randomization is defined as a "dropout". If a patient prematurely discontinues study treatment and does not wish to continue with the remaining scheduled visits, the investigator should take all possible effort to complete a final evaluation, and the patient should be asked for his agreement to schedule an early termination visit as soon as possible, at which time point all assessments scheduled for Visit 4 / EOT are to be performed.

General procedures

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

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Any patient removed from the study will remain under medical supervision until discharge or transfer is medically acceptable.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12).

6.3.2 Replacement

Patients who discontinue the study during the mandatory screening period may be replaced.

There will be no replacement of dropouts during this study.

6.4 Patient identification

After a patient has signed the ICF, the patient identification number that has been assigned to the patient will be provided to the investigator by IXRS.

The patient number is a 9-digit number consisting of:

- first 2 digits = country code
- next 3 digits = center number within the country
- last 4 digits = current patient number within the center.

7. Treatments

7.1 Treatments to be administered - *amended*

This section was changed in Amendment 4, see Section 15.1.2.10.

Riociguat/BAY 63-2521 film-coated tablets will be used in this study at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg.

Tablets will be administered orally.

Note that patients randomized to the riociguat arm will have a washout period before starting titration period of riociguat (see "wash-out period" in Section 5 for details). The starting dose is 1 mg TID; the intervals between drug intakes should be 6 to 8 hours. The dosage should be increased by 0.5 mg increments in 2 week intervals to 1.5 mg, 2.0 mg, and 2.5 mg TID (maximal total daily dose). Patients should be maintained on lower doses if higher doses are not tolerated (minimal dose of 0.5 mg TID). After the titration period (i.e., during the maintenance period) riociguat should be continued at the optimal individual dose as determined at the end of the titration period (Week 8; see Figure 7–1). Dose reductions or discontinuation of riociguat for safety reasons are allowed at any time, as well as dose increases in 0.5 mg increments (up to 2.5 mg) at the discretion of the investigator (see Section 5).

Patients randomized to the control arm will continue to receive stable doses of tadalafil (daily dose 20 to 40 mg) or sildenafil (daily dose at least 60 mg) as well as other supportive treatments at the discretion of the investigator.

Concomitant treatment with ERA is not subject of the research of this study; therefore, ERA are not considered study drug. However, as these are effective specific PAH drugs, their doses need to remain stable in combination with PDE-5i within 6 weeks prior to randomization and throughout the study. Any change in dose or application of ERA needs to be documented.

7.2 Identity of study treatment - *amended*

This section was changed in Amendment 4, see Section 15.1.2.11.

All study drugs (investigational medicinal products [IMP]) will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

A system of numbering in accordance with all requirements of Good Manufacturing Practice will be used, ensuring that each dose of riociguat can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance group.

A complete record of riociguat batch numbers and expiry dates as well as the labels will be maintained in the sponsor's study file.

See Table 7–1 for details on the study treatment.

Treatment administered in the control arm (tadalafil, sildenafil) is considered standard of care.

Storage requirements:

All investigational drugs used during the study will be stored at the investigational sites in a place inaccessible to unauthorized personnel, i.e., in a locked cabinet.

No special storage conditions are required for Riociguat. Please note that PDE5i must be stored below 30°C.

Table 7–1: Identity of investigational product

Riociguat arm	
International non-proprietary name (INN)	Riociguat
Sponsor's internal reference number	BAY 63-2521
Formulation	
Galenical form	Round immediate-released tablets, diameter 6 mm
Composition	Active ingredient: *Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo [3,4 b]pyridine-3-yl]-5-pyrimidinyl (methyl)carbamate* Empirical formula: $C_{20}H_{19}FN_8O_2$ Molar mass: 422.42 g/mol (molarity) Excipients: lactose, microcrystalline cellulose, magnesium stearate, crospovidone, hypromellose, and sodium lauryl sulphate Coating: hydroxypropyl cellulose, hypromellose, propylene glycol, iron oxide (red and yellow), and titanium dioxide.
Strength	0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg
Material numbers	83296470 BAY 63-2521 tablet 0.5 mg 511 COAT 83296535 BAY 63-2521 tablet 1.0 mg 512 COAT 83296543 BAY 63-2521 tablet 1.5 mg 513 COAT 83296578 BAY 63-2521 tablet 2.0 mg 504 COAT 83296608 BAY 63-2521 tablet 2.5 mg 515 COAT
Packaging	High-density polyethylene bottles
Control arm	
Tadalafil	
Material name	ADCIRCA 20MG 56 TAB
Active substance	Tadalafil
Formulation	Film-coated tablets
Description	Amygdaloid, debossed with 4467 on one side
Strength	20mg, 40mg
Dosage unit	20mg/tablet
Mode of administration	Oral
Packaging	Wallet containing 5 blister, each blister containing 14 tablets (total of 70 tablets)

Table 7–1: Identity of investigational product

Sildenafil	
Material name	REVATIO 20MG TAB B90 GER
Active substance	Sildenafil citrate
Formulation	Film-coated tablets
Description	Round biconvex, debossed with RVT 20 on one side and Pfizer on the other
Strength	Daily doses of 60mg, 80mg, 100mg, 120mg, 140mg, 160mg, 180mg, 200mg, 220mg, 240mg, 260mg, 280mg, 300mg
Dosage unit	20mg/tablet
Mode of administration	Oral
Packaging	Wallet containing 6 blister, each blister containing 15 tablets (total of 90 tablets)

7.3 Treatment assignment - *amended*

This section was changed in Amendment 4, see Section 15.1.2.12.

Patients will be randomized 1:1 to remain on current PAH-specific treatment (the control arm) or to replace the PDE-5i treatment with riociguat (the riociguat arm). Central randomization (by IXRS) is planned, stratified by etiology of PAH by:

- Idiopathic (I)PAH/ heritable (H)PAH/ PAH drug and toxin induced
- PAH-CHD, PAH-portopulmonary PAH (PoPH)
- PAH- CTD

Following washout (see "wash-out period" in Section 5 for details), all eligible patients randomized to the riociguat arm will receive a starting dose of riociguat of 1 mg TID in this open-label study. The starting dose of 1 mg may be down-titrated to 0.5 mg at the discretion of the investigator and at any point during the 8-week titration period.

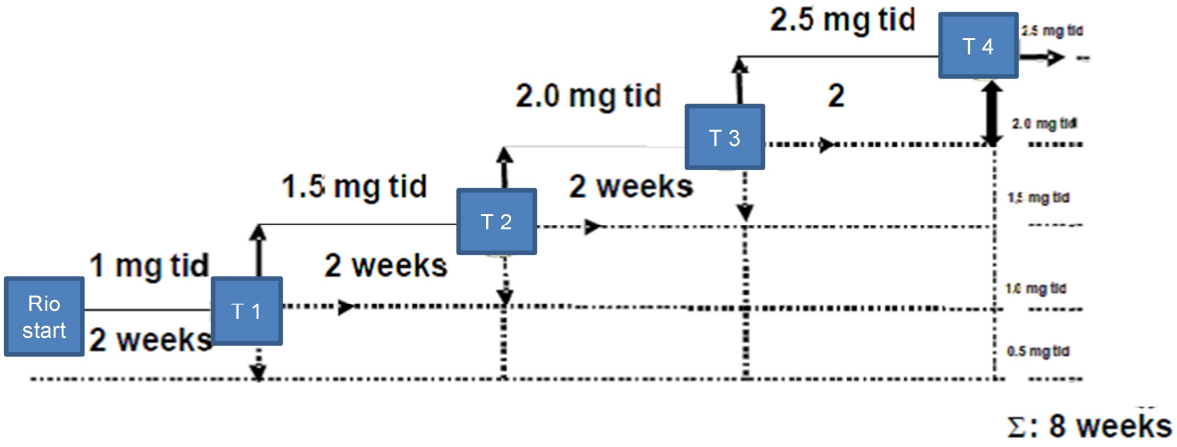
Patients randomized to the control arm will remain on their current PAH-specific treatment. Patients on combination therapy with ERA need to continue at a stable dose in both treatment arms.

7.4 Dosage and administration

Riociguat will be administered TID as film-coated immediate-release tablets with or without food. The starting dose will be 1 mg TID, followed by a dose adjustment period of 8 weeks (titration period), and an overall treatment duration of 24 weeks.

Dose increase or decrease criteria are described in Section 5 and the titration scheme is presented in Figure 7–1.

Figure 7–1: Titration Scheme



T = Titration (visit); TID = three times daily.

7.5 Blinding

This is an open-label study.

There will only be blinded assessments for the 6MWD test as described in Section 9.7.1 and for the determination of WHO FC as described in Section 9.7.4.

7.6 Drug logistics and accountability

All study treatments will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/contract research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study treatment via IXRS. The personnel will use the study treatment only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study treatment must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

7.7 Treatment compliance

Any discrepancies between actual and expected amount of returned study treatment must be discussed with the patient at the time of the visit, and any explanation must be documented in the source records.

The packages of the investigational drug have to be brought back to the investigational site, and tablets will be counted for a compliance check.

The respective compliance should be between 80% and 120% of the calculated dose, based on the information on tablet count and exposure for the entire period of study participation.

8. Non-study therapy

8.1 Prior and concomitant therapy - *amended*

This section was changed in Amendment 4, see Section 15.1.2.13.

The intake of the following concomitant medication is not allowed at any time while a patient is on riociguat:

- PDE-5i (e.g., sildenafil, tadalafil or vardenafil) must not be co-administered with riociguat
- Non-specific PDE-inhibitors (e.g., dipyridamole, theophylline)
- NO donors (e.g., nitrates, amyl nitrite)

The intake of the following concomitant medication is not allowed within 30 days prior to and at randomization:

- PCA and PRA by any administration route within 30 days before randomization (except for vasoreactivity testing).

Patients, who require respective medications (except for PCA) need to be withdrawn from the study drug (refer to Section 6.3.1).

Specific PAH medication:

Dose changes in PAH-specific medication (i.e., PDE-5i or ERA) should be avoided during the study. Dose changes considered clinically necessary by the investigator need to be documented. Notably hospitalization for initiation of intravenous or subcutaneous prostanoid therapy fulfills the criterion of clinical worsening, as may disease progression with a need for any additional specific PAH targeted medication (see also Section 10.3.2.1 for Definition of Clinical Worsening). The patient may remain in the study even if escalation of PAH therapy is required to maintain or improve the clinical status of the patient. The decision to keep the patient in the study is at the discretion of the investigator.

Other concomitant medication:

- The concomitant use of riociguat with strong multi-pathway cytochrome P450 (CYP) and P-glycoprotein 1 (P-gp)/breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g., ketoconazole, itraconazole) or human

immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir) is not recommended, due to the pronounced increase in riociguat exposure (see also 'Interaction with other medicinal products and other forms of interaction' in Section 4.5 of the current Company Core Data Sheet).

- The concomitant use of riociguat with strong CYP1A1 (CYP family 1, subfamily A, polypeptide 1) inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-gp/BCRP inhibitors, such as the immunosuppressive agent cyclosporine A, may increase riociguat exposure (see Section 'Interaction with other medicinal products and other forms of interaction' in Section 4.5 of the current Company Core Data Sheet). These drugs should be used with caution. BP should be monitored and dose reduction of riociguat considered.

Other medications considerations (detailed information can be found in the current IB):

- Pre- and comedication with the proton pump inhibitor omeprazole (40 mg once daily) reduced riociguat mean area under the curve (AUC) by 26% and mean maximum observed concentration (C_{max}) by 35%. This is not considered clinically relevant.
- Co-administration of the antacid aluminum hydroxide/magnesium hydroxide reduced riociguat mean AUC by 34% and mean C_{max} by 56%. Antacids should be taken at least 1 hour after riociguat.

Other treatments considerations:

- Supportive treatments which may also be used for the treatment of PAH such as oral anticoagulants, diuretics, digitalis, calcium channel blockers or oxygen supplementation are permitted. However, treatment with diuretics should be stable for at least 30 days before randomization.
- Patients with supplemental long-term oxygen therapy may be included.

Concomitant treatment in case of clinical deterioration:

- In case of a clinically relevant deterioration of the patient's signs or symptoms of PAH, it is at the discretion of the investigator to perform additional invasive hemodynamic measurements according to practice guidelines; this needs to be documented in the eCRF.

8.2 Post-study therapy - *amended*

This section was changed in Amendment 4, see Section 15.1.2.14.

Further medical treatment of patients at the end of the study will be decided by the investigator at Visit 4 / EOT. In case riociguat is indicated for further treatment, patients will be prescribed riociguat / Adempas. The sponsor is going to ensure that patients will receive riociguat treatment after completion of the study in countries where riociguat is not reimbursed/commercially available. Based on the local regulations, the sponsor is going to identify and take appropriate measures, in agreement with the center/treating physician, such

as allowing the patient access to a drug supply study, to a compassionate use, or other drug supply programs.

9. Procedures and variables

9.1 Tabular schedule of evaluations

See schedule of procedures in Section 16.1.

Patients will be contacted via telephone every 4 weeks, if there is no scheduled visit to the study center.

9.2 Visit description

9.2.1 Mandatory screening period (Week -2 ± 2 days, Visit 0) - *amended*

This section was changed in Amendment 4, see Section 15.1.2.15.

The mandatory screening period starts 2 weeks prior to randomization (baseline visit) and includes primary diagnostic procedures and the verification of the following eligibility criteria:

- Signed ICF.

Patients who sign the ICF will undergo the following investigations:

- Check for inclusion/exclusion criteria (see Sections 6.1 and 6.2)
- Lung function test (see exclusion criterion 13 in Sections 6.2 and 9.7.2)
- Pulse oximetry (see exclusion criterion 14 in Sections 6.2 and 9.7.1)
- Echocardiography (LVEF) (see exclusion criterion 15 in Section 6.2)
- Medical history (see Section 9.3.2)
- Smoking status, including number of cigarettes per day
- Specific PAH medication (see Section 8.1)
- Patient's demographics (see Section 9.3.1)
- Pregnancy test (women of childbearing potential only; see Section 9.6.2)
- Physical examination (see Section 9.6.3.1)
- Weight and height
- 6MWD test (blinded assessment, see Section 9.7.1)
- WHO FC (blinded assessment, see Section 9.7.4)
- Safety laboratory measurements (see Section 9.6.3.4)

- Vital signs, including sitting BP and pulse rate (see Section 9.6.3.2)
- Electrocardiogram (ECG) (see Section 9.6.3.3)
- Concomitant medication (see Section 8.1)
- Adverse event (AE) assessment and reporting (see Section 9.6.1). The recording period of AEs begins with the signature of the ICF.

9.2.2 Randomization (Baseline visit, Week 0, Visit 1) - *amended*

This section was changed in Amendment 4, see Section 15.1.2.16.

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

The following procedures will be performed at baseline prior to randomization:

- Inclusion/exclusion criteria (see Sections 6.1 and 6.2)
- Pulse oximetry (see exclusion criterion 14 in Section 6.2 and Section 9.7.1)
- Smoking status, including number of cigarettes per day
- Specific PAH medication (see Section 8.1)
- Pregnancy test (women of childbearing potential only, see Section 9.6.2)
- 6MWD test (blinded assessment, see Section 9.7.1)
- Biomarkers (central laboratory; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- mRRS (see Section 16.4)
- LPH (QoL) questionnaire (see Section 16.5)
- Vital signs, including sitting BP and pulse rate (see Section 9.6.3.2)
- Concomitant medication (see Section 8.1)
- AE assessment and reporting (see Section 9.6.1)
- Cardiac magnetic resonance imaging (cMRI; exploratory, reported separately)
- Randomization – via IXRS (see Section 7.3).

