International CTEPH Association (ICA)

PEA Bridging Study

A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Prospective Study to Assess Efficacy of Riociguat in Patients With Operable CTEPH Prior to Pulmonary Endarterectomy With High Preoperative Pulmonary Vascular Resistance

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Protocol

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CLINICAL STUDY PROTOCOL

EUDRACT: 2017-001121-40

A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Prospective Study to Assess Efficacy of Riociguat in Patients With Operable CTEPH Prior to Pulmonary Endarterectomy With High Preoperative Pulmonary Vascular Resistance

PEA Bridging Study

Sponsor:	International CTEPH Association (ICA) c/o Artax Fide Consult AG Gartenstrasse 95 CH-4002 Basel Switzerland Email: info@cteph-association.org
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Version of Protocol:	Version 3.0
Date of Protocol:	26 April 2018

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title	A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Prospective Study to Assess Efficacy of Riociguat in Patients With Operable CTEPH Prior to Pulmonary Endarterectomy With High Preoperative Pulmonary Vascular Resistance
Brief Title	Riociguat in patients with operable CTEPH prior to pulmonary endarterectomy
Study Acronym	PEA bridging study
Protocol Date	26 April 2018

Protocol accepted and approved by:

Gérald Simonneau (Chairman of the ICA)
Hôpital Bicetre, Université Paris-Sud 11
Paris, France

Signature	26 April 2018
	Date

Protocol Approval – Principal/Coordinating Investigator

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Protocol accepted and approved by:

Principal Investigator

David Jenkins, MD
Papworth Hospital NHS Foundation Trust
Papworth Everard
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United Kingdom

Signature

26 April 2018
Date

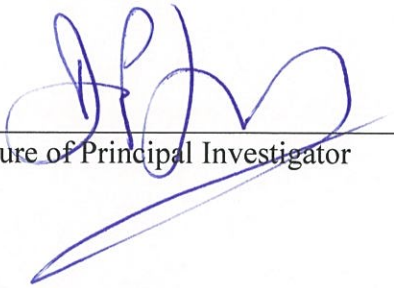
Declaration of Investigator

I have read and understood all sections of the protocol entitled "Riociguat in patients with operable CTEPH prior to pulmonary endarterectomy" and the accompanying investigator's brochure, version 18.0, dated 23 Feb 2018.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, dated 26 April 2018, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with ICA or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorised to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorisation from ICA.



Signature of Principal Investigator

26 April 2018
Date

David Jenkins, MD

Printed Name of Principal Investigator

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Protocol Synopsis

Study Acronym:	PEA bridging study
Title:	A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Prospective Study to Assess Efficacy of Riociguat in Patients With Operable CTEPH Prior to Pulmonary Endarterectomy with High Preoperative Pulmonary Vascular Resistance
Brief Title:	Riociguat in patients with operable CTEPH prior to pulmonary endarterectomy (PEA)
Sponsor:	International CTEPH Association c/o Artax Fide Consult AG Gartenstrasse 95 CH-4002 Basel Switzerland
Study Phase:	Phase 2
Study Sites:	Four sites
Indication:	Patients with operable chronic thromboembolic pulmonary hypertension (CTEPH) with high preoperative pulmonary vascular resistance (PVR) and planned for PEA
Rationale:	Based on the pivotal Phase 2 and Phase 3 studies, riociguat tablets can provide reduction in PVR in patients with CTEPH, and can also improve other haemodynamic parameters. Riociguat is approved in patients with inoperable CTEPH or patients with persistent or recurring CTEPH after surgical treatment.
Objectives:	Primary Objective: To assess the efficacy of riociguat on preoperative PVR in patients with operable CTEPH. Secondary Objectives: • To assess the efficacy of riociguat on other preoperative pulmonary haemodynamic parameters in patients with operable CTEPH • To assess the efficacy of riociguat on postoperative pulmonary haemodynamic parameters in patients with operable CTEPH • To assess the effect of riociguat on safety and efficacy aspects during PEA in patients with operable CTEPH • To assess the safety and tolerability of riociguat in patients with operable CTEPH

Patient Population:

Inclusion Criteria

1. Is a male or nonpregnant and nonlactating female patient aged from 18 to 80 years, both inclusive
2. Is diagnosed with operable CTEPH and anticipating symptomatic and/or prognostic benefit from PEA
3. Has PVR >800 $dyn \cdot s \cdot cm^{-5}$
4. Has undergone right heart catheterisation (RHC) not more than 180 days before Visit 1
5. Has been treated with anticoagulants for at least 90 days before Visit 1
6. Has ability to swallow oral medication
7. Has ability and willingness to participate and access to the health facility
8. Is capable of understanding the written informed consent and provides signed and witnessed written informed consent
9. Female patient must be either surgically sterile, postmenopausal (no menses for the previous 12 months), or must be practicing an effective method of birth control as determined by the investigator (eg, oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or male partner with vasectomy or complete abstinence)