Patients will be randomized 1:1 to either the control arm (standard of care) or the riociguat arm on the same day.

Patients randomized to the control arm

Patients will continue to receive tadalafil (dose range between 20 and 40 mg/day) or sildenafil (dose at least 60 mg/day) as well as other standard of care treatments at the discretion of the investigator up to Week 24.

Patients randomized to the riociguat arm

Riociguat will be dispensed (note the dose titration scheme for riociguat arm, see Figure 7–1).

Date and time of the last PDE-5i dose will be documented by the investigator. Patients will have the following **wash-out periods**:

- Patients pretreated with a stable dose of sildenafil (dose at least 60 mg/day) will be switched to riociguat after a wash-out period of **24 hours following the last dose of sildenafil**
- Patients pretreated with a stable dose of tadalafil (dose range 20 to 40 mg/day) will be switched to riociguat after a wash-out period of **48 hours following the last dose of tadalafil**.

Riociguat dosing start

Based on the time of the last PDE-5i dose, date and time of the first dose of riociguat after the wash-out period will be determined by the investigator and communicated to the patient. Before the first dose of riociguat, BP measurements need to be performed to ensure that SBP is ≥ 95 mmHg. **If the BP is below this value, riociguat must not be administered (BP measurement may be repeated within the next 24 hours).** Measurement of BP and application of first riociguat dose may be performed at the study center or by an experienced nurse at home (see Section 9.6.3.2).

Date and time of intake of the first dose of riociguat need to be documented by the investigator.

The nurse will contact the center for this purpose via phone. The dosage will then be individually adjusted during the titration period (H 1 to V 2).

Home Visits 1, 2, 3 (Weeks 2, 4, 6 ± 2 days)

Home visits may be facilitated by experienced nurses, measuring BP and agreeing on the next dose in phone contact with the treating investigator at the center. Prior to start of any study-related activities, the experienced nurse needs to be trained on the Study Protocol. The training needs to be documented in the investigator site file. The nurse will follow the instructions given by the treating investigator.

The experienced nurse is responsible for the Drug Accountability, and dispensing riociguat medication. When performing home visits, the experienced nurse will collect the following information and report to treating investigator at the site.

The following procedures will be performed:

- Dispense of study medication (see Section 7.4)
- Drug accountability (see treatment compliance in Section 7.7)
- Dose of riociguat (see Section 7.4)
- Vital signs, including sitting BP and pulse rate (see Section 9.6.3.2)
- Change in concomitant medication (see Section 8.1)
- AE assessment and reporting (see Section 9.6.1)

- At Week 4 only: smoking status, including number of cigarettes per day
- At Week 4 only: pregnancy test (women of childbearing potential only see Section 9.6.3.4).

In the riociguat arm, the investigator will decide about the dose adjustment of riociguat based on the vital signs and wellbeing of the patient, enter it into the IXRS and retrieve a new dose box number (initial dose adjustment period, see Section 7.4).

The procedures of home nurse service and drug delivery must be in agreement with local medical practice and local legal requirements.

At the discretion of the investigators and if applicable (e.g., short distance to study center) these visits may also be performed at the study center.

9.2.3 Visit 2 (Week 8 ± 2 days) - *amended*

This section was changed in Amendment 4, see Section 15.1.2.17.

Titration step 4 takes place at Visit 2.

The following procedures will be performed:

- Smoking status, including number of cigarettes per day
- Pregnancy test (women of childbearing potential only see Section 9.6.3.4)
- Dispense of study medication (see Section 7.4)
- Drug accountability (see treatment compliance in Section 7.7)
- Dose of riociguat (see Section 7.4)
- 6MWD (blinded assessment, see Section 9.7.1)
- Biomarkers (central laboratory; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- Vital signs, including sitting BP and pulse rate (see Section 9.6.3.2)
- Change in concomitant medication (see Section 8.1)
- AE assessment and reporting (see Section 9.6.1).

9.2.4 Telephone Contact (Week 12 ± 2 days) - *amended*

This section was changed in Amendment 4, see Section 15.1.2.18.

The following will be recorded:

- Smoking status, including number of cigarettes per day
- Pregnancy test (women of childbearing potential only, see Section 9.6.2)
- Change in concomitant medication (see Section 8.1)
- AE assessment and reporting (see Section 9.6.1).

9.2.5 Visit 3 (Week 16 ± 2 days) - *amended*

This section was changed in Amendment 4, see Section 15.1.2.19.

The following procedures will be performed:

- Smoking status, including number of cigarettes per day
- Pregnancy test (women of childbearing potential only, see Section 9.6.2)
- Dispense of study medication (see Section 7.4)
- Drug accountability (see treatment compliance in Section 7.7)
- Dose of riociguat (see Section 7.4)
- 6MWD (blinded assessment, see Section 9.7.1)
- Biomarkers (central laboratory; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- mRRS (see Section 16.4)
- Safety laboratory measurements (local laboratory; Section 9.6.3.4)
- Vital signs, including sitting BP and pulse rate (see Section 9.6.3.2)
- Change in concomitant medication (see Section 8.1)
- AE assessment and reporting (see Section 9.6.1).

9.2.6 Telephone Contact (Week 20 ± 2 days) - *amended*

This section was changed in Amendment 4, see Section 15.1.2.20.

The following will be recorded:

- Smoking status, including number of cigarettes per day
- Pregnancy test (women of childbearing potential only, see Section 9.6.2)
- Change in concomitant medication (see Section 8.1)
- AE assessment and reporting (see Section 9.6.1).

9.2.7 Visit 4 / End of Treatment (EOT) (Week 24 ± 4 days) - *amended*

This section was changed in Amendment 4, see Section 15.1.2.21.

The Visit 4 / EOT visit will be performed at Week 24 ± 4 days after the last dose of riociguat, sildenafil or tadalafil, and a decision on further treatment will be made.

The following procedures will be performed:

- Smoking status, including number of cigarettes per day
- Pregnancy test (women of childbearing potential only, see Section 9.6.2)

- Physical examination (see Section 9.6.3.1)
- Drug accountability (see treatment compliance in Section 7.7)
- 6MWD (blinded assessment, see Section 9.7.1)
- Biomarkers (central laboratory; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- mRRS (see Section 16.4)
- LPH (QoL) questionnaire (see Section 16.5)
- Safety laboratory measurements (local laboratory; see Section 9.6.3.4)
- Vital signs, including sitting BP and pulse rate (see Section 9.6.3.2)
- Change in concomitant medication (see Section 8.1)
- AE assessment and reporting (see Section 9.6.1)
- cMRI (exploratory, reported separately).

9.2.8 Safety follow-up visit (30 days ± 5 days) - *amended*

This section was changed in Amendment 4, see Section 15.1.2.22.

The following assessments will be performed and documented in the eCRF:

- Smoking status, including number of cigarettes per day
- Pregnancy test (women of childbearing potential only, see Section 9.6.2)
- Vital signs, including sitting BP and pulse rate (see Section 9.6.3.2)
- AE assessment and reporting (see Section 9.6.1).

9.3 Population characteristics

9.3.1 Demographics

The following demographic data will be recorded:

- Age
- Sex
- Ethnicity
- Weight and height (screening only)
- Smoking status including number of cigarettes per day.

9.3.2 Medical history

Medical history findings (i.e., previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the patient's study eligibility
- Time of first diagnosis of PAH
- Date of most recent RHC
- Time of first PAH specific treatment.

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 9.6.1.1.

9.4 Efficacy

A complete list of variables to be analyzed for this study and the methods of analysis will be provided in the statistical analysis plan (SAP).

Standard efficacy outcomes at Week 24:

- Change from baseline in 6MWD (blinded assessment, see Section 9.7.1)
- Change from baseline in NT-proBNP
- Change from baseline in WHO FC (blinded assessment, see Section 9.7.4)
- Clinical worsening (for definition, see Section 10.3.2.1)
- Change from baseline in QoL: LPH (see Section 16.5)
- Change from baseline in mRRS and mRRS category (see Section 16.4).

Approach to the analysis

Oral monotherapy or upfront combination therapy is recommended by the ERS/ESC guidelines for treatment of PAH patients with a low or intermediate risk according to their prognostic evaluation. There is increasing evidence that the concept of combining different signaling pathways in PAH-specific combination therapy may provide additional benefit to patients.

The general treatment goal is to achieve a low risk status for the individual PAH patient as defined by determinants of prognosis such as WHO FC, 6MWD, or NT-proBNP.

Interim results from the uncontrolled open-label RESPITE study showed that transition of PDE-5i to riociguat in patients not reaching treatment goals results in improvements in these clinically and prognostic relevant parameters. To the widely accepted concept of combination therapy, this adds the concept of optimizing a pathway by transition to a more effective drug.

It has been agreed by key experts that a randomized study would be needed to confirm the concept. The study design of REPLACE comes as close as possible in matching the real clinical situation in which a patient in on stable PDE-5i and ERA–combination therapy, or on PDE-5i monotherapy and does not reach treatment goals. Treatment escalation may not be imminent but would be the next step. Patients will be randomized to remain on their stable treatment or to transition their PDE-5i treatment component to riociguat.

Recent studies in PAH as AMBITION applied an event-driven design with a clinical worsening endpoint. Due to the low event rate on active treatment these studies would require large patient numbers and lengthy studies until results are available. In recent expert discussions moving away from the rather defensive strategy of counting deterioration to a composite endpoint of clinical improvement has been discussed as a pragmatic necessity. This is supported by the fact that mortality never made a difference between treatment groups in these studies. The REPLACE composite endpoint reflects the concept of clinical improvement in the absence of events of clinical worsening. This reflects what the clinician and the treatment guidelines define as treatment goals: improvement in parameters relevant clinically and for prognosis and thus reducing the risk of deterioration in the individual patient.

Similar endpoints were applied successfully in the AIR-study with inhaled iloprost and as secondary endpoint in AMBITION. The criteria when applied to our data from PATENT1/2 or RESPITE showed that improvement with riociguat treatment can nicely be demonstrated.

This also holds true when the component of NT-proBNP improvement was added to the composite endpoint. This has been recommended by the Study Core Advisory Committee considering the more objective nature of this parameter in an unblinded randomized study.

Baseline Demographics

A prevalent patient population similar to the one in RESPITE is expected, with the difference that also PAH associated with CTD will be included, and expected to form up to 20% of the overall study population. Mean age: 54 years, slight female predominance of 60%; 75% IPAH/HPAH; mean time on PDE-5i treatment 2 years; 80% on ERA-PDE-5i combination at baseline; mean 6MWD at baseline 370 m; all patients WHO FC III.

9.5 Pharmacokinetics/pharmacodynamics

Not applicable.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g., physical examination findings, symptoms, diseases, laboratory.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as AEs. This includes intercurrent illnesses.

Definition of serious adverse event

A serious adverse event (SAE) is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours

- The admission is preplanned (e.g., elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
- The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability/incapacity.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly/birth defect

f. Is another serious or important medical event as judged by the investigator.

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe.

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of study treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the case report form (CRF).

Causality should be assessed separately for each study treatment as detailed in the CRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g., owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”.

An assessment of “no” would include:

1. The existence of a clear alternative explanation, e.g., mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g., the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism, and excretion) of the study treatment, coupled with the individual patient’s pharmacodynamics should be considered.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a “reasonable causal relationship” to protocol-required procedure(s).

Possible answers are “yes” or “no”.

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown.

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other.

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown.

9.6.1.3 Assessments and documentation of adverse events - *amended*

This section was changed in Amendment 4, see Section 15.1.2.23.

The investigator has to record on the respective eCRF pages (additionally to the source data) all AEs occurring in the period between the signing of the informed consent and the safety FU visit at 30 days (± 5 days) after last intake of study treatment (for details, please also refer to Sections 5 and 16.1); after that, there is no requirement to actively collect AEs, including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness, and causal relationship to study treatment.

9.6.1.4 Reporting of serious adverse events

The definition of SAEs is given in Section 9.6.1.1.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the eCRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs/IRBs

Notification of the independent ethics committees (IECs)/institutional review boards (IRBs) about all relevant events (e.g., SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g., SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events - *amended*

This section was changed in Amendment 4, see Section 15.1.2.24.

For this study, the applicable reference document is the most current version of the IB for Adempas and the EU SmPC / local SPC for Revatio (sildenafil) and Adcirca (tadalafil).

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

In this study, the events of disease progression based on the definition given in Section 10.3.2.1, will be part of the adjudication as efficacy endpoints, e.g.,:

Disease progression (adjudicated):

- 6MWD decrease ≥ 15% from baseline (2 measurements on 2 separate days), **and**
- Worsening in WHO FC.

OR

- 6MWD decrease ≥ 15% (2 measurements on 2 separate days), **and**
- Need of new PAH-targeted medication or decompensated right sided heart failure.

For the purposes of this trial, these events will be considered expected and will not be subject to expedited reporting process, if reported as serious adverse drug reactions. They will be captured in the Global Pharmacovigilance database, in the eCRF and undergo adjudication and review.

9.6.1.6 Adverse events of special safety interest - *amended*

This section was changed in Amendment 4, see Section 15.1.2.25.

Symptomatic hypotension and serious hemoptysis (which includes pulmonary hemorrhage) are considered AEs of special interest and must be reported to Bayer within the same timelines as an SAE by reporting them on the AE page of the eCRF. Events of symptomatic hypotension and non-serious hemoptysis should not automatically be upgraded by the reporting investigator to serious. Declaration of an event as serious should only occur where the seriousness criterion (as defined in Section 9.6.1.1) is applicable.

9.6.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study patient during her participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For the patient, the outcome of the pregnancy should be followed up carefully, and any outcome of the mother or the child should be reported.

Bayer usually does not gather information of drug exposure via the father, however, if those cases are reported, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

For female patients of reproductive potential, in addition to the tests during the scheduled visits, monthly pregnancy tests are required, which can be performed at home. The results will be followed up during telephone contacts and home visits.

Pregnancy tests during the scheduled visits will be performed in urine or blood, locally, at the time points specified in the Schedule of Procedures in Section 16.1.

9.6.3 Further safety

9.6.3.1 Physical examination

Physical examination will be performed as per schedule of procedures (see Section 16.1).

Abnormal physical examination findings are recorded either as medical history or as AEs (see Section 9.6.1.1).

9.6.3.2 Vital signs

Pulse rate and BP will be assessed according to the schedule of procedures (Section 16.1). Any clinically relevant measurements or changes are to be reported as AEs.

BP and pulse rate will be measured after the patient has been at rest for 15 minutes in a sitting position, and the same arm should be used for every examination.

9.6.3.3 12-lead ECG

12-lead ECGs will be performed at screening and at any other time during the study at the investigator's discretion and should be reported in the unscheduled procedure page (see Section 16.1).

For deriving the ECGs, a supine position of the patient and a resting period of 10 minutes are recommended. In addition, the investigator will print out the ECGs locally and review the ECGs for potential AEs.

9.6.3.4 Laboratory assessments - *amended*

This section was changed in Amendment 4, see Section 15.1.2.26.

The following safety laboratory parameters will be measured in the local laboratory:

- Hematology: white blood cell differential count, erythrocytes, hemoglobin, hematocrit, platelets
- Coagulation tests: prothrombin time (INR), only for patients under anticoagulation therapy
- Clinical chemistry: AST, ALT, total bilirubin, serum albumin, creatinine, potassium.

The following biomarkers will be analyzed in the central laboratory:

- NT-proBNP
- ADMA
- cGMP (from plasma)
- GDF-15
- ST-2.