Exclusion Criteria

1. Has unstable disease in need of urgent PEA surgery as determined by the treating physician
2. Has known hypersensitivity, allergic, or adverse reactions to riociguat or any of the excipients comprising riociguat tablets
3. Has known active hepatitis A immunoglobulin M, hepatitis B surface antigen, or hepatitis C antibody
4. Is human immunodeficiency virus positive
5. Has pulmonary veno-occlusive disease

6. Has symptomatic hypotension
7. Has symptomatic carotid disease
8. Has significant coronary atherosclerotic disease in need of intervention
9. Has severe left heart disease in need of intervention
10. Has redo sternotomy
11. Has received any background therapy for PAH in the preceding 30 days before Visit 1 including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, or prostanoids
12. Is receiving nitrates, nitric oxide donors (eg, amyl nitrite), endothelin receptor antagonists, prostanoids, specific phosphodiesterase-5 inhibitors, nonspecific phosphodiesterase inhibitors (eg, dipyridamole, theophylline)
13. Is receiving strong cytochrome P450 and P-glycoprotein/breast cancer resistance protein inhibitors
14. Is receiving strong cytochrome P450 3A inducers
15. Has creatinine clearance <15 mL/min or is on any form of dialysis
16. Has severe hepatic impairment classified as Child-Pugh B or C
17. Has received an investigational drug within the past 4 weeks before Visit 1
18. Is a lactating or pregnant (as demonstrated by a serum or urine dipstick pregnancy test) woman, or not willing to take measures not to become pregnant during the 3-month treatment study period and 1 month after the last dose of study drug administered
19. Has smoked or used tobacco in any form, including snuff or chewing, within 3 months prior to Visit 1
20. Has idiopathic interstitial pneumonitis

Study Design: This is a randomised, double-blind, placebo-controlled, multicentre, multinational, prospective study in patients with operable CTEPH prior to PEA with high preoperative PVR

	(>800 dyn·s·cm^{-5}). Patients will undergo a screening period of up to 90 days prior to baseline visit (Visit 1). Following completion of the screening period, eligible patients will be randomly assigned on Day 1 to receive either riociguat or matching placebo 3 times a day (tid) in a 1:1 ratio for 3 months. The study drug will be initiated at 1 mg and the dosage can be increased by 0.5 mg at 2-week intervals based on tolerability (systolic blood pressure [SBP]) up to a maximum dose of 2.5 mg tid. The study drug will be initiated no later than 180 days after RHC (used for screening of patients) and within 90 days of planned RHC before PEA. At Visit 2, RHC will be performed per site procedures no more than 1 week prior to PEA, which will be conducted by the principal surgeon of the site. The study drug will be discontinued once PEA is performed. The last study dose will be given on the morning of PEA surgery. The patient will remain hospitalised per the investigator's discretion. A follow-up visit is planned at 6 months after PEA, at which time RHC will also be performed per study site procedures. A telephone call visit is planned during treatment period and at Day 186±10 during follow-up period, where treating physician or designee will call patient to ask questions related to patient's well-being and any adverse event. The end of the study is defined as when the last patient completes the last visit of the study ie, 6-month follow-up visit (Visit 4). An unblinded, independent data safety monitoring board will periodically review safety data and other study information during the conduct of the study.
Estimated Study Duration:	The approximate study duration is 1 year for each patient including a screening period of 3 months, double-blind treatment period of 3 months, and a safety follow-up period of 6 months.
Efficacy Assessments:	The efficacy measures include reduction in PVR, cardiac index, mean right atrial pressure, mean pulmonary arterial pressure, pulmonary artery wedge pressure, number and cause of deaths during the study, pulmonary hypertension-related hospitalisation, need for PAH-targeted and other medications, change in World Health Organization functional class for PAH, perioperative findings that include circulatory arrest time and surgery-related complications, surgical evaluation of specimen, withdrawal during the treatment phase, N-terminal pro–B-type natriuretic peptide, length of hospital and intensive care unit stay, and time on mechanical ventilation.

Safety Assessments:	Safety assessments include monitoring of adverse events, vital sign measurements, electrocardiogram measurements, physical examinations, clinical laboratory examinations, and pregnancy testing.
Study Drug, Dosage, and Route of Administration:	Patients will initiate the treatment with either riociguat 1 mg or matching placebo tablets tid orally for 3 months. The study drug will be initiated no later than 180 days after RHC (used for screening of patients) and within 90 days of planned RHC before PEA. The dose can be increased by 0.5 mg at 2-week intervals based on the tolerability (SBP) up to a maximum dose of 2.5 mg tid. The individual study drug dose of the next titration step will be determined every 2 weeks at home according to the peripheral SBP measured at trough before intake of the morning dose under consideration of the following algorithm: • If trough SBP ≥95 mmHg, increase dose (+0.5 mg tid) • If trough SBP <95 mmHg without symptoms of hypotension, maintain the dose • If any SBP <95 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, stop study drug; restart after 24 hours with reduced dose (-0.5 mg tid) The BP measuring device will be supplied along with study drug to each patient to monitor BP at home. If the dose is interrupted for 3 or more days, restart the dose with 1 mg tid and follow the up-titration algorithm. The up-titration will be monitored by study staff contacting the patient by telephone at home.
Sample Size:	A total of 88 patients, accounting for a 10% dropout rate, will be randomly assigned into riociguat or placebo groups at a ratio of 1:1 in the study. The sample size for this study is not based on the required statistical power to test any specific hypothesis but feasibility to initially assess the safety and efficacy of riociguat on preoperative pulmonary haemodynamics in patients with operable CTEPH.