All time points for collection of safety laboratory parameters and biomarker are provided in Section 16.1.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g., clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

In women of childbearing potential, pregnancy tests in urine or blood will be performed at the local laboratory, at the time points specified in Section 16.1.

9.7 Other procedures and variables

9.7.1 Pulse oximetry - *amended*

This section was changed in Amendment 4, see Section 15.1.2.27.

The patient's oxygen saturation will be measured with a noninvasive method expressing the SpO_2 (peripheral oxygen saturation) percentage.

If the patient receives supplemental oxygen, the amount [L/min] will be recorded in the eCRF.

9.7.2 Lung function testing

The FEV_1 [L/s] and FEV_1, % of predicted and TLC [L] should preferably be analyzed by body plethysmography or alternatively by inert gas dilution (helium, argon, neon) or nitrogen washout at screening.

Available lung function testing results will be considered as baseline if they are not older than 180 days at V1 and analyzed by one of the below mentioned methods. Diffusing capacity of the lung for carbon monoxide (DLCO) must be newly determined. In case that the respective lung function test results are not available, measurements need to be performed during the pre-treatment phase.

The measured values have to be transferred into the eCRF.

Lung function measurement:

- Actual time
- Date
- FEV_1[L/s]
- FEV_1 % of predicted
- TLC [L]
- TLC, % of predicted.

The predicted forced expiratory volume in one second (FEV_1) is a calculated value. For the calculation the following formulas need to be applied:

- Predicted forced expiratory volume (FEV) (women) = 3.95 * height [m] – 0.025 * age [years] – 2.60.
- Predicted FEV (man) = 4.30 * height [m] – 0.029 * age [years] – 2.49.

The predicted TLC is a calculated value. For the calculation the following formulas need to be applied:

- Predicted TLC (women) = 6.60 * height [m] - 5.79.
- Predicted TLC (man) = 7.99 * height [m] – 7.08.

DLCO predicted will be newly determined by the single breath technique according to the standards recommended by the American Thoracic Society (and the European Respiratory Society) (16).

9.7.3 6MWD test - *amended*

This section was changed in Amendment 4, see Section 15.1.2.28.

The 6MWD test will be performed in accordance with the American Thoracic Society Guideline without assessing Borg-Dyspnoea-Index (17). Test results will be recorded on the eCRF.

To ensure a blinded assessment from the randomization visit (baseline), adequate measures need to be taken at the study center when performing the 6MWD:

- The test has to be performed by a physician or study nurse who is blinded to the study treatment of the patient.
- The person performing the test must not be involved in the process of study drug administration.
- The person performing the test should record the results on a separate work sheet and, where possible, a different person (could be the person who is involved in the study treatment administration) should enter them into the eCRF.

For details on time points refer to Section 16.1, for further details on assessment refer to Section 16.2.

9.7.4 Determination of WHO FC - *amended*

This section was changed in Amendment 4, see Section 15.1.2.29.

The patients' WHO FC will be determined according to the WHO classification. Test results will be recorded on the eCRF.

The person assessing the WHO FC must be suitably trained (referred to as "assessor" below). To ensure blinded assessment of the WHO FC from the randomization visit (baseline), the following adequate measures also need to be taken at the study center:

- The assessor must be blinded to the study treatment of the patient
- The assessor must not be involved in the process of study drug administration.
- The assessor should record the test results on a separate work sheet and, where possible, a different person (could be the same person who is involved in the treatment administration) should enter them into the eCRF.

Ideally, the WHO FC assessment should always be performed by the same person.

For details on time points refer to Section 16.1, for further details on the assessment refer to Section 16.3.

9.7.5 cMRI

cMRI will be performed on a subset of patients participating in this study. A separate manual will be produced and provided to the site.

Objective measurements of pulmonary hemodynamics assessed by RHC have been applied in PAH studies using primary endpoints, in which parameters of subjective nature were the main components (e.g., 6MWD or WHO FC). For the feasibility of this Phase 4 study, RHC investigation was not considered. Instead, as an alternative, cMRI was recommended because it is well standardized and provides an accurate and objective assessment of parameters of right ventricular function with established prognostic relevance. Based on the characteristics of this method, assessment will even be possible if a subset of patients from centers with expertise and technical requirements is to be included. The assessment of cMRI parameters is considered an important element of this study as it will provide essential complementary information on right ventricular function and remodeling; both of which are closely related to the major study objectives and will therefore be relevant for supporting the interpretation of the clinical endpoints.

9.8 Appropriateness of procedures/measurements

All procedures and measurements are standard variables/methods in clinical studies and/or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics (mean, standard deviation, minimum, median, quartiles, and maximum). If not mentioned otherwise, all statistical tests will be performed with a type I two-sided error rate of 5%.

Statistical analyses will be performed using Statistical Analysis System (SAS) version 9.2 or later.

10.2 Analysis sets

Analyses will be performed for three analysis sets: full analysis set (FAS), per protocol set (PPS) and safety analysis set. The FAS will be the primary analysis set.

All patients randomized and treated (at least one treatment after randomization) will be valid for the FAS, hence the number of patients in the safety and FAS will be identical.

A patient is valid for the per protocol analysis, if the patient is valid for the safety analysis set/FAS, has an adequate investigation of all primary variable components at baseline and

shows no major protocol deviations (refer to the SAP for details on major protocol deviations).

Primary endpoint components are: assessments of clinical worsening (as defined in Section 10.3.2.1), 6MWD, WHO FC, and NT-proBNP.

Final decisions regarding validity will be made during the Validity Review Meeting and documented in the Validity Review Report.

10.3 Variables and planned statistical analyses

10.3.1 Demographic and baseline characteristics

All demographic variables and baseline characteristics will be summarized for all analysis sets. Medical history findings and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) codes and medications by Anatomical Therapeutic Chemical class according to the WHO-Drug Dictionary (WHO-DD).

10.3.2 Efficacy endpoints

An efficacy analysis will be performed in patients valid for FAS (primary analysis) and PPS. Both groups (riociguat vs. active control) will be compared using a stratified Mantel-Haenzel test with a two-sided alpha level of 5%. Stratum is the disease class (definition see Section 7.3).

The null hypothesis tested for the primary endpoint of efficacy is that there is no difference in the satisfactory clinical response rates (OR) when treated with riociguat compared to patients that remain on their previous therapy (i.e., H0: OR = 1). The two-sided alternative is that there is a difference (i.e., H1: OR $\neq$ 1).

For statistical analysis of the primary endpoint with missing endpoint data, the last observation carried forward (LOCF) will be utilized. The reason for LOCF is given in the following: the primary endpoint measures improvements, thus, using LOCF will (a) not yield favorable results in the riociguat arm and (b) yield favorable results in the active control arm. Because of the inclusion criterion “stable on PDE5-i one expects the first case (a) to be much more frequent. Thus, LOCF is not in favor for the whole study. For composite endpoints each single component is independently replaced with the last available observation, respectively.

To assess the influence of missing data, a supportive analysis without LOCF will be performed with a generalized estimating equations approach (binomial distribution) utilizing all adequate investigations of all primary variable components at any time from including baseline up to Week 24.

Both methods above cover missing values of type 'missing completely at random'. In this open-label study there might also be missing values of type 'missing not at random'. To assess the influence of these missing values a sensitivity analysis is planned. A multiple imputation with penalty will be performed where the penalty is given by crossed improvement rates in both arms.

- Riociguat arm: imputation with a clinical improvement rate observed in active control arm
- Control arm: imputation with a clinical improvement rate observed in riociguat arm

Thus, the highest sensible rate of clinical improvement is the rate in the riociguat arm and this is applied to the control arm in the imputation process. Further, the lowest sensible rate of clinical improvement is the rate in the control arm and this is applied to the riociguat arm in the imputation process.

Additionally, a tipping point analysis is performed (a detailed definition will be given in the SAP).

A multiplicity correction is not necessary for the primary endpoint because only one primary endpoint is defined. Secondary endpoints are tested hierarchically. An alpha level of 5% is used for secondary endpoints (each) as well as for exploratory endpoints.

The null hypothesis tested for the secondary efficacy endpoints is that there is no difference when treated with riociguat compared to patients who remain on their previous therapy. The two-sided alternative is that there is a difference, respectively (details are given in the SAP).

10.3.2.1 Primary efficacy endpoint - *amended*

This section was changed in Amendment 4, see Section 15.1.2.30.

The primary efficacy endpoint 'satisfactory clinical response' is defined as the composite endpoint comprising the following components (independent central adjudication):

- **2 of 3 must be fulfilled**
  - 6MWD increase by ≥ 10% or ≥ 30 m from baseline to Week 24
  - WHO FC I or II at Week 24
  - NT-proBNP reduction ≥ 30% from baseline to Week 24 (NT-proBNP ratio Week 24/baseline ≤ 0.7), AND
- **No clinical worsening** (for definition, see below)

'Satisfactory clinical response' is defined as 'YES' only if the 2 major composites ('2 of 3' and 'No clinical worsening') are both 'YES'. The component '2 of 3' is 'YES' if at least 2 of its 3 sub-components are 'YES'. In all other cases 'satisfactory clinical response' is defined as 'NO'. The biomarker is given the same importance as the clinical parameters to introduce more objectivity to the endpoint and reduce possible open-label bias.

Definition of Clinical Worsening:

- Death of any cause
- Hospitalization due to worsening PAH (adjudicated)
  - Non-elective hospitalization due to PAH, or
  - Initiation of intravenous/subcutaneous prostanoid therapy.
- Disease progression (adjudicated)
  - 6MWD decrease ≥ 15% from baseline (2 measurements on 2 separate days), **and**
  - Worsening in WHO FC.

  OR
  - 6MWD decrease ≥ 15% (2 measurements on 2 separate days), **and**
  - Need of new PAH-targeted medication or decompensated right sided heart failure [1].

10.3.2.2 Secondary efficacy endpoints

Standard efficacy outcomes (hierarchical testing in the order specified below) at Week 24:

- Change from baseline in 6MWD (blinded assessment, see Section 9.7.1)
- Change from baseline in NT-proBNP
- Change from baseline in WHO FC (blinded assessment, see Section 9.7.4)
- Clinical worsening (for definition, see Section 10.3.2.1).

10.3.2.3 Exploratory endpoints

A complete list of variables to be analyzed for this study and the methods of analysis will be provided in the SAP.

- cMRI (core laboratory, reported separately)
- Change from baseline in QoL: LPH (see Section 16.5)
- Change from baseline in mRRS and mRRS category (see Section 16.4)
- Change in other biomarkers (ADMA, cGMP, GDF-15 [plasma], ST-2).

[1] Decompensated right-sided heart failure is defined as the appearance or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy (need for intravenous diuretic therapy and/or inotropic drugs).

10.3.3 Safety endpoints

Adverse events

The safety analysis will be performed in the population of patients valid for FAS. All tabulations will be descriptive only.

The incidence of treatment-emergent AEs will be tabulated overall. AEs are considered to be treatment-emergent if they have started or worsened after the first treatment administration up to 2 days after end of treatment. Further tables will be produced for serious and/or drug-related treatment-emergent AEs. The incidence of AEs during pre-treatment and during follow-up (i.e., AEs occurring more than 2 days after the end of treatment) will be tabulated separately.

Other safety parameters

Mortality in 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.

The safety evaluation of laboratory data will include:

- Incidence rates of treatment-emergent laboratory values outside of normal range
- Incidence rates of pre-specified laboratory data abnormalities
- Descriptive analysis of continuous laboratory parameters, and their changes from baseline by visit.

Descriptive analysis of vital signs, and their changes from baseline, will be performed by visit.

10.3.4 Subgroups

Subgroup analyses will be performed for following subgroups:

- PAH class as defined in randomization strata
- Pre-treatment with combination therapy with ERAs and PDE-5i versus pre-treatment with PDE-5i monotherapy
- Gender
- 6MWD at baseline
- Pre-treatment with tadalafil or sildenafil.

Subgroup analyses will be applied on primary and secondary endpoints. Further details (e.g., thresholds) will be defined in the SAP.

10.4 Determination of sample size

Sample size is determined based on results of Studies 12934/12935/16719 (PATENT-1/2, RESPITE) for riociguat. The estimate for the 'satisfactory clinical response' rate at Week 24 is 40% for the riociguat arm. Assuming a treatment effect of 50% (relative reduction, see next subsections) to the active control the estimate for a 'satisfactory clinical response' in the active control arm is 20%. The sample size of 218 patients is calculated using SAS Version 9.2 (proc power, two-sample-frequency, $\chi 2$-test, two-sided alpha = 5%, power = 90%).

The screening failure rate is estimated at 15% and therefore a screening number of 257 patients is required. As it is planned to use LOCF for the primary analysis, no adjustment for dropouts is needed.

Estimate riociguat arm

The estimate for the 'satisfactory clinical response' rate at Week 24 is 40% for the riociguat arm.

Table 10–1 presents the patient level analyses of Bayer's PATENT-1/2 and RESPITE studies for Week 24. A satisfactory clinical outcome of 48.1% was observed on 231 patients of the individual titration arm. For the subset of pretreated patients with WHO FC III at baseline, the satisfactory clinical outcome was 41.6%. The latter subset was the closest PATENT-1/2 subset to REPLACE. The RESPITE data, closest set to REPLACE, are in the same range with a focus in NT-proBNP; however, the number of patients is low. Given the fact that a slightly lower net effect due to the more effective treatment than in PATENT-1/2 is expected and a lower NT-proBNP reduction due to another baseline definition in RESPITE is expected, an assumption of 40% satisfactory clinical response is reasonable.

Table 10–1: Improvement of endpoints in PATENT-1/2 at Week 24 and RESPITE at Week 24 for all patients and the subgroup: pretreated and WHO FC III at baseline

	Week 24 PATENT-2	**Week 24 PATENT-2 WHO FC III Pre-treated = TRUE**	**Week 24 RESPITE**
Endpoint	Riociguat (N=231)	Riociguat (N=77)	Riociguat (N=30)
WHO	35.5	50.6	43.3
6MWD	64.1	53.2	43.3
NT-proBNP	42.9	23.4	66.7
Clinical worsening	3.0	3.9	13.3
Satisfactory Clinical Outcome	48.1	41.6	53.3

Abbreviations: 6MWD = 6-minute walking distance; N = number of patients; NT-proBNP = N-terminal pro-brain natriuretic peptide; WHO FC = World Health Organization Functional Class.

The numbers are the percentages of improvements in the categories. For example NT-proBNP: percentage of patients with a proBNP-reduction of 30% from baseline to follow-up. Placebo was skipped because patients were shifted to riociguat therapy. The pretreated subset of RESPITE is not shown due to the low number of patients.

Estimate active control arm

For the active control arm, no reliable patient-level data for Week 24 exist, but endpoint-related analyses for Week 12 are available based on PATENT-1 (Table 10–2). The satisfactory clinical response rates for the placebo patients in Week 12 are 8.3% for the total number (109 patients) and 3.3% (30 patients) for the subgroup, whereas the rates of the treatment arm are comparable to the Week 24 results. The placebo arm rates of the single endpoints are in the range of 15% to 30%. Thus, the low numbers of the satisfactory clinical response are due to a poor association of the single endpoints. Whether this low association is observed just by chance or is a systematical feature cannot be judged by this data solely. From a medical point of view a complete missing of association seems to be unrealistic. Therefore, a conservative 20% satisfactory clinical response for the active control arm is assumed, postulating a higher association of the sub-endpoints in the REPLACE study. The high-level data given in AMBITION, GRIPHON, SERAPHIN and COMPASS-2 indicate a reasonable similarity to PATENT-1/2 data. The 50% reduction (100% improvement) assumed in this study (40% to >20%) is at the upper range of the observed effects in these studies, most of which analysed clinical worsening.

Table 10–2: Improvement of endpoints in PATENT-1/2 at Week 12 for all patients and the subgroup: pretreated and WHO FC III at baseline

	Week 12		**Week 12 WHO FC III Pre-treated = TRUE**	
Endpoint	Riociguat (N=231)	Placebo (N=109)	Riociguat (N=77)	Placebo (N=30)
WHO	21.6	17.4	36.4	23.3
6MWD	50.6	31.2	44.3	23.3
NT-proBNP	42.9	14.7	26.0	16.7
Clinical worsening	0,0	0.0	0.0	0.0
Satisfactory Clinical Outcome	34.6	8.3	32.5	3.3

Abbreviations: 6MWD = 6-minute walking distance; N = number of patients; NT-proBNP = N-terminal pro-brain natriuretic peptide; WHO FC = World Health Organization Functional Class.

The numbers are the percentages of improvements in the categories. For example NT-ProBNP: percentage of patients with a proBNP-reduction of 30% from baseline to follow-up. The data base is the subset which continued in the long term study Patent-2, which was required for the 24-week data. (Therefore, no clinical worsening was counted. The rates in PATENT-1 were very low, thus this endpoint has a very small impact in this analysis.)

10.4.1 Sample size sensitivity

Additionally, a sensitivity analysis for the power has been performed where the rate of the active control arm is varied. The results are presented in Table 10–3 (assuming a sample size of 218 patients, 2-sided alpha = 5%, SAS 9.2, proc power, two-sample-frequency, χ^2-test).

Table 10–3: Sensitivity analysis

24-week satisfactory clinical response rate [%]		Relative improvement [%]	Approximate Power [%]
Riociguat	Active control		
40	18	122.2	95.2
40	19	110.5	93.0
40	20	100.0	90.2
40	21	90.5	86.7
40	22	81.8	82.4
40	23	73.9	77.5
40	24	66.7	71.9
40	29	37.9	40.0

10.5 Planned interim analyses

No interim analysis is planned.

11. Data handling and quality assurance

11.1 Data recording

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the site. The site must implement processes to ensure this happens. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

Data recorded from screening failures

At a minimum, the following data should be recorded in the eCRF:

- Demographic information (patient number; year of birth/age; sex; if applicable race/ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the eCRF in addition to the data specified above:

- All information related to the SAE such as:
    - The SAE itself
    - Concomitant medication
    - Medical history
    - Other information needed for SAE complementary page.

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes)
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g., IXRS, laboratory, ECG, adjudication committees).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

11.4 Missing data - *amended*

This section was changed in Amendment 4, see Section 15.1.2.31.

Due to the short period of the study, it is expected that the amount of missing data will only be minor. Every effort will be made to collect data until the EOT visit for all patients unless a patient withdraws consent and collection of further information is not allowed.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IECs/IRBs are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g., treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g., SAEs)
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; dropout rate; data quality; protocol compliance) does not suggest a proper completion of the study within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IECs/IRBs; competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing patients must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.3.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel - *amended*

This section was changed in Amendment 4, see Section 15.1.2.33.

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, IEC/IRB, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

External data evaluation bodies

Advisory Committee

The Advisory Committee has guided the development of the study concept and protocol. It will also provide feedback and expert advice on any modification/amendment of the protocol as well as on the conduct of the study. It will be kept updated on all new relevant information during study conduct and all relevant information on riociguat safety and efficacy that may influence the study.

The Advisory Committee is composed of experts in PH.

Clinical Endpoint Committee

An independent Clinical Endpoint Committee (CEC) will review and confirm the correctness of the assessments of clinical worsening (see Section 10.3.2.1) as well as of the other components of the primary endpoint in a blinded fashion. In the situation where despite all efforts to ensure protocol compliance, a second 6MWD could not be performed as confirmation of clinical worsening of PAH, the CEC will adjudicate on the clinical worsening.

Details of the CEC will be provided in a separate charter.

Central Laboratory

Analyses of biomarkers will be performed centrally by the sponsor. For details please refer to the Laboratory Manual.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure

according to all applicable legal requirements. All relevant documentation will be filed in the study master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IECs/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g., IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Patient information and consent - *amended*

This section was changed in Amendment 4, see Section 15.1.2.34.

All relevant information on the study will be summarized in an integrated patient information sheet and ICF provided by the sponsor or the study center. A sample patient information and ICF is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient, prior to his/her entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each patient will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers EOT assessments as specified in the visit description described in Section 9.2.7 to be conducted after withdrawal of consent.
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the SAP. The patient has the right to object to the generation and processing of this post-withdrawal data. The patient's oral objection may be documented in the patient's source data.

Each patient will have ample time and opportunity to ask questions.

Only if the patient voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The patient/legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed ICF is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that screening study procedures are performed, the study record or patient's clinical record must clearly show that informed consent was obtained prior to these procedures.

If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and/or the written ICF. The investigator will inform the patient/legal representative or proxy consenter of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval/favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of patients/insurance

The sponsor maintains clinical study insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the eCRF, and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient’s identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

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15. Protocol amendments

15.1 Amendment 4

Amendment 4 is the first global amendment dated 6 JAN 2017. The following is an overview of the changes made to the original Protocol Version 1.0.

15.1.1 Overview of changes

The original protocol was amended for the following reasons:

1). Administrative changes (e.g. addition of sponsor for US territory [Bayer HealthCare Pharmaceuticals Inc.], which is and has been sponsor for US territory for this study as set forth in FDA Investigational New Drug (IND) form 1571; the reference on the protocol was incomplete in this regard)

2). To reiterate that the benefit-risk balance for the population in this study (i.e. pulmonary arterial hypertension [PAH], Dana Point Group 1) is positive, despite the potential safety issue in Study 13605 in patients with PH-IIP (Dana Point Group 3) which had led to its early termination

3). To add the requirement for adequate use of effective contraceptive methods during this study

4). To include other biomarkers (in addition to NT-proBNP) at the request of the advisory committee, to further elucidate the value of selected NO-pathway related biomarkers for treatment decision in this controlled study and in comparison with biomarker results from the previous, uncontrolled RESPITE study

5). To include details for consistency with the Company Core Data Sheet (e.g. titration rules) and other studies using riociguat (e.g. extending the time for collecting AE information)

6). To improve clarity and correct typographical errors, inconsistencies and unintended omissions.

Sections affected include:

- Section 1 Title page
- Section 2 Synopsis
- Section 3 Introduction
- Section 5 Study design
- Section 6.1 Inclusion criteria
- Section 6.2 Exclusion criteria
- Section 6.3.1 Withdrawal
- Section 6.3.1.1 Discontinuation of study treatment

- Section 6.3.1.2 Discontinuation of study
- Section 7.1 Treatments to be administered
- Section 7.2 Identity of study treatment
- Section 7.3 Treatment assignment
- Section 8.1 Prior and concomitant therapy
- Section 8.2 Post-study therapy
- Section 9.2.1 Mandatory screening period (Week -2 ± 2 days, Visit 0)
- Section 9.2.2 Randomization (Baseline visit, Week 0, Visit 1
- Section 9.2.3 Visit 2 (Week 8 ± 2 days
- Section 9.2.4 Telephone Contact (Week 12 ± 2 days)
- Section 9.2.5 Visit 3 (Week 16 ± 2 days
- Section 9.2.6 Telephone Contact (Week 20 ± 2 days)
- Section 9.2.7 Visit 4 / End of Treatment (EOT) (Week 24 ± 4 days
- Section 9.2.8 Safety follow-up visit (30 days ± 5 days)
- Section 9.6.1.3 Assessments and documentation of adverse events
- Section 9.6.1.5 Expected adverse events
- Section 9.6.1.6 Adverse events of special safety interest
- Section 9.6.3.4 Laboratory assessments
- Section 9.7.1 Pulse oximetry
- Section 9.7.3 6MWD test
- Section 9.7.4 Determination of WHO FC
- Section 10.3.2.1 Primary efficacy endpoint
- Section 11.4 Missing data
- Section 13.1 Investigator(s) and other study personnel
- Section 13.4 Patient information and consent
- Section 16.1 Schedule of procedures
- Section 16.2 6 Minute Walking Distance (6MWD) Test.

15.1.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol.

In the display of modifications, the "old text" refers to the protocol version preceding this amendment.

Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text". Corrections of typographical errors or omissions are not highlighted in this amendment.

15.1.2.1 Section 1 Title page

Old text:

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

~~Short title:~~ **R**iociguat r**E**placing **P**DE-5i therapy eva**L**uated **A**gainst **C**ontinued PDE-5i th**E**rapy

~~Acronym:~~ REPLACE

Test drug:	BAY 63-2521/ riociguat / Adempas		
Study purpose:	To demonstrate the effectiveness of riociguat as replacement of PDE-5i therapy in PAH patients		
Clinical study phase:	4	Date:	~~31 MAY~~ 2016
Registration:	EudraCT: no. 2016-001067-36	Version no.:	~~1~~.0
Sponsor's study no.:	~~IMPACT no.~~ 18588		
Sponsor:	**Bayer AG, D-51368 Leverkusen, Germany**		

[…]

New text:

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

Riociguat r**E**placing **P**DE-5i therapy eva**L**uated **A**gainst **C**ontinued PDE-5i th**E**rapy

REPLACE

Test drug:	BAY 63-2521/ riociguat / Adempas		
Study purpose:	To demonstrate the effectiveness of riociguat as replacement of PDE-5i therapy in PAH patients		
Clinical study phase:	4	Date:	6 JAN 2017
Registration:	EudraCT: no. 2016-001067-36	Version no.:	2.0
Sponsor's study no.:	18588		
Sponsor:	Non- US territory: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA		

[…]

15.1.2.2 Section 2 Synopsis

Old text:

Diagnosis and main criteria for inclusion /exclusion	[…] Patients with symptomatic PAH according to WHO FC III and 6MWD of 165-440 m at screening and at randomization, with a pulmonary vascular resistance (PVR) of > 400 dyn*sec*cm-5, mean pulmonary artery pressure ≥ 25 mmHg, and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg as assessed by right heart catheterization ~~within 12 months~~ prior to screening. Alternatively, PCWP can be replaced by left ventricular end-diastolic pressure. […]

New text:

Diagnosis and main criteria for inclusion /exclusion	[…] Patients with symptomatic PAH according to WHO FC III and 6MWD of 165-440 m at screening and at randomization, with a pulmonary vascular resistance (PVR) of > 400 dyn*sec*cm-5, mean pulmonary artery pressure ≥ 25 mmHg, and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg as assessed by right heart catheterization <u>in medical history</u> prior to screening <u>to confirm the diagnosis</u>. Alternatively, PCWP can be replaced by left ventricular end-diastolic pressure. […]

15.1.2.3 Section 3 Introduction

Old text:

[…]

The RESPITE study was conducted to investigate whether it is safe, feasible, and beneficial to replace PDE-5i therapy with riociguat in PAH patients demonstrating insufficient response to PDE-5 inhibition. ~~Interim analysis~~ data of this hypothesis-generating single arm study showed that patients failing to respond to PDE-5i could benefit from replacing a PDE-5i with riociguat by improving 6MWD, WHO FC, and NT-proBNP. The data indicate that transition of PDE-5i to riociguat may serve as a treatment strategy for PAH patients.

~~However, a randomized controlled~~ study is ~~required~~ to confirm the potential clinical benefit of ~~transition~~.

Benefit-risk assessment

[…]

The overall benefit-risk balance of riociguat is considered positive if used in adherence to this clinical study protocol and in accordance with the recommendations and guidance given in the Investigator's Brochure (IB). […]

New text:

[…]

The RESPITE study was conducted to investigate whether it is safe, feasible, and beneficial to replace PDE-5i therapy with riociguat in PAH patients demonstrating insufficient response to PDE-5 inhibition. The final data of this hypothesis-generating single arm study showed that patients failing to respond to PDE-5i could benefit from replacing a PDE-5i with riociguat by improving 6MWD, WHO FC, and NT-proBNP. The data indicate that transition of PDE-5i to riociguat may serve as a treatment strategy for PAH patients.

The rationale of the study is to confirm the potential clinical benefit of switch within the NO-sGC-cGMP pathway in a randomized controlled study.

Benefit-risk assessment

[…]

Recently, results of a study on efficacy and safety of riociguat in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) showed an increased risk of mortality and serious adverse events among patients who received riociguat compared to those who received placebo, and an absence of apparent clinical benefit. The study was terminated early upon the advice of its data monitoring committee (DMC). It was concluded that the benefit risk balance of riociguat in patients with PH-IIP is negative. Riociguat is contraindicated in patients with PH-IIP.

The REPLACE study (18588) will only include patients with subtypes of Pulmonary Arterial Hypertension (PAH), Dana Point Group 1 (14). Patients with all other types of PH/ Dana Point Groups are excluded, also comprising patients with PH-IIP, according to the protocol.

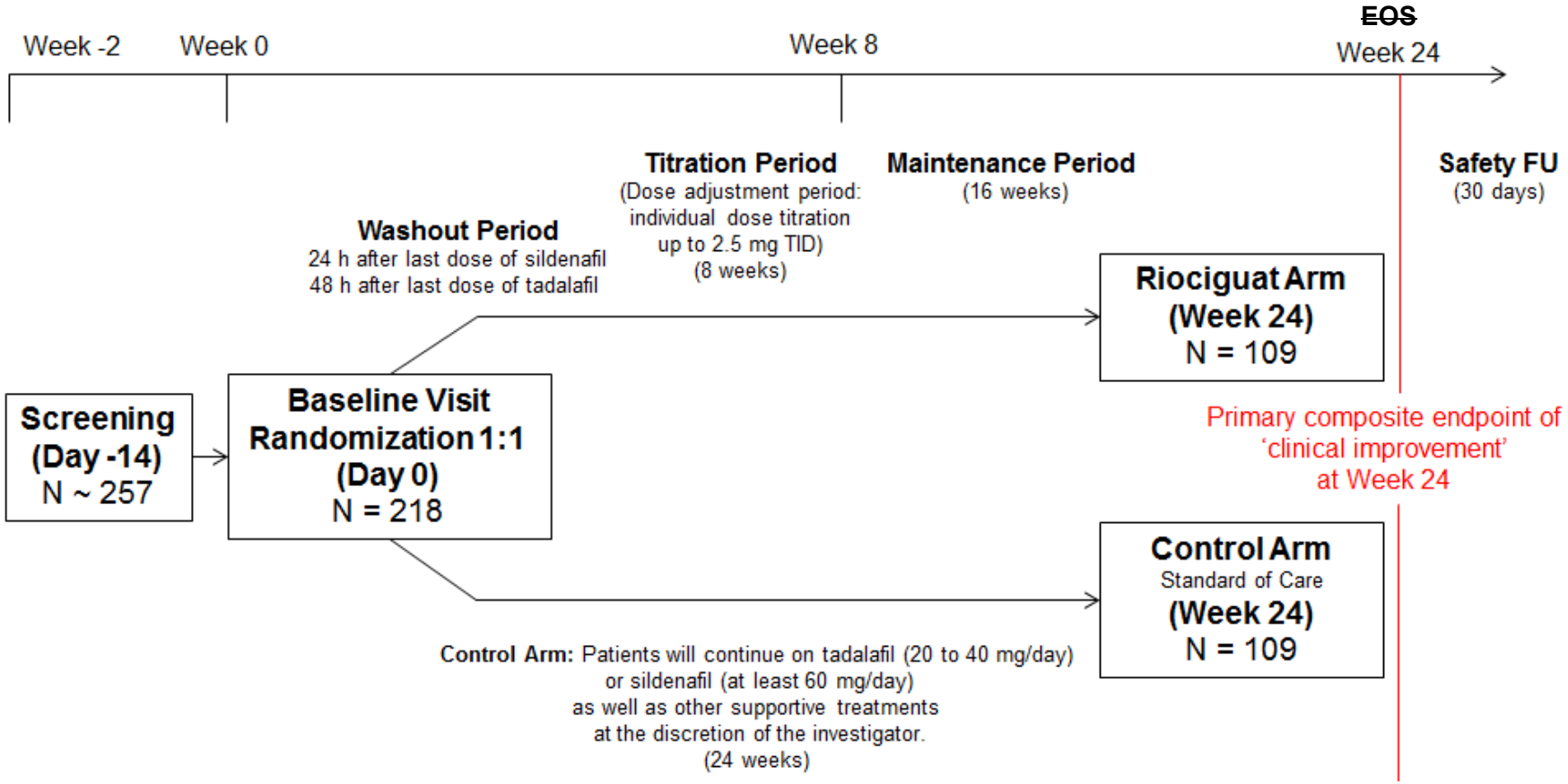
The overall benefit-risk balance of riociguat is considered positive if used in adherence to this clinical study protocol and in accordance with the recommendations and guidance given in the Investigator's Brochure (IB). […]

15.1.2.4 Section 5 Study design

Old text:

[…]

Figure 5-1: Study Design Overview



Abbreviations: ~~EOS~~ = ~~End of Study~~; FU = Follow-up; N = number of patients; TID = three times daily.