Statistical Methods:	Statistical analysis will be performed using SAS® software Version 9.3 or later. Statistical methods to be used will be mainly descriptive. Summary statistics will be tabulated and represented graphically, whenever appropriate. Continuous variables will be summarised using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages. Data will be listed in data listings. Time to event data will be analysed using Kaplan-Meier method. Details of the statistical analyses, methods, and data conventions will be described in the statistical analysis plan. Unless otherwise specified, statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% (2-sided) confidence intervals. Modelling techniques will be used in an exploratory sense. No adjustments for multiplicity are made. Covariates may be defined in the statistical analysis plan as appropriate.
Date of Protocol:	26 April 2018

List of Abbreviations

Abbreviation	Definition
AE	adverse event
BP	blood pressure
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CTEPH	chronic thromboembolic pulmonary hypertension
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
ERA	endothelin receptor antagonist
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HR	heart rate
ICA	International CTEPH Association
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
ILD	interstitial lung disease
IRB	institutional review board
ITT	intent to treat
IWRS	interactive web response system
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	mean pulmonary arterial pressure
mRAP	mean right atrial pressure
NT-proBNP	N-terminal pro–B-type natriuretic peptide
NO	nitric oxide
PAH	pulmonary arterial hypertension
PAWP	pulmonary artery wedge pressure
PDE5	phosphodiesterase-5
PEA	pulmonary endarterectomy
PH	pulmonary hypertension

Abbreviation	Definition
PHIIP	pulmonary hypertension associated with idiopathic interstitial pneumonias
PPS	per-protocol set
PVR	pulmonary vascular resistance
QTcF	QT interval Fridericia correction
RHC	right heart catheterisation
RVSP	right ventricular systolic pressure
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
sGC	soluble guanylate cyclase
TEAE	treatment-emergent adverse event
tid	3 times a day
WHO	World Health Organization

1 Introduction

1.1 Background

Chronic thromboembolic pulmonary disease is an important cause of severe pulmonary hypertension (PH) and is associated with significant morbidity and mortality. It is estimated that 3.8% of patients suffering from an acute pulmonary embolus will develop chronic thromboembolic pulmonary hypertension (CTEPH) (Pengo Vet al 2004). Furthermore, even in patients receiving appropriate treatment for an acute pulmonary embolism, incomplete resolution occurs in a significant proportion of patients, placing them at risk of developing CTEPH. Chronic thromboembolic pulmonary hypertension is characterised by obstruction of the pulmonary vasculature by residual organised thrombi and varying degrees of concomitant small vessel disease leading to increased pulmonary vascular resistance (PVR), progressive PH, and right ventricular failure.

In some patients, PH persists after pulmonary endarterectomy (PEA) despite adequate macroscopic clearance of the chronic thromboembolic material. Patients with untreated CTEPH are likely to develop progressive disease and have a high risk of death due to right heart failure (Hoeper et al 2006). The first step in the management of CTEPH is the initiation of anticoagulant therapy (Lewczuk et al 2001). In addition, drugs such as bosentan, prostacyclin, and iloprost have been used with varying efficacy as a bridge to PEA in unstable patients, in patients with residual PH post-PEA, and as definitive treatment in patients with CTEPH unsuitable for surgery. Other anticoagulant treatments or sometimes antiplatelet agents have also been used for underlying disorders such as essential thrombocythaemia.

Pulmonary endarterectomy is the surgical procedure that removes the obstructing thromboembolic material, resulting in significant improvements (or normalisation) in pulmonary haemodynamics and right ventricular function. Pulmonary endarterectomy targets the accessible mechanical component contributing to PH and is a potentially curative treatment in CTEPH. Long-term survival and functional status were demonstrated to improved post-PEA (Cannon et al 2016). Accordingly, careful patient selection and complete and thorough endarterectomy are critical for the best outcome from PEA. However, even from experienced centres, the perioperative mortality rate was 4.7% (Pepke-Zaba et al 2011). This risk is higher in patients with high preoperative PVR (Jensen et al 2009). In the European CTEPH registry, an almost linear relationship between high preoperative PVR (>900-1100 $dyn \cdot s \cdot cm^{-5}$) and in-hospital mortality was observed (Mayer et al 2011). An important cause of the high PVR and postoperative mortality can be linked

to the concomitant small vessel disease in CTEPH (Galiè and Kim 2006). The long-term prognosis of operable patients is nowadays excellent and better than the outcome of inoperable patients (Delcroix et al 2016).

1.2 Riociguat

Riociguat is the first of a new class of drugs, the soluble guanylate cyclase (sGC) stimulators. Direct pharmacological stimulation of sGC, either alone or in combination with nitric oxide (NO), may provide a novel approach for the treatment of PH. Riociguat has a dual mode of action: it sensitises sGC to the body's own NO and can also increase sGC activity in the absence of NO. Nitric oxide activates the sGC, resulting in increased intracellular cyclic guanosine monophosphate (cGMP) concentrations (which induce vasorelaxation), inhibition of cell proliferation and migration, as well as inhibition of platelet adhesion and aggregation.