[…]

Titration period (Riociguat arm, duration: 8 weeks)

[…]

The investigators will apply the following blood pressure (BP) based titration rules for their dose decision:

~~The individual riociguat dose will be titrated under consideration of the following algorithm (= individual dose titration scheme):~~

- ~~If trough SBP ≥ 95 mmHg, increase dose (+ 0.5 mg TID)~~
- ~~If trough SBP 90 to 94 mmHg, maintain dose~~
- ~~If trough SBP < 90 mmHg without symptoms of hypotension, reduce dose (- 0.5 mg TID)~~
- ~~If any SBP < 90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, stop treatment; restart after 24 hours with reduced dose (- 0.5 mg TID).~~

[…]

Premature discontinuation of study treatment

In case of premature discontinuation of study treatment, the process detailed in Section ~~6.3.1~~ should be followed.

~~End of Study~~ (Week 24 ± 2 days)

~~At~~ the last visit of the maintenance period~~, i.e., at the EOS visit~~, all relevant efficacy and safety measurements will be performed.

Safety follow-up ~~phase~~ (30 days ± 5 days)

A safety ~~follow-up~~ (FU) visit ~~30 days (± 5 days) after discontinuation of treatment intake should~~ be performed ~~for both arms~~.

[…]

Justification of the design

[…]

End of Study

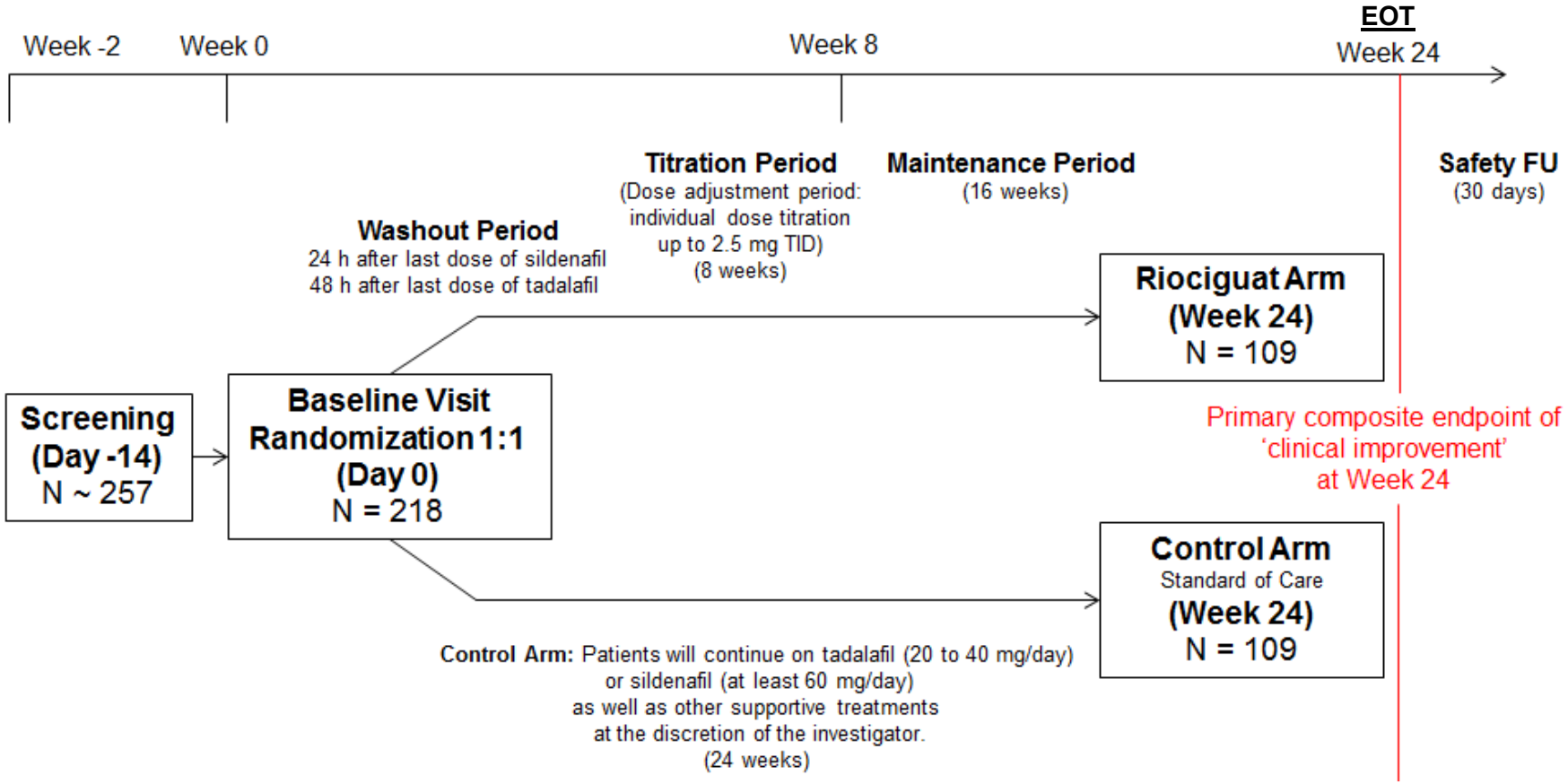
The end of the study as a whole will be reached as soon as ~~the end of the study~~ according to the above definition has been reached in all participating countries (European Union [EU] and non-EU).

[…]

New text:

[…]

Figure 5-1: Study Design Overview



Abbreviations: EOT = End of Treatment; FU = Follow-up; N = number of patients; TID = three times daily.

[…]

Titration period (Riociguat arm, duration: 8 weeks)

[…]

The investigators will apply the following blood pressure (BP) based titration rules for their dose decision:

> Dosage should be increased in 2-week intervals by 0.5 mg increments to a maximum of 2.5 mg three times daily, if SBP is ≥95 mmHg and the patient has no signs or symptoms of hypotension. If SBP falls below 95 mmHg, dosage should be maintained provided the patient does not show any signs or symptoms of hypotension. If at any time during the up-titration phase systolic blood pressure decreases below 95 mmHg, and the patient shows signs or symptoms of hypotension, the current dose should be decreased by 0.5 mg tid.

[…]

Premature discontinuation of study treatment

In case of premature discontinuation of study treatment, the process detailed in Section 6.3.1.1 should be followed.

Visit 4 / End of Treatment (EOT) (Week 24 ± 4 days)

All patients randomized to either treatment arm should perform Visit 4 / EOT. This is the last visit of the maintenance period, when all relevant efficacy and safety measurements will be performed.

Safety Follow-Up (FU) visit (30 days ± 5 days after last intake of study treatment)

A safety FU visit is to be performed 30 days (± 5 days) after the planned end of study treatment OR 30 days (± 5 days) after premature discontinuation of study treatment.

Justification of the design

[…]

While it may appear inappropriate to randomize patients who are not "at treatment goal" to the control arm, where their current PAH-specific treatment regimen will just be continued, in the absence of a clear definition of treatment response, the definition for this study is inspired by the ESC/ ERS table for assessment (15) and based on 6MWD and WHO FC only. Other parameters of prognostic relevance including pulmonary hemodynamics may well be in the range of low risk/ at treatment goal according to guidelines. It can be assumed that a large number of patients on mono-or combination therapy with PAH-targeted drugs are in a stable clinical situation, but do not reach WHO FC I/II or a 6MWD > 440 m. Clinical stability at randomization will be ensured by requirements such as stable doses of PAH-therapy and

diuretics, and the mandatory 14-day screening period. By this, the study design intends to represent the real-life clinical situation of PAH patients, in which close follow-up of prognostically relevant parameters is required for the decision on a next step of treatment escalation. As there will be rater-blinded assessments and central adjudication, but no blinding of the study treatment arms, the investigator will at any time be able to decide about any necessary treatment escalation. Thus, even treatment of a patient randomized to the control or maintenance arm will stringently follow treatment guidelines.

End of Study

The end of the study as a whole will be reached as soon as the last safety FU visit of the last patient according to the above definition has been reached in all participating countries (European Union [EU] and non-EU).

[…]

15.1.2.5 Section 6.1 Inclusion criteria

Old text:

2. Patients with symptomatic PAH with a pulmonary vascular resistance (PVR) > 400 dyn*sec*cm-5, mean pulmonary artery pressure ≥ 25 mmHg, and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg as assessed by the most recent right heart catheterization (RHC) ~~within 12 months~~ prior to screening. Alternatively, PCWP can be replaced by left ventricular end-diastolic pressure (≤ 15 mmHg).

[…]

7. Patients who are able to understand and follow instructions and who are able to participate in the study for the entire study.
8. Patients must have given their written informed consent to participate in the study after having received adequate previous information and prior to any study-specific procedures.

New text:

2. Patients with symptomatic PAH with a pulmonary vascular resistance (PVR) > 400 dyn*sec*cm-5, mean pulmonary artery pressure ≥ 25 mmHg, and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg as assessed by the most recent right heart catheterization (RHC) from medical history prior to screening to confirm the diagnosis. Alternatively, PCWP can be replaced by left ventricular end-diastolic pressure (≤ 15 mmHg).

[…]

7. Patients who are able to understand and follow instructions and who are able to participate in the study for the entire study.
8. Women of childbearing potential must agree to use adequate contraception when sexually active. Adequate contraception is defined as any combination of at least 2 effective methods of birth control, of which at least 1 is a physical barrier (e.g. condom with hormonal contraception like implants or combined oral contraceptives, condom with intrauterine devices). This applies beginning with signing of the informed consent form until 30 (+5) days after the last administration of study drug.
9. Patients must have given their written informed consent to participate in the study after having received adequate previous information and prior to any study-specific procedures.

15.1.2.6 Section 6.2 Exclusion criteria

Old text:

[…]

4. Pregnant women (i.e., positive serum ß-human-chorionic-gonadotropin test or other signs of pregnancy), or breast feeding women, or women with childbearing potential not using a combination of ~~safe~~ contraception methods.

[…]

11. Participation at a supportive physical training program, defined as a structured exercise and rehabilitation program supervised by a physician and/or a physiotherapist ~~is not allowed during the pretreatment and the treatment phase of the study (up to the EOS visit)~~.

[…]

13. Exclusion criteria related to pulmonary disease:
    a. All types of PH except subtypes of Dana Point Group I specified in the inclusion criteria.

    […]

14. Exclusion criterion related to hypoxia (pulse oximeter at rest):
    a. Peripheral capillary oxygen saturation (SpO_2) < 88% despite supplemental oxygen therapy (≤ 4 L/min) at rest.

[…]

16. Exclusion criteria related to disorders in organ function:

    […]
    b. Signs of severe hepatic insufficiency (e.~~g., impaired albumin synthesis, with an albumin < 25 g/L, hepatic encephalopathy > Grade 3~~), and/or

    […]

New text:

[…]

4. Pregnant women (i.e., positive serum ß-human-chorionic-gonadotropin test or other signs of pregnancy), or breast feeding women, or women with childbearing potential not using a combination of 2 effective contraception methods (as laid out in inclusion criterion no. 8) throughout the study.

[…]

11. Participation at a supportive physical training program, defined as a structured exercise and rehabilitation program supervised by a physician and/or a physiotherapist within 12 weeks prior to screening. Participants enrolled in an exercise program for pulmonary rehabilitation > 12 weeks prior to screening may enter the study if they agree to maintain their current level of rehabilitation during the screening and the 24 weeks of the study.

[…]

13. Exclusion criteria related to pulmonary disease:

    a. All types of PH (including PH-IIP) except subtypes of Dana Point Group I specified in the inclusion criteria.

    […]

14. Exclusion criterion related to hypoxia (pulse oximeter at rest):

    a. Peripheral capillary oxygen saturation (SpO_2) < 88% despite supplemental oxygen therapy (<= 4 L/min) at rest.

[…]

16. Exclusion criteria related to disorders in organ function:

    […]

    c. Signs of severe hepatic insufficiency (Child Pugh C), and/or

    […]

15.1.2.7 Section 6.3.1 Withdrawal

Old text:

Study treatment (riociguat or control) discontinuation for any reason does not represent withdrawal from the study and should not result in withdrawal of the patient from the study.
[…]

Depending on the time point of withdrawal, a withdrawn patient is referred to as either "screening failure" or "dropout" as specified below:
[…]

New text:

6.3.1.1 Discontinuation of study treatment

Study treatment (riociguat or control) discontinuation for any reason does not represent withdrawal from the study and should not result in withdrawal of the patient from the study.
[…]

6.3.1.2 Discontinuation of study

Depending on the time point of withdrawal, a withdrawn patient is referred to as either "screening failure" or "dropout" as specified below:
[…]

15.1.2.8 Section 6.3.1.1 Discontinuation of study treatment

Old text:

Study treatment (riociguat or control) discontinuation for any reason does not represent withdrawal from the study and should not result in withdrawal of the patient from the study. Patients who prematurely discontinue from the study treatment will still be followed up for collection of safety and efficacy data until ~~the EOS visit~~. If ~~a~~ patient refuses to continue with the remaining visits, the ~~EOS visit will be performed as soon as the study treatment was discontinued. This will include all efficacy and safety relevant measurements that would have been performed at the EOS visit (at Week 24)~~.

In all cases, the reason for ~~temporary or permanent~~ study treatment discontinuation must be recorded in the electronic case report form (eCRF) and in the patient's medical records.