Different sGC stimulators have shown beneficial effects in different models of acute and chronic PH. Nitric oxide–independent sGC stimulators offer great therapeutic potential by restoration of the NO/sGC/cGMP pathway, which is impaired in different forms of acute and chronic pulmonary vasculopathy (Bayer AG 2017).

Riociguat exerts strong effects on pulmonary haemodynamics and exercise capacity in patients with PH. Riociguat is indicated for the treatment of cardiovascular diseases, especially PH. No other structurally related sGC stimulators are currently under development for this indication (Bayer AG 2017).

1.3 Nonclinical Data of Riociguat

Nonclinical studies were performed to characterise the biopharmaceutical and pharmacodynamic properties of riociguat. Riociguat is an NO-independent but haeme-dependent stimulator of the sGC and effective in several cardiopulmonary animal models.

In anaesthetised dogs after intravenous administration, riociguat caused a dose-dependent decrease in mean arterial blood pressure, increases in coronary blood flow and oxygen saturation in the coronary sinus blood, and a moderate increase in heart rate (HR). In anaesthetised rats after intravenous and oral administration, riociguat produced a dose-dependent and long-lasting decrease in blood pressure with only minor influences on HR.

A long-lasting and dose-dependent decrease in BP and reflectory increase in HR was observed in conscious spontaneously hypertensive rats after oral administration of riociguat. After development of PH during chronic hypoxia in mice, treatment with riociguat significantly reduced right ventricular systolic pressure (RVSP), ventricular hypertrophy, myocardial fibrosis, and structural remodelling of the lung vasculature. Thus, it is concluded that continuous stimulation of sGC partially reverses haemodynamic and structural remodelling in chronic hypoxia-induced experimental PH.

In rats, monocrotaline induced severe PH with marked increase in RVSP, PVR, and right heart hypertrophy after 21 and 35 days. Daily treatment of these rats with riociguat significantly decreased RVSP and right heart hypertrophy.

In rats, mice, and dogs, the toxicological profile was mainly characterised by consequences of cGMP-related smooth muscle cell relaxation, with the cardiovascular and the gastrointestinal organs being mainly involved.

1.4 Summary of Clinical Studies

There were 9 studies completed with riociguat: six Phase 2 studies, two Phase 3 studies, and one Phase 3b study. Five Phase 2 studies were completed in the PH indication. All three of the Phase 3 completed studies were carried out in patients with PH.

At this time, ten Phase 2, 3, and 4 studies are ongoing. Of these, Study 13605 is a Phase 2 study for PH associated with idiopathic interstitial pneumonias (study drug terminated on 06 May 2016), and 2 studies are long-term extension (LTE) studies in PH associated with interstitial lung disease (ILD) (Study 12916) and PH associated with left ventricular systolic dysfunction (Study 14308). Four Phase 3 studies are ongoing, of which two are LTE studies in the approved indications PAH (Study 12935) and CTEPH (Study 11349). They are being conducted with the objective of assessing the long-term safety and tolerability of riociguat until the drug's commercial availability. A Phase 3 study (Study 15681) is investigating the paediatric use in PAH. One Phase 3b study (Study 16719) is ongoing. Two Phase 4 studies are ongoing: a noninterventional, postauthorisation safety study (Study 16657, EXPERT registry) and an interventional study (Study 18694, RIALTO), which is an LTE study of riociguat in patients with symptomatic PAH.

Phase 2 studies in patients with PH demonstrated that riociguat administered at doses of 1 to 2.5 mg 3 times a day (tid) over 12 weeks exerted significant, strong, and favourable effects on pulmonary haemodynamics and functional capacity.

Study 11874 was a single-dose proof-of-concept study looking at invasive haemodynamics in 19 patients with PAH, CTEPH, and ILD-associated PH that demonstrated that riociguat favourably influenced all main haemodynamic parameters in patients with PH without altering gas exchange or inducing a ventilation-perfusion mismatch.

Study 11917 was in patients with PAH stable for 6 weeks and treated with sildenafil along with riociguat. In addition to sildenafil, single doses of 0.5 mg and 1 mg riociguat had an additive but not significant effect on the parameters of the systemic circulation and a less additive effect on the parameters of the pulmonary circulation.

Study 12915 was a single-dose proof-of-concept study that demonstrated clinically relevant haemodynamic effects in patients with COPD-associated PH.

Study 12166 was a 12-week, open-label study that assessed safety, tolerability, and pharmacodynamics including invasive haemodynamics of riociguat at doses of 1.0 to 2.5 mg tid in 75 evaluable patients with PAH or CTEPH. Riociguat exerted significant, strong, and favourable effects on pulmonary haemodynamics and functional capacity in patients with PAH or CTEPH. In the main phase (up to Day 84 of treatment), 243 treatment-emergent adverse events (TEAEs) were reported for 65 of 75 patients. Of these, 237 were of mild or moderate intensity and 6 events were of severe intensity. The most commonly reported TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term were dyspepsia (n=18 [24%]), headache (n=12 [16%]), hypotension (n=11 [15%]), peripheral oedema (n=9 [12%], and tachycardia (n=9 [12%]).