Patients may decide to withdraw their consent to participate in the study and to no longer attend study visits and take the study treatment (if not already discontinued); they may object to generation and processing of post-study treatment discontinuation data. Patient decision will be recorded in the eCRF. Patients who withdraw from the study will have the vital status (alive or dead) reported in the eCRF at ~~EOS (Week 24)~~. The contact can be by visit, phone or e-mail, and also by family members. Every effort should be made to contact the patient by telephone at the times the study visits were scheduled for the remaining duration of the study,

to determine if any of the primary, secondary, or other endpoints have been reached. All attempts to retrieve information about the patients should be documented in the ~~subject~~'s records. In addition to withdrawing their consent for attending the study visits, patients may also object to releasing any other information regarding their health status. For this, the patient must sign a corresponding declaration of objection; alternatively, the patient's oral objection may be documented in the source data. In such cases, every effort should be made to obtain vital status (alive or dead) information through consultation of public databases, wherever allowed by local regulations.

Withdrawal ~~criteria~~

Patients *must* be withdrawn from study treatment if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study treatment would be harmful to the patient's well-being.
- Occurrence of adverse events (AEs) or intercurrent diseases which the investigator judges unacceptable for continuation of participation in the study.
- Occurrence of adverse drug reactions, which have from the investigator's point of view, a negative impact on the patient's individual risk-benefit ratio. (Investigators are obliged to reassess the patient's individual risk-benefit ratio on a continuous basis. Factors like anticipated treatment effect, progression of underlying disease, occurrence of side effects and alternative treatment options have to be considered).
- Pertinent non-compliance with the conditions for the study or instructions by the investigator

[…]

Although not preferred, patients may interrupt their intake of study treatment due to reasonable circumstances/reasons at any time (e.g., hospitalization in a remote hospital without study treatment access, safety reasons, side effects). If an interruption lasts longer than 14 days in a row, it is at the discretion of the investigator to discontinue the study participation, and the eCRF of the termination visit ~~/EOS visit~~ must be completed.

[…]

New text:

6.3.1.1 Discontinuation of study treatment

Study treatment (riociguat or control) discontinuation for any reason does not represent withdrawal from the study and should not result in withdrawal of the patient from the study. Please see definitions for premature discontinuation from the study in Section 6.3.1.2.

Patients who prematurely discontinue from the study treatment will still be followed up for collection of safety and efficacy data at Visit 4 / EOT at Week 24 (± 4 days) and should also perform the safety FU visit at 30 days (± 5 days) after the last intake of study drug. Note that the safety FU visit may occur before Visit 4 / EOT if premature discontinuation from treatment occurs early during the study.

In all cases, the reason for study treatment discontinuation must be recorded in the electronic case report form (eCRF) and in the patient's medical records.

Patients may decide to withdraw their consent to participate in the study and to no longer attend study visits and take the study treatment (if not already discontinued); they may object to generation and processing of post-study treatment discontinuation data. Patient decision will be recorded in the eCRF. Patients who withdraw from the study will have the vital status (alive or dead) reported in the eCRF at Visit 4 / EOT. The contact can be by visit, phone or e-mail, and also by family members. Every effort should be made to contact the patient by telephone at the times the study visits were scheduled for the remaining duration of the study, to determine if any of the primary, secondary, or other endpoints have been reached. All attempts to retrieve information about the patients should be documented in the patient's records. In addition to withdrawing their consent for attending the study visits, patients may also object to releasing any other information regarding their health status. For this, the patient must sign a corresponding declaration of objection; alternatively, the patient's oral objection may be documented in the source data. In such cases, every effort should be made to obtain vital status (alive or dead) information through consultation of public databases, wherever allowed by local regulations.

Criteria for withdrawal from study treatment

Patients *must* be withdrawn from study treatment if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study treatment would be harmful to the patient's well-being.
- Occurrence of adverse events (AEs) or intercurrent diseases which the investigator judges unacceptable for continuation of participation in the study.
- Occurrence of adverse drug reactions, which have from the investigator's point of view, a negative impact on the patient's individual risk-benefit ratio. (Investigators are obliged to reassess the patient's individual risk-benefit ratio on a continuous

basis. Factors like anticipated treatment effect, progression of underlying disease, occurrence of side effects and alternative treatment options have to be considered).

- In case a patient is diagnosed with pulmonary veno-occlusive disease (PVOD) while on treatment with study drug, the administration of riociguat has to be stopped immediately
- Pertinent non-compliance with the conditions for the study or instructions by the investigator

[…]

Although not preferred, patients may interrupt their intake of study treatment due to reasonable circumstances/reasons at any time (e.g., hospitalization in a remote hospital without study treatment access, safety reasons, side effects). If an interruption lasts longer than 14 days in a row, it is at the discretion of the investigator to discontinue the study participation, and the eCRF of the early termination visit must be completed.

[…]

15.1.2.9 Section 6.3.1.2 Discontinuation of study

Old text:

[…]

Dropout

A patient who discontinues study participation prematurely for any reason after randomization is defined as a "dropout".

New text:

[…]

Dropout

A patient who discontinues study participation prematurely for any reason after randomization is defined as a "dropout". If a patient prematurely discontinues study treatment **and** does not wish to continue with the remaining scheduled visits, the investigator should take all possible effort to complete a final evaluation, and the patient should be asked for his agreement to schedule an early termination visit as soon as possible, at which time point all assessments scheduled for Visit 4 / EOT are to be performed.

15.1.2.10 Section 7.1 Treatments to be administered

Old text:

[…]

The starting dose is 1 mg TID; the intervals between drug intakes should be 6 to 8 hours.

[…]

New text:

[…]

Note that patients randomized to the riociguat arm will have a washout period before starting titration period of riociguat (see "wash-out period" in Section 5 for details). The starting dose is 1 mg TID; the intervals between drug intakes should be 6 to 8 hours.

[…]

15.1.2.11 Section 7.2 Identity of study treatment

Old text:

~~Riociguat~~ will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

[…]

See Table 7-1 for details on the study treatment.

Treatment administered in the control arm is considered standard of care.

Table 7-1: Identity of investigational product

International non-proprietary name (INN)	Riociguat
[…]	[…]

[…]

Storage requirements:

[…]

No special storage conditions are required.

New text:

All study drugs (investigational medicinal products [IMP]) will be labeled according to the requirements of local law and legislation. Label text will be approved according to the

sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

[…]

See Table 7-1 for details on the study treatment.

Treatment administered in the control arm (tadalafil, sildenafil) is considered standard of care.

Table 7-1: Identity of investigational products

Riogicuat arm	
International non-proprietary name (INN)	Riociguat
[…]	[…]
Control arm	
Tadalafil	
Material name	ADCIRCA 20MG 56 TAB
Active substance	Tadalafil
Formulation	Film-coated tablets
Description	Amygdaloid, debossed with 4467 on one side
Strength	20mg, 40mg
Dosage unit	20mg/tablet
Mode of administration	Oral
Packaging	Wallet containing 5 blister, each blister containing 14 tablets (total of 70 tablets)
Sildenafil	
Material name	REVATIO 20MG TAB B90 GER
Active substance	Sildenafil citrate
Formulation	Film-coated tablets
Description	Round biconvex, debossed with RVT 20 on one side and Pfizer on the other
Strength	Daily doses of 60mg, 80mg, 100mg, 120mg, 140mg, 160mg, 180mg, 200mg, 220mg, 240mg, 260mg, 280mg, 300mg
Dosage unit	20mg/tablet
Mode of administration	Oral
Packaging	Wallet containing 6 blister, each blister containing 15 tablets (total of 90 tablets)

[…]

Storage requirements:

[…]

No special storage conditions are required for Riociguat. Please note that PDE5i must be stored below 30°C.

15.1.2.12 Section 7.3 Treatment assignment

Old text:

[…]

All eligible patients randomized to the riociguat arm will receive a starting dose of riociguat of 1 mg TID in this open-label study. The starting dose of 1 mg may be down-titrated to 0.5 mg at the discretion of the investigator and at any point during the 8-week titration period.

Patients randomized to the control arm will remain on their current PAH-specific treatment.

Patients on ~~specific~~ combination therapy with ~~PDE-5i and~~ ERA need to continue ~~taking ERA~~ at a stable dose in both treatment arms.

New text:

[…]

Following washout (see "wash-out period" in Section 5 for details), all eligible patients randomized to the riociguat arm will receive a starting dose of riociguat of 1 mg TID in this open-label study. The starting dose of 1 mg may be down-titrated to 0.5 mg at the discretion of the investigator and at any point during the 8-week titration period.

Patients randomized to the control arm will remain on their current PAH-specific treatment.

Patients on combination therapy with ERA need to continue at a stable dose in both treatment arms.

15.1.2.13 Section 8.1 Prior and concomitant therapy

Old text:

[…]

The intake of the following concomitant medication is not allowed within 30 days prior to and at randomization:

- PCA by any administration route within 30 days before randomization (except for vasoreactivity testing).

~~Patients, who require respective medications (except for PCA) need to be withdrawn from the study drug (refer to Section 6.3.1)~~.

Specific PAH medication:

Dose changes in PAH-specific medication (i.e., PDE-5i or ERA) should be avoided during the study. Dose changes considered clinically necessary by the investigator need to be documented. Notably hospitalization for initiation of intravenous or subcutaneous prostanoid therapy fulfills the criterion of clinical worsening, as ~~does~~ disease progression with a need for any additional specific PAH targeted medication. ~~If possible,~~ the patient ~~should~~ remain in the

study for follow-up of vital status even if escalation of PAH therapy is required to maintain or improve the clinical status of the patient. The decision to keep the patient in the study is at the discretion of the investigator.

[…]

New text:

[…]

The intake of the following concomitant medication is not allowed within 30 days prior to and at randomization:

- PCA and PRA by any administration route within 30 days before randomization (except for vasoreactivity testing).

Specific PAH medication:

Dose changes in PAH-specific medication (i.e., PDE-5i or ERA) should be avoided during the study. Dose changes considered clinically necessary by the investigator need to be documented. Notably hospitalization for initiation of intravenous or subcutaneous prostanoid therapy fulfills the criterion of clinical worsening, as may disease progression with a need for any additional specific PAH targeted medication (see also Section 10.3.2.1 for Definition of Clinical Worsening). The patient may remain in the study even if escalation of PAH therapy is required to maintain or improve the clinical status of the patient. The decision to keep the patient in the study is at the discretion of the investigator

[…]

15.1.2.14 Section 8.2 Post-study therapy

Old text:

~~After treatment with riociguat, further treatment and dosage~~ will be decided by the investigator at the EOS visit. In case riociguat is indicated for further treatment, patients will be prescribed Adempas.

[…]

New text:

Further medical treatment of patients at the end of the study will be decided by the investigator at Visit 4 / EOT. In case riociguat is indicated for further treatment, patients will be prescribed riociguat / Adempas.

[…]

15.1.2.15 Section 9.2.1 Mandatory screening period (Week -2 ± 2 days, Visit 0)

Old text:

- […]
- Lung function test (see exclusion criterion 13 in Section 6.2)
- Blood gases (see exclusion criterion 14 in Section 6.2)
- […]
- Pregnancy test (women of childbearing potential only; see Section ~~9.6.3.4~~)
- […]

New text:

- […]
- Lung function test (see exclusion criterion 13 in Sections 6.2 and 9.7.2)
- Pulse oximetry (see exclusion criterion 14 in Sections 6.2 and 9.7.1)
- […]
- Pregnancy test (women of childbearing potential only; see Section 9.6.2)
- […]

15.1.2.16 Section 9.2.2 Randomization (Baseline visit, Week 0, Visit 1

Old text:

- Inclusion/exclusion criteria (see Sections 6.1 and 6.2)
- Smoking status, including number of cigarettes per day
- Specific PAH medication (see Section 8.1)
- Pregnancy test (women of childbearing potential only, see Section ~~9.6.3.4~~)
- 6MWD test (blinded assessment, see Section 9.7.1)
- Biomarker ~~NT-proBNP~~ (central laboratory; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- mRRS (see Section 16.4)
- LPH (QoL) questionnaire~~, provided at start of each visit~~ (see Section 16.5)
- […]

[…]

Patients randomized to the riociguat arm

Riociguat will be dispensed (note the ~~wash-out period~~ for riociguat arm, see ~~Section 7.4~~).

[…]

Riociguat dosing start

Based on the time of the last PDE-5i dose, date and time of the first dose of riociguat after the wash-out period will be determined by the investigator and communicated to the patient. Before the first dose of riociguat, BP measurements need to be performed to ensure that SBP is ≥ 95 mmHg. **If the BP is below this value, riociguat must not be administered (BP measurement may be repeated within the next 24 hours).** Measurement of BP and application of first riociguat dose may be performed at the study center, or by an experienced nurse ~~in the outpatient setting~~ (see Section 9.6.3.2).

[…]

Home Visits 1, 2, 3 (Weeks 2, 4, 6 ± 2 days)

[…]

~~Based on the vital signs and wellbeing of the patient~~, the investigator will decide about the dose adjustment of riociguat~~, and~~ enter it into IXRS and retrieve a new dose box number.

[…]

New text:

- Inclusion/exclusion criteria (see Sections 6.1 and 6.2)
- Pulse oximetry (see exclusion criterion 14 in Section 6.2 and Section 9.7.1)
- Smoking status, including number of cigarettes per day
- Specific PAH medication (see Section 8.1)
- Pregnancy test (women of childbearing potential only, see Section 9.6.2)
- 6MWD test (blinded assessment, see Section 9.7.1)
- Biomarkers (central laboratory; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- mRRS (see Section 16.4)
- LPH (QoL) questionnaire (see Section 16.5)
- […]

[…]

Patients randomized to the riociguat arm

Riociguat will be dispensed (note the dose titration scheme for riociguat arm, see Figure 7–1).

[…]

Riociguat dosing start

Based on the time of the last PDE-5i dose, date and time of the first dose of riociguat after the wash-out period will be determined by the investigator and communicated to the patient. Before the first dose of riociguat, BP measurements need to be performed to ensure that SBP is ≥ 95 mmHg. **If the BP is below this value, riociguat must not be administered (BP measurement may be repeated within the next 24 hours).** Measurement of BP and application of first riociguat dose may be performed at the study center or by an experienced nurse at home (see Section 9.6.3.2).

[…]

Home Visits 1, 2, 3 (Weeks 2, 4, 6 ± 2 days)

[…]

In the riociguat arm, the investigator will decide about the dose adjustment of riociguat based on the vital signs and wellbeing of the patient, enter it into the IXRS and retrieve a new dose box number (initial dose adjustment period, see Section 7.4).

[…]

15.1.2.17 Section 9.2.3 Visit 2 (Week 8 ± 2 days

Old text:

- […]
- Drug accountability (see treatment compliance in Section 7.7)
- 6MWD (blinded assessment, see Section 9.7.1)
- ~~NT-proBNP~~ (central laboratory; see Section 9.6.3.4)
- […]

New text:

- […]
- Drug accountability (see treatment compliance in Section 7.7)
- Dose of riociguat (see Section 7.4)
- 6MWD (blinded assessment, see Section 9.7.1)
- Biomarkers (central laboratory; see Section 9.6.3.4)
- […]

15.1.2.18 Section 9.2.4 Telephone Contact (Week 12 ± 2 days)

Old text:

- […]
- Pregnancy test (women of childbearing potential only; see Section ~~9.6.3.4)~~
- […]

New text:

- […]
- Pregnancy test (women of childbearing potential only; see Section 9.6.2)
- […]

15.1.2.19 Section 9.2.5 Visit 3 (Week 16 ± 2 days

Old text:

- […]
- Pregnancy test (women of childbearing potential only; see Section ~~9.6.3.4~~)
- Dispense of study medication (see Section 7.4)
- Drug accountability (see treatment compliance in Section 7.7)
- 6MWD (blinded assessment, see Section 9.7.1)
- ~~NT-proBNP~~ (~~C~~central lab; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- mRRS (see Section 16.4)
- Safety laboratory measurements (Local lab; Section 9.6.3.4)
- […]

New text:

- […]
- Pregnancy test (women of childbearing potential only; see Section 9.6.2)
- Dispense of study medication (see Section 7.4)
- Drug accountability (see treatment compliance in Section 7.7)
- Dose of riociguat (see Section 7.4)
- 6MWD (blinded assessment, see Section 9.7.1)
- Biomarkers (central laboratory; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)

- mRRS (see Section 16.4)
- Safety laboratory measurements (local laboratory; Section 9.6.3.4)
- […]

15.1.2.20 Section 9.2.6 Telephone Contact (Week 20 ± 2 days)

Old text:

- […]
- Pregnancy test (women of childbearing potential only; see Section ~~9.6.3.4~~)
- […]

New text:

- […]
- Pregnancy test (women of childbearing potential only; see Section 9.6.2)
- […]

15.1.2.21 Section 9.2.7 Visit 4 / End of Treatment (EOT) (Week 24 ± 4 days)

Old text:

9.2.7 End of ~~Study~~ (Week 24 ± ~~5~~ days)

The ~~EOS~~ visit will be performed at Week 24 ± ~~5~~ days after the last dose of riociguat, sildenafil or tadalafil, and a decision on further treatment will be made.