Study 12916 was an ongoing, multicentre, nonrandomised, nonblinded, noncontrolled study that investigated the effects of multiple doses of riociguat on safety, tolerability, and efficacy parameters in 22 patients with PH due to ILD. Interim data showed riociguat exerted moderate effects on haemodynamics and functional capacity in patients with PH due to ILD. At the cut-off date for the interim report, 101 TEAEs were reported for all 22 patients (100%). Of these, 55 were of mild or moderate intensity and 29 events were of severe intensity. The most commonly reported TEAEs by MedDRA preferred term were peripheral oedema (n = 8 [36.4%]), dyspnoea (n = 7 [31.8%]), dyspepsia (n = 5 [22.7%]), nasopharyngitis (n = 5 [22.7%]), and headache (n = 4 [18.2%]). Prior to the cut-off date, 4 patients died during the LTE period. None of the events leading to death were classified by the investigator as related to study drug. During the ongoing extended treatment in the study, serious TEAEs were reported in 20 of 22 patients (90.9%) at the cut-off date. Oedema peripheral was the most frequently reported TEAE (40.9%), followed by dyspnea (36.4%). Adverse event (AE) was the reason for 50% of total discontinuations. The

majority of patients had events related to the progression of their disease (pulmonary fibrosis, respiratory failure).

Study 14308 is an ongoing randomised, double-blind, placebo-controlled, multicentre, multinational study to assess the efficacy and safety of oral riociguat in patients with symptomatic PH associated with left ventricular systolic dysfunction. In 16-week interim results, there was no significant difference in treatment effect between the riociguat 2.0 mg group and the placebo group for mean pulmonary arterial pressure (mPAP). The estimated overall treatment effect was -2.71 mmHg (95% confidence interval [CI]: -5.99 mmHg to 0.57 mmHg; $P = 0.104$). For venous oxygen saturation, transpulmonary pressure gradient, and pulmonary capillary wedge pressure (secondary efficacy variables), as well as for systolic PAP and diastolic PAP, the estimated mean treatment effects indicated a greater improvement with riociguat 2.0 mg than with placebo but with wide CIs. At the end of the 16-week placebo-controlled study, AEs occurred in 91% of patients in the riociguat 2.0 mg treatment group, 85% in the 1.0 mg treatment group, 81% in the 0.5 mg treatment group, and 83% in the placebo group. The most frequent TEAEs reported in at least 10.0% of patients in the riociguat 2.0 mg group were diarrhoea (n = 12 [17.9%]), nausea (n = 11 [16.4%]), dizziness (n = 11 [16.4%]), headache (n = 10 [14.9%]), cardiac failure (n = 9 [13.4%]), and hypotension (n = 8 [11.9%]). Three deaths occurred during the blinded phase of this study. None of the events leading to death were classified by the investigator as related to study drug. As of the Mar 2016 cut-off, 19 patients (12.7%) died in the LTE phase of the study.

Study 15096 was a randomised, double-blind, placebo-controlled, multicentre, multinational, dose-titration study to assess the effect of riociguat administered simultaneously with sildenafil 20 mg tid on BP in patients with symptomatic PAH. The study was terminated by the sponsor as the benefit-risk balance was not positive. The primary endpoint was maximum change in supine systolic blood pressure (SBP) from baseline within 4 hours of dosing with riociguat or placebo and a greater decrease was observed in the riociguat group than in the placebo group. The secondary efficacy endpoints, including maximum changes in supine and standing SBP, diastolic blood pressure, HR and area under effect curve values for each of these variables (except supine SBP) were also improved in the riociguat group compared with the placebo group. In the double-blind main phase of the study, the most frequent preferred terms for TEAEs in the riociguat group were oedema peripheral (4 of 12 patients), hypokalaemia (4 of 12 patients), and headache (3 of 12 patients). No deaths were reported in the main study. One death

occurred in the LTE phase that was not related to study drug as classified by the investigator.

Study 11348 (CHEST-1) was a Phase 3, randomised, double-blind, placebo-controlled, multicentre, multinational study assessing the efficacy and safety of oral riociguat in patients with inoperable CTEPH or recurrent or persisting PH after surgical treatment. Study 12934 (PATENT-1) was a Phase 3, randomised, double-blind, placebo-controlled, multicentre, multinational study that assessed the efficacy and safety of oral riociguat in treatment-naive patients and patients pretreated with an ERA or a prostacyclin analogue with symptomatic PAH. In both the studies, the primary objective was achieved by demonstrating statistically significant and clinically relevant improvement in 6-minute walking distance from baseline to Week 16 (last observation until Week 16) compared to placebo. Secondary efficacy variables PVR, N-terminal pro–B-type natriuretic peptide (NT-proBNP), World Health Organization (WHO) functional class, time to clinical worsening, Borg CR 10 scale, and EQ-5D™ utility score were also improved compared to placebo. In the CHEST-1 study, AEs were reported by 92% of patients in the riociguat treatment groups and by 86% of placebo patients. Most of the AEs were assessed by the investigators as mild to moderate. In both treatment groups (riociguat and placebo), 11% of patients had AEs assessed as severe. In the PATENT-1 study, AEs were reported by approximately 90% of patients in the riociguat treatment groups and by 86% of placebo patients. Most of the AEs were assessed by the investigators as mild to moderate. Of the patients with AEs that were assessed as severe, 11% of patients were in the riociguat treatment group and 15% were in the placebo group. The most frequently reported AEs in the pooled analysis of these 2 studies with a higher rate in the riociguat treatment group were headache (27% vs. 17%) followed by dizziness (19% vs. 12%) and dyspepsia (18% vs. 8%). Long-term extension Studies 11349 (CHEST-2) and 12935 (PATENT-2) (both Phase 3), in two approved PH indications are ongoing until all patients can be transitioned to the commercial drug. The overall incidence rate of TEAEs in the CHEST-2 study was 99.2% at the 27 Mar 2016 cut-off. Most of the TEAEs were assessed by the investigators as mild (12.7%) to moderate (40.1%). Overall 108 (45.6%) patients had TEAEs that were assessed as severe. At the cut-off, there were 33 deaths out of 237 patients (13.9%) over a mean treatment duration of 1165.4 days. In the PATENT-2 study, at the cut-off, the overall incidence rate of TEAE was 99.2%. Half of the TEAEs were assessed by the investigators as mild (12.6%) to moderate (37.4%). Overall 195 (49.2%) patients had TEAEs that were assessed as severe. The incidence rate of AE-related deaths was 64 out of 396 patients (16.2%) over a mean treatment duration of 1248.8 days. In both CHEST-2 and PATENT-2

studies, most of the deaths were related to the primary disease progression or associated comorbidities.

Study 16097 was an open-label, uncontrolled, long-term surveillance study to assess safety, tolerability, and clinical effects while providing early access of riociguat to patients with inoperable CTEPH, or recurrent or persisting PH after surgical treatment who were not satisfactorily treated and could not participate in any other CTEPH trial. A total of 300 patients were treated with the starting dose of 1.0 mg, which could be uptitrated every 2 weeks depending on tolerability. A positive effect on the 6MWD was seen based on the mean and median changes from baseline that started within 4 weeks of treatment and persisted during the study treatment. During the course of the study, the majority of the patients were stable regarding their WHO functional class (67.3%), but a higher percentage of patients had an improvement in functional class (25.0%) compared to a deterioration in functional class (7.4%). The most frequently reported TEAEs were dyspepsia (20.0%), dizziness (18.7%), headache and peripheral oedema (each 18.0%), diarrhea (15.0%), nausea (14.3%), cough (12.7%), vomiting (11.3%), as well as constipation, gastroesophageal reflux disease, and nasopharyngitis (each 10.3%). Serious TEAEs were reported for 89 patients (29.7%). The most frequently reported serious TEAE was syncope in 17 patients (5.7%). Overall, 6 patients died during the study: 5 patients during the treatment phase (pneumonia, head injury, cardiac failure, pulmonary embolism, and pleomorphic malignant fibrous histiocytoma) and 1 patient during the follow-up phase (posttreatment AE of cardiogenic shock). None of the cases were assessed by the investigator as related to the study drug.

Study 16719 (RESPITE) is an open-label, international, multicentre, single-arm, uncontrolled, Phase 3b pilot study of riociguat in patients with PAH who demonstrated an insufficient response to treatment with phosphodiesterase-5 (PDE5) inhibitor. Deaths were reported in 2 patients on-study (1 subdural haematoma and 1 pneumonia [subject died after withdrawal from the study] and in 3 patients during the extended drug supply phase period (1 femoral fracture, 1 respiratory tract infection, and 1 death nonspecified). Serious AEs were reported in 10 (16.4%) patients overall (most frequent right ventricular failure with 3 subjects). Frequent AEs were dyspepsia, headache, and diarrhea.

1.5 Benefit-Risk Assessment

An evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

Riociguat (BAY 63-2521) is the first of a new class of drugs, the sGC stimulators. It is approved for 2 forms of PH (PAH and CTEPH) and is under investigation in other indications.

The cumulative worldwide exposure to riociguat (Adempas®) since start of marketing authorisation is estimated at 102,844 patient-months or approximately 8,570 patient-years, excluding interventional clinical studies.

At very high doses, riociguat showed maternal and fetal toxicity. The findings can be associated with the exaggerated pharmacological effects (vasodilation, blood pressure lowering) of the fetus. They are not considered prohibitive for the inclusion of women with childbearing potential if reliable contraception is provided. Riociguat should not be administered to pregnant women.

Patients with severe hepatic impairment (Child-Pugh C) have not been studied and therefore use of riociguat is contraindicated in these patients. Patients with moderate hepatic impairment (Child-Pugh B) showed a higher exposure to this medicine. Particular care should be exercised during individual dose titration.

Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis. Therefore, use of riociguat is not recommended in these patients. Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to this medicine. There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Riociguat is effective in treating patients with inoperable and persistent CTEPH after PEA, as well as patients with PAH. In patients with PAH, riociguat is effective either when administered alone or in combination with endothelin receptor antagonists (ERAs) or prostanoids. The AE profile observed in the patient populations tested was within the range expected in these chronically ill patient groups. In these severely ill patients, the overall rates of serious AEs (SAEs), AEs resulting in discontinuation of study drug and death were lower in riociguat-treated patients than in patients receiving placebo. Overall, riociguat was safe and well tolerated and did not present untoward side effects not already identified in the patient populations studied.

Patients participating in the proposed study are expected to have the same benefit of the treatment as patients previously treated with riociguat. Any positive effect on the

postoperative outcome as a result of the preoperative treatment with riociguat remains to be determined.

Also, the surgical risk depends on preoperative PVR. Riociguat can decrease the preoperative PVR and hence, can decrease the surgical risk.

Overall, the anticipated benefit-risk profile supports the investigation of riociguat in the patient population chosen for this study.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of riociguat on preoperative PVR in patients with operable CTEPH.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the efficacy of riociguat on other preoperative pulmonary haemodynamic parameters in patients with operable CTEPH
- To assess the efficacy of riociguat on postoperative pulmonary haemodynamic parameters in patients with operable CTEPH
- To assess the effect of riociguat on safety and efficacy aspects during PEA in patients with operable CTEPH
- To assess the safety and tolerability of riociguat in patients with operable CTEPH

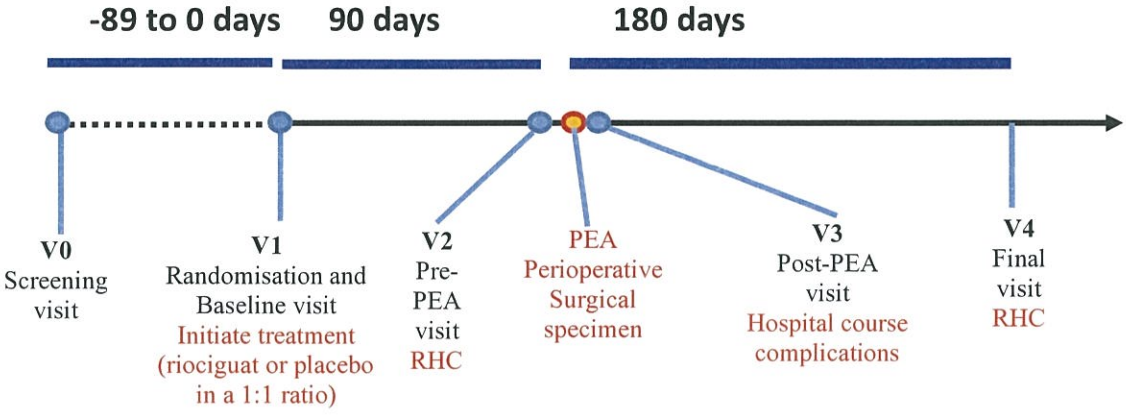
3 Investigational Plan

3.1 Study Design

This is a randomised, double-blind, placebo-controlled, multicentre, multinational, prospective study in patients with operable CTEPH prior to PEA with high preoperative PVR (>800 dyn·s·cm^{-5}). Eligible patients will be randomly assigned to riociguat or matching placebo tid in a 1:1 ratio. A total of 88 patients are planned to randomly assign at 4 sites in North America and Europe.

A schematic of the study design is presented in Figure 3-1.

Figure 3-1 Study Schematic



Abbreviations: PEA, pulmonary endarterectomy; RHC, right heart catheterisation; V, visit

Patients will undergo a screening period of up to 89 days prior to baseline (Visit 1). Following completion of the pretreatment screening phase, eligible study patients will be randomly assigned into the study.

The study will comprise 3 study periods:

- **Screening Period (Day -89 to Day 1)**: The screening period of up to 90 days will be used to assess eligibility of patients and to allow for the washout of prohibited medications. Screening visit (V0) and randomisation visit (V1) can occur on the same day.

- **Treatment Period (Day 1 [Baseline] through Day 90)**: Patients will be randomly assigned on Day 1 to receive either riociguat or matching placebo tid in a 1:1 ratio for 3 months. The study drug will be initiated at 1 mg and the dosage can be increased by 0.5 mg at 2-week intervals based on tolerability (SBP) up to a maximum dose of 2.5 mg tid based on the algorithm mentioned in Section 5.2. The study drug will be initiated no later than 180 days after right heart catheterisation (RHC) (used for screening of patients) and within 90 days of planned RHC before PEA. At Visit 2, RHC will be performed per site procedures no more than 1 week prior to PEA, which will be conducted by the principal surgeon of the site. The study drug will be discontinued once PEA is performed. The last study dose will be given on the morning of PEA surgery. The patient will remain hospitalised per the investigator's discretion.

- **Follow-up Period**: A follow-up visit is planned at 6 months after PEA, at which time RHC will also be performed per study site procedures.

A telephonic call visit is planned during treatment period and at Day 186±10 during follow-up period, where treating physician or designee will call patient to ask questions related to patient's well-being and any adverse events.