The following procedures will be performed:

- […]
- Pregnancy test (women of childbearing potential only; see Section ~~9.6.3.4~~)
- […]
- ~~NT-proBNP~~ (~~C~~central lab; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- mRRS (see Section 16.4)
- LPH (QoL) questionnaire~~, provided at start of each visit~~ (see Section 16.5)
- […]

New text:

9.2.7 Visit 4 / End of Treatment (EOT) (Week 24 ± 4 days)

The Visit 4 / EOT visit will be performed at Week 24 ± 4 days after the last dose of riociguat, sildenafil or tadalafil, and a decision on further treatment will be made.

The following procedures will be performed:

- […]
- Pregnancy test (women of childbearing potential only; see Section 9.6.2)
- […]
- Biomarkers (central laboratory; see Section 9.6.3.4)
- WHO FC (blinded assessment, see Section 9.7.4)
- mRRS (see Section 16.4)
- LPH (QoL) questionnaire (see Section 16.5)
- […]

15.1.2.22 Section 9.2.8 Safety follow-up visit (30 days ± 5 days)

Old text:

- […]
- Pregnancy test (women of childbearing potential only; see Section ~~9.6.3.4~~)
- […]

New text:

- […]
- Pregnancy test (women of childbearing potential only; see Section 9.6.2)
- […]

15.1.2.23 Section 9.6.1.3 Assessments and documentation of adverse events

Old text:

The investigator has to record on the respective eCRF pages (additionally to the source data) all AEs occurring in the period between the signing of the informed consent ~~and at the end of study visit~~; after ~~the end of study visit~~, there is no requirement to actively collect AEs, including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.
[…]

New text:

The investigator has to record on the respective eCRF pages (additionally to the source data) all AEs occurring in the period between the signing of the informed consent and the safety FU visit at 30 days (± 5 days) after last intake of study treatment (for details, please also refer to Sections 5 and 16.1); after that, there is no requirement to actively collect AEs, including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.
[…]

15.1.2.24 Section 9.6.1.5 Expected adverse events

Old text:

For this study, the applicable reference document is the most current version of the IB.
[…]

New text:

For this study, the applicable reference document is the most current version of the IB for Adempas and the EU SmPC / local SPC for Revatio (sildenafil) and Adcirca (tadalafil).
[…]

15.1.2.25 Section 9.6.1.6 Adverse events of special safety interest

Old text:

Symptomatic hypotension and serious hemoptysis are considered AEs of special interest and must be reported to Bayer within the same timelines as an SAE by reporting them on the AE page of the eCRF. […]

New text:

Symptomatic hypotension and serious hemoptysis (which includes pulmonary hemorrhage) are considered AEs of special interest and must be reported to Bayer within the same timelines as an SAE by reporting them on the AE page of the eCRF. […]

15.1.2.26 Section 9.6.3.4 Laboratory assessments

Old text:

The following parameters ~~may~~ be ~~included~~:

- Hematology: white blood cell differential count, erythrocytes, hemoglobin, hematocrit, platelets
- Coagulation tests: prothrombin time, only for patients under anticoagulation therapy
- Clinical chemistry: AST, ALT, total bilirubin, serum albumin, creatinine, potassium.

~~NT-proBNP~~

- ~~NT-proBNP will be analyzed centrally at the time points specified in Section 16.1.~~

[…]

New text:

The following safety laboratory parameters will be measured in the local laboratory:

- Hematology: white blood cell differential count, erythrocytes, hemoglobin, hematocrit, platelets
- Coagulation tests: prothrombin time (INR), only for patients under anticoagulation therapy
- Clinical chemistry: AST, ALT, total bilirubin, serum albumin, creatinine, potassium.

The following biomarkers will be analyzed in the central laboratory:

- NT-proBNP
- ADMA
- cGMP (from plasma)
- GDF-15
- ST-2.

All time points for collection of safety laboratory parameters and biomarker are provided in Section 16.1.

[…]

In women of childbearing potential, pregnancy tests in urine or blood will be performed at the local laboratory, at the time points specified in Section 16.1.

15.1.2.27 Section 9.7.1 Pulse oximetry

Old text:

9.7.1 ~~Blood gas analysis~~

~~SaO_2 (%), PaO_2 (mmHg), $PaCO_2$ (mmHg) will be measured by capillary or arterial blood gas analysis at screening.~~

~~If the patient receives supplemental oxygen, the amount [L/min] will be recorded in the eCRF.~~

~~Blood gases are to be obtained from the arterial blood or from arterialized capillary blood. All samples should be obtained with the patient resting in a sitting or supine position for at least 10 min. If possible no supplementary oxygen should be given during the resting period and while blood samples are drawn. If the patient requires oxygen, care should be taken that all samples are drawn with the same flow of oxygen throughout the study whenever possible. The measured values have to be transferred into the eCRF.~~

~~Blood gas measurement:~~

- ~~Actual time~~
- ~~Date~~
- ~~SaO_2 [%]~~
- ~~PaO_2 [mmHg]~~
- ~~$PaCO_2$ [mmHg].~~

New text:

9.7.1 Pulse oximetry

The patient's oxygen saturation will be measured with a noninvasive method expressing the SpO_2 (peripheral oxygen saturation) percentage.

If the patient receives supplemental oxygen, the amount [L/min] will be recorded in the eCRF.

15.1.2.28 Section 9.7.3 6MWD test

Old text:

The 6MWD test will be performed in accordance with the American Thoracic Society Guideline (17). The ~~test will be performed 4 hours after the previous dose~~. Test results will be recorded on the eCRF.

To ensure a blinded assessment from the randomization visit (baseline), adequate measures need to be taken at the study center when performing the 6MWD:

- The test has to be performed by a physician or study nurse who is blinded to the study treatment of the patient.

- The person performing the test must not be involved in the process of study drug administration~~, and must be unaware of the immediate reaction of the patient's BP and heart rate after dosing~~.
- The person performing the test should record the results on a separate work sheet and, where possible, a different person (could be the person who is involved in the study treatment administration) should enter them into the eCRF.

For details on time points refer to Section 16.1, for further details on assessment refer to Section 16.2.

New text:

The 6MWD test will be performed in accordance with the American Thoracic Society Guideline without assessing Borg-Dyspnoea-Index (17). Test results will be recorded on the eCRF.

To ensure a blinded assessment from the randomization visit (baseline), adequate measures need to be taken at the study center when performing the 6MWD:

- The test has to be performed by a physician or study nurse who is blinded to the study treatment of the patient.
- The person performing the test must not be involved in the process of study drug administration.
- The person performing the test should record the results on a separate work sheet and, where possible, a different person (could be the person who is involved in the study treatment administration) should enter them into the eCRF.

For details on time points refer to Section 16.1, for further details on assessment refer to Section 16.2.

15.1.2.29 Section 9.7.4 Determination of WHO FC

Old text:

The patients' WHO FC will be determined according to the WHO classification. Test results will be recorded on the eCRF.

To ensure blinded assessment of the WHO FC from the randomization visit (baseline), adequate measures need to be taken at the study center:

- The ~~physician~~ must be blinded to the study treatment of the patient.
- The ~~physician~~ must not be involved in the process of study drug administration and be unaware of the immediate reaction of the patient's BP and heart rate after dosing.
- The ~~physician~~ should record the test results on a separate work sheet and, where possible, a different person (could be the same person who is involved in the treatment administration) should enter them into the eCRF.

Ideally, the WHO FC assessment should always be performed by the same person.

For details on time points refer to Section 16.1, for further details on the assessment refer to Section 16.3.

New text:

The patients' WHO FC will be determined according to the WHO classification. Test results will be recorded on the eCRF.

The person assessing the WHO FC must be suitably trained (referred to as "assessor" below). To ensure blinded assessment of the WHO FC from the randomization visit (baseline), the following adequate measures also need to be taken at the study center:

- The assessor must be blinded to the study treatment of the patient
- The assessor must not be involved in the process of study drug administration.
- The assessor should record the test results on a separate work sheet and, where possible, a different person (could be the same person who is involved in the treatment administration) should enter them into the eCRF.

Ideally, the WHO FC assessment should always be performed by the same person.

For details on time points refer to Section 16.1, for further details on the assessment refer to Section 16.3.

15.1.2.30 Section 10.3.2.1 Primary efficacy endpoint

Old text:

Definition of Clinical Worsening:

- ….
- Disease progression (adjudicated)
  - 6MWD decrease ≥ 15% from baseline (2 measurements on 2 separate days), **and**
  - Worsening in WHO FC.

  OR

  - 6MWD decrease ≥ 15% (2 measurements on 2 separate days), **and**
  - Need of new PAH-targeted medication or decompensated right sided heart failure.

New text:

Definition of Clinical Worsening:

- ….
- Disease progression (adjudicated)
  - 6MWD decrease ≥ 15% from baseline (2 measurements on 2 separate days), **and**
  - Worsening in WHO FC.

  OR

  - 6MWD decrease ≥ 15% (2 measurements on 2 separate days), **and**
  - Need of new PAH-targeted medication or decompensated right sided heart failure [1].

Footnote 1 added: Decompensated right-sided heart failure is defined as the appearance or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy (need for intravenous diuretic therapy and/or inotropic drugs)

15.1.2.31 Section 10.3.2.3 Exploratory endpoints

Old text:

A complete list of variables to be analyzed for this study and the methods of analysis will be provided in the SAP.

- cMRI (core laboratory, reported separately)
- Change from baseline in QoL: LPH (see Section 16.5)
- Change from baseline in mRRS and mRRS category (see Section 16.4).

New text:

A complete list of variables to be analyzed for this study and the methods of analysis will be provided in the SAP.

- cMRI (core laboratory, reported separately)
- Change from baseline in QoL: LPH (see Section 16.5)
- Change from baseline in mRRS and mRRS category (see Section 16.4)
- Change in other biomarkers (ADMA, cGMP, GDF-15 [plasma], ST-2).

15.1.2.32 Section 11.4 Missing data

Old text:

Due to the short period of the study, it is expected that the amount of missing data will only be minor. Every effort will be made to collect data until the ~~EOS~~ visit for all patients unless a patient withdraws consent and collection of further information is not allowed.

New text:

Due to the short period of the study, it is expected that the amount of missing data will only be minor. Every effort will be made to collect data until the EOT visit for all patients unless a patient withdraws consent and collection of further information is not allowed.

15.1.2.33 Section 13.1 Investigator(s) and other study personnel

Old text:

[…]

Central Laboratory

Analyses of ~~NT-proBNP~~ will be performed centrally by the sponsor. For details please refer to the Laboratory Manual.

New text:

[…]

Central Laboratory

Analyses of biomarkers will be performed centrally by the sponsor. For details please refer to the Laboratory Manual.

15.1.2.34 Section 13.4 Patient information and consent

Old text:

[…]

Each patient will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers ~~EOS~~ assessments as specified in the visit description described in Section 9.2.7 to be conducted after withdrawal of consent.
- […]

New text:

[…]

Each patient will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers EOT assessments as specified in the visit description described in Section 9.2.7 to be conducted after withdrawal of consent.
- […]

15.1.2.35 Section 16.1 Schedule of procedures

Old text:

Measurement	**Mandatory Screening period (2 weeks)**	**Rando-mization (baseline)**	**Overall treatment period (24 weeks)**								**Follow-up ~~phase~~**
Visit	**V 0**	**V 1 [a]**	**H 1 [b]**	**H 2 [b]**	**H 3 [b]**	**V 2 [c]**	**Tele-phone contact [d]**	**V 3**	**Tele-phone contact [d]**	**EOS~~S~~**	**Safety FU [e]**
Week/Days	**W -2 (± 2 D)**	**W 0 (± 2 D)**	**W 2 (± 2 D)**	**W 4 (± 2 D)**	**W 6 (± 2 D)**	**W 8 (± 2 D)**	**W 12 (± 2 D)**	**W 16 (± 2 D)**	**W 20 (± 2 D)**	**W 24 (± ~~5~~ 5 D)**	**30 D (± 5 D)**
[…]											
Echocardiography (LVEF)	X										
[…]											
Dispense of ~~riociguat~~ medication [g]			X	X	X	X	X	X			
[…]											
~~NT-proBNP~~ (central lab)		X				X		X		X	
[…]											
LPH (QoL) [1]		X								X	

Abbreviations: 6MWD = 6-minute walking distance; AE = adverse event; cMRI = cardiac magnetic resonance imaging; D = Days; ECG = electrocardiogram; EO~~S~~ = end of ~~study~~; FU = Follow-up; LVEF = left ventricular ejection fraction; mRRS = modified Reveal Risk Score; NT-proBNP = N-terminal pro-brain natriuretic peptide; LPH =Living with Pulmonary Hypertension Questionnaire; PAH = Pulmonary Arterial Hypertension; QoL = Quality of Life; W = Week; WHO FC = World Health Organization Functional Class.

[…]

[e] Safety F~~ollow-up~~ visit after last dose of study drug.

[…]

[g] For the riociguat arm IXRS consultation IXRS consultation will be performed ~~to supply drug~~.

[…]

[k] This will be performed by the core laboratory and reported separately.

[l] To be performed if not available within last 6 months.

New text:

Measurement	**Mandatory Screening period (2 weeks)**	**Rando-mization (baseline)**	**Overall treatment period (24 weeks)**								**Follow-up visit**
Visit	**V 0**	**V 1 [a]**	**H 1 [b]**	**H 2 [b]**	**H 3 [b]**	**V 2 [c]**	**Tele-phone contact [d]**	**V 3**	**Tele-phone contact [d]**	**V4 / EOT [e]**	**Safety FU [e]**
Week/Days	**W -2 (± 2 D)**	**W 0 (± 2 D)**	**W 2 (± 2 D)**	**W 4 (± 2 D)**	**W 6 (± 2 D)**	**W 8 (± 2 D)**	**W 12 (± 2 D)**	**W 16 (± 2 D)**	**W 20 (± 2 D)**	**W 24 (± 4 D)**	**30 D (± 5 D)**
[…]											
Echocardiography (LVEF) [l]	X										
[…]											
Dispense study medication [g]			X	X	X	X	X		X		
[…]											
Biomarkers (central laboratory); see Section 9.6.3.4)		X					X		X		X	
[…]											
LPH (QoL)		X								X	

Abbreviations: 6MWD = 6-minute walking distance; AE = adverse event; cMRI = cardiac magnetic resonance imaging; D = Days; ECG = electrocardiogram; EOT = end of treatment; FU = Follow-up; LVEF = left ventricular ejection fraction; mRRS = modified Reveal Risk Score; NT-proBNP = N-terminal pro-brain natriuretic peptide; LPH =Living with Pulmonary Hypertension Questionnaire; PAH = Pulmonary Arterial Hypertension; QoL = Quality of Life; W = Week; WHO FC = World Health Organization Functional Class.

[…]

[e] Safety FU visit at 30 days (±5 days) after last dose of study drug. Note that although the safety FU visit is depicted above as occurring after Visit 4 / EOT, the safety FU visit may be performed before Visit 4 / EOT if a patient prematurely discontinues study treatment early in the study. If a patient prematurely discontinues study treatment and does not wish to continue with the remaining scheduled visits, an early termination visit should be agreed upon as soon as possible, and all activities scheduled for Visit 4 / EOT should be performed during this visit.

[…]

[g] For the riociguat arm IXRS consultation will be performed at every visit that involves dispense of study medication (V1, H1, H2, H3, V2 and V3). For the control arm, IXRS consultation will only be performed by sites which source the comparator centrally at V1, V2 and V3.

[…]

[k] This will be performed by the core laboratory and reported separately, only at selected sites. The cMRI should be performed at V1 or within 5 days before randomization.

[…]

[l] To be performed if not available within last 6 months from screening.

15.1.2.36 Section 16.2 6 Minute Walking Distance (6MWD) Test

Old text:

The 6MWD test must be performed in accordance with the American Thoracic Society Guideline (17).

To ensure a blinded assessment, it has to be performed by a second person who is not involved in the process of study drug ~~titration and~~ is unaware of the ~~immediate reaction of the patient's BP and heart rate after dosing~~.

[…]

New text:

The 6MWD test must be performed in accordance with the American Thoracic Society Guideline without assessing Borg-Dyspnoea-Index (17).

To ensure a blinded assessment, it has to be performed by a second person who is not involved in the process of study drug dispensation or is unaware of the treatment arm.

[…]

16. Appendices

16.1 Schedule of procedures – *amended*

This section was changed in Amendment 4, see Section 15.1.2.35.

Measurement	**Mandatory Screening period (2 weeks)**	**Rando-mization (baseline)**		**Overall treatment period (24 weeks)**								**Follow-up visit**
Visit	**V 0**	**V 1 [a]**		**H 1 [b]**	**H 2 [b]**	**H 3 [b]**	**V 2 [c]**	**Tele-phone contact [d]**	**V 3**	**Tele-phone contact [d]**	**V4 / EOT [e]**	**Safety FU [e]**
Week/Days	**W -2 (± 2 D)**	**W 0 (± 2 D)**	**Rio Start**	**W 2 (± 2 D)**	**W 4 (± 2 D)**	**W 6 (± 2 D)**	**W 8 (± 2 D)**	**W 12 (± 2 D)**	**W 16 (± 2 D)**	**W 20 (± 2 D)**	**W 24 (± 4 D)**	**30 D (± 5 D)**
Informed consent	X											
Check of inclusion/ exclusion criteria	X	X										
Lung function test	X											
Pulse oximetry	X	X										
Echocardiography (LVEF) [l]	X											
Medical history	X											
Smoking status	X	X			X		X	X	X	X	X	X
Specific PAH medication	X	X										
Demographics	X											
Pregnancy test [f]	X	X			X		X	X	X	X	X	X
Physical examination	X										X	
Weight and height	X											
Dispense study			X	X	X	X	X		X			

Measurement	Mandatory Screening period (2 weeks)	Rando-mization (baseline)	Overall treatment period (24 weeks)								Follow-up visit
Visit	**V 0**	**V 1 [a]**	**H 1 [b]**	**H 2 [b]**	**H 3 [b]**	**V 2 [c]**	**Tele-phone contact [d]**	**V 3**	**Tele-phone contact [d]**	**V4 / EOT [e]**	**Safety FU [e]**
Week/Days	**W -2 (± 2 D)**	**W 0 (± 2 D)**	**W 2 (± 2 D)**	**W 4 (± 2 D)**	**W 6 (± 2 D)**	**W 8 (± 2 D)**	**W 12 (± 2 D)**	**W 16 (± 2 D)**	**W 20 (± 2 D)**	**W 24 (± 4 D)**	**30 D (± 5 D)**
		Rio Start									
medication [g]											
Drug accountability			X	X	X	X		X		X	
6MWD (blinded) [h]	X [i]	X				X		X		X	
Biomarkers (central laboratory); see Section 9.6.3.4)		X				X		X		X	
WHO FC (blinded) [h]	X [i]	X				X		X		X	
mRRS		X						X		X	
LPH (QoL)		X								X	
Safety laboratory (local laboratory)	X							X		X	
Vital signs	X	X	X	X	X	X		X		X	X
ECG [j]	X										
Change in concomitant medication [h]	X	X	X	X	X	X	X	X	X	X	
AE assessment and reporting [h]	X	X	X	X	X	X	X	X	X	X	X
cMRI (exploratory, reported separately) [k]		X								X	

Abbreviations: 6MWD = 6-minute walking distance; AE = adverse event; cMRI = cardiac magnetic resonance imaging; D = Days; ECG = electrocardiogram; EOT = end of treatment; FU = Follow-up; LVEF = left ventricular ejection fraction; mRRS = modified Reveal Risk Score; NT-proBNP = N-terminal pro-brain natriuretic peptide; LPH =Living with Pulmonary Hypertension Questionnaire; PAH = Pulmonary Arterial Hypertension; QoL = Quality of Life; W = Week; WHO FC = World Health Organization Functional Class.

[a] Riociguat wash-out, first dose and dose titration:

Patients in the riociguat arm will have a **wash-out period between discontinuation of PDE-5i and the first dose of riociguat**: 24-hour wash-out following last dose of sildenafil and 48-hour wash-out following last dose of tadalafil.

Based on the time of the last PDE-5i dose, date and time of the first dose of riociguat after the wash-out period will be determined by the investigator and communicated to the patient. Before the first dose of riociguat a blood pressure measurement needs to be performed to ensure that systolic blood pressure is ≥ 95 mmHg. If the blood pressure is below this value, it can be measured again within 24 hours and if still below 95 mmHg, riociguat must not be administered. Measurement of blood pressure and application of first riociguat dose may be performed at the study center, or by an experienced nurse in the outpatient setting. Date and time of intake of the first dose of riociguat need to be documented by the investigator. The nurse will contact the center for this purpose via phone.

Patients in the control arm will continue their current specific PAH treatment (PDE-5i +/-ERA).

[b] Home Visits (H1, H2, H3):

These visits will be conducted by an experienced nurse at the patient's (both treatment arms) home. At the discretion of the investigators and if applicable (e.g., short distance to study center) these visits may also be performed at the study center.

For the riociguat arm, these visits are part of the titration period that will be performed according to the titration scheme (until Week 8, Visit 2). While in the titration period dose increase can only occur at the scheduled visits, a dose decrease (-0.5 mg) can be performed at any time based on the patient's systolic blood pressure and well-being. In both arms blood pressure will be measured; in the riociguat arm the next riociguat dose will be decided in phone contact with the center according to the titration scheme.

[c] Visit 2, Week 8: This is the first regular visit at the center after randomization. For the riociguat arm it will also be the last visit of the titration period. Following the titration period, patients will continue to receive riociguat TID at the optimal dose achieved at Week 8 (start of maintenance period).

[d] Patients will be contacted via telephone every 4 weeks, if there is no scheduled visit to the study center.

[e] Safety FU visit at 30 days (±5 days) after last dose of study drug. Note that although the safety FU visit is depicted above as occurring after Visit 4 / EOT, the safety FU visit may be performed before Visit 4 / EOT if a patient prematurely discontinues study treatment early in the study. If a patient prematurely discontinues study treatment and does not wish to continue with the remaining scheduled visits, an early termination visit should be agreed upon as soon as possible, and all activities scheduled for Visit 4 / EOT should be performed during this visit.

[f] Only women of childbearing potential will have a urine or serum test, depending on local routine at each study site. If the test is performed > 48 hours before randomization, the test will need to be repeated.

[g] For the riociguat arm IXRS consultation will be performed at every visit that involves dispense of study medication (V1, H1, H2, H3, V2 and V3). For the control arm, IXRS consultation will only be performed by sites which source the comparator centrally at V1, V2 and V3.

[h] Forms part of the clinical worsening assessment.

[i] Blinded assessment starts at randomization.

[j] An ECG can be done at any time during the study, at the discretion of the investigator. It should be reported in the unscheduled procedure page.

[k] This will be performed by the core laboratory and reported separately, only at selected sites. The cMRI should be performed at V1 or within 5 days before randomization.

[l] To be performed if not available within 6 months from screening.

16.2 6 Minute Walking Distance (6MWD) Test - *amended*

This section was changed in Amendment 4, see Section 15.1.2.36.

The 6MWD test must be performed in accordance with the American Thoracic Society Guideline without assessing Borg-Dyspnoea-Index (17).

To ensure a blinded assessment, it has to be performed by a second person who is not involved in the process of study drug dispensation or is not aware of the treatment arm. Test results should be recorded on a separate work sheet and, where possible, should be entered by a different person into the eCRF.

According to the guideline, the 6MWD test should be carried out indoors, along a long, flat, straight, enclosed corridor with hard surface that is seldom traveled. The walking course should be preferably 30 m in length, but not less than 25 m (longer walking courses should be shortened to 30 m). The length of the corridor and turnaround points should be marked.

Patients will be instructed to walk alone, not run, from one end to the other end of the walking course, at their own pace, while attempting to cover as much ground as possible in 6 minutes.

During the walk, patients are allowed to stop, lean against the wall and rest, but should resume walking as soon as they feel able to do so.

A “warm-up” period before the test should not be performed. The patients should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.

Investigators should not walk with the patients. Moreover, only standardized phrases for encouragement must be used during the test. To allow reproducibility, standardized phrases should be used every minute according to the following pattern:

- After the first minute, tell the patient the following (in even tones): “You are doing well. You have 5 minutes to go.”
- When the timer shows 4 minutes remaining, tell the patient the following: “Keep up the good work. You have 4 minutes to go.”
- When the timer shows 3 minutes remaining, tell the patient the following: “You are doing well. You are halfway done.”
- When the timer shows 2 minutes remaining, tell the patient the following: “Keep up the good work. You have only 2 minutes left.”
- When the timer shows only 1 minute remaining, tell the patient: “You are doing well. You have only 1 minute to go.”

To reduce the variability of the 6MWD tests, it is of utmost importance that the eligibility test, the baseline-test and all following tests are performed under the same conditions:

- If a supplemental oxygen therapy was implemented already at baseline, all subsequent 6MWD tests have to be performed under the same “baseline”

conditions (same flow of oxygen, same application route, and same way of carrying the oxygen bottle).

- Even if a supplemental oxygen therapy is implemented or modified during the study (e.g., increase of oxygen flow), it is not permitted to perform the subsequent 6MWD tests under conditions other than the baseline conditions.
- Patients, who used walking aids already at the eligibility-test and the baseline-test (e.g., cane, walker), need to use the same walking aids at every subsequent 6MWD test.

For quality reasons, the inhalation of supplemental oxygen and the use of walking aids during the 6MWD tests must be documented in the eCRF.

In case a patient has never performed a 6MWD test, a familiarization test should be performed during the pretreatment phase. To avoid any interactions, it is not permitted to perform the familiarization test on the same day as the eligibility 6MWD test.

16.3 WHO FC

The patient's functional class will be determined by using the WHO classification (Class I to IV) (18):

- I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
- II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

16.4 Modified REVEAL Risk Score

The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL®) risk score calculator is a validated assessment tool that has been developed to predict the 1-year survival of patients with PAH. Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk).

For the study a modified version of the REVEAL risk score calculator will be used, since echocardiographic and hemodynamic data, as well as diffusing capacity of the lung for carbon

monoxide will not be available. The mRRS algorithm will incorporate the following parameters: WHO Group I subgroup, renal insufficiency, age/sex, WHO FC, resting SBP, heart rate, 6MWD, NT-proBNP. In this mRRS algorithm, calculated risk score could range from 1 (lowest risk) to 15 (highest risk).

WHO Group I Subgroup	(APAH CTD)	(APAH-PoPH [a])	FPAH	**Score**
	+1	+2	+2	
Demographics and comorbidities	Renal insufficiency		Males age >60 years	
	+1		+2	
NYHA/WHO FC	I	III	IV	
	-2	+1	+2	
Vital signs	SBP <110 mmHg		HR>92 bpm	
	+1		+1	
6MWD	≥440 m		<165 m	
	-1		+1	
NT-proBNP	<300 pg/mL		>1500 pg/mL	
	-2		+1	
	Sum of above			
	+			6
	= REVEAL Risk Score			

[a] Excluded from study

Abbreviations: APAH = associated PAH, BP = blood pressure, bpm = beats per minute, CTD = connective tissue disease, DLCO = diffusing capacity of the lung for carbon monoxide, FPAH = familial PAH, HR = heart rate, 6MWD = 6 minute walking distance, mRAP = mean right atrial pressure, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association, PAH = pulmonary arterial hypertension, PoPH = portopulmonary PAH, PVR = pulmonary vascular resistance, RHC = right heart catheterization, SBP = systolic blood pressure, WHO = World Health Organization, WHO FC = World Health Organization Functional Class

Risk scores and predicted 1-year survival for 5 specified risk strata:

Risk score ranges	**Risk group**	**Predicted 1-year survival**
1 – 7	low-risk	95% to 100%
8	average-risk	90% to <95%
9	moderately high-risk	85% to <90%
10 – 11	high-risk	70% to <85
≥ 12	very high-risk	<70%

16.5 Living with Pulmonary Hypertension questionnaire (LPH [QoL])

The LPH questionnaire is designed to measure the effects of PH and PH specific treatments on an individual's quality of life. The LPH is a self-report questionnaire and needs to be completed by the patient (questionnaires will be provided in local language). However, if the patient has problems completing the questionnaire, an attempt should be made to explain the questions in a neutral and unpersuasive manner.

After the patient has filled in the questionnaire, the questionnaire is transferred to the study personnel, who will enter the content into the eCRF.

To measure the effects of symptoms, functional limitations, psychological distress on an individual's quality of life, the LPH asks patients to indicate using a 6-point, zero to five, Likert scale how much each of 21 facets prevented them from living as they desired.

LIVING WITH PULMONARY HYPERTENSION

The following questions ask how much your pulmonary hypertension affected your life during the past 7 days. After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your pulmonary hypertension prevent you from living as you wanted during the past 7 days by-	**No**	**Very Little**				**Very Much**
1. causing swelling in your ankles, legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during	0	1	2	3	4	5
3. making it difficult to walk about or climb	0	1	2	3	4	5
4. making it difficult to work around the	0	1	2	3	4	5
5. making it difficult to go anywhere away	0	1	2	3	4	5
6. making it difficult to sleep well at night?	0	1	2	3	4	5
7. making it difficult to have relationships	0	1	2	3	4	5
8. making it difficult to work to earn a	0	1	2	3	4	5
9. making your recreational pastimes,	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or lacking in	0	1	2	3	4	5
14. making you stay in hospital?	0	1	2	3	4	5

Did your pulmonary hypertension prevent you from living as you wanted during the past 7 days by-	No	Very Little				Very Much
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5