Based on the quality of the RHC data and the experience of the referring site, a referred patient (a patient where the previous RHC was performed at a site other than the study site) can be enrolled in the study based on investigator's discretion. The data of haemodynamic parameters at screening will be collected from the previous RHC.

Patients who permanently discontinue study drug for any reason (ie, due to meeting the protocol-mandated safety monitoring criteria) or who withdraw from the study prematurely (prior to the end of the double-blind treatment period) will participate in the end-of-study safety follow-up visit.

Efficacy and safety assessments will be performed throughout the study, as presented in the schedule of events (Table 12-1). The primary efficacy measure is the reduction in PVR.

Additional efficacy measures include cardiac index, mean right atrial pressure (mRAP), mPAP, pulmonary artery wedge pressure (PAWP), number and cause of deaths during the study, PH-related hospitalisation, need for PAH-targeted and other medications, change in WHO functional class for PAH, perioperative findings that include circulatory arrest time and surgery-related complications, surgical evaluation of specimen, withdrawal during the treatment phase, NT-proBNP concentration, length of hospital and intensive care unit (ICU) stay, and time on mechanical ventilation.

Safety assessments include monitoring of AEs, vital sign measurements, electrocardiogram (ECG) measurements, physical examinations, clinical laboratory examinations, and pregnancy testing.

The end of the study is defined as when the last patient completes the last visit of the study ie, 6-month follow-up visit (Visit 4).

An unblinded, independent data safety monitoring board will periodically review safety data and other study information during the conduct of the study.

3.1.1 Rationale of Study Design

Riociguat, an sGC stimulator, is the first approved treatment of persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity. Riociguat is also authorised for the indication of PAH. The primary endpoint in the pivotal study, CHEST-1, was change from baseline to Week 16 in the 6-minute walking distance. An increase of 39 meter was observed in the riociguat group compared to a decrease of 6 meter in the placebo group. Pulmonary vascular resistance decreased by 226 $dyn \cdot s \cdot cm^{-5}$ in patients treated with riociguat compared to an increase of 23 $dyn \cdot s\ cm^{-5}$ in the placebo group. Significant improvements were also observed in other haemodynamic variables including pulmonary artery pressure and cardiac output (Ghofrani et al 2013). Improving pulmonary haemodynamics before surgery could potentially reduce the morbidity and mortality associated with PEA. Two case series examined a total of 21 patients treated with intravenous epoprostenol prior to PEA. An improvement in pre-PEA haemodynamics, but no change in post-PEA haemodynamics was observed compared to controls, possibly due to controls having less severe disease (Bresser et al 2004; Nagaya et al 2003). A prospective study with inhaled iloprost in 10 patients demonstrated a worsening of haemodynamics during surgery but an improvement was seen in the ICU with continued treatment with inhaled iloprost compared to inhaled saline (Kramm et al 2003). In a randomised study, pretreatment with bosentan for 6 months demonstrated a reduction in

pre-PEA, PVR, mPAP, and mRAP but no difference in post-PEA haemodynamics compared to controls (Reesink et al 2010). To date there is no convincing evidence that preoperative treatment of technically operable CTEPH with ERAs, PDE5 inhibitors, or prostanoids is beneficial.

This study will investigate if pre-PEA treatment with riociguat in technically operable CTEPH can improve preoperative pulmonary haemodynamics and key clinical outcomes after PEA. The current study is a randomised, double-blind, placebo-controlled, multicentre, prospective study of a 3-month treatment period followed by a 6-month safety follow-up period in patients with operable CTEPH with high preoperative PVR.

This study requires blinded comparison of active treatment with placebo treatment. As the use of a placebo control offers substantial protections against bias, a double-blind, placebo-controlled clinical trial is the most rigorous test of treatment efficacy. Use of placebo provides an opportunity to obtain information regarding the full treatment effect size for riociguat and also best enables the determination of whether AEs are due to treatment or to the disease condition. For these reasons, double-blind, placebo-controlled trials are almost always mandated for regulatory approval of an investigational drug for a specific disease indication.

Furthermore, it should be noted that placebo (or active drug) is used as premedication in addition to planned PEA. Placebo and active treatment will be compared in an "add-on" approach to patients scheduled to receive surgical treatment of CTEPH. Therefore, the trial does not include additional risks associated with the treatment with placebo. The patients will be fully informed of the risks involved in assignment to the placebo group.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 88 patients will be enrolled at 4 high-volume experienced sites in North America and Europe. Patients will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Is a male or nonpregnant and nonlactating female patient aged from 18 to 80 years, both inclusive
2. Is diagnosed with operable CTEPH and anticipating symptomatic and/or prognostic benefit from PEA
3. Has PVR >800 $dyn \cdot s \cdot cm^{-5}$
4. Has undergone RHC not more than 180 days before Visit 1
5. Has been treated with anticoagulants for at least 90 days before Visit 1
6. Has ability to swallow oral medication
7. Has ability and willingness to participate and access to the health facility
8. Is capable of understanding the written informed consent and provides signed and witnessed written informed consent
9. Female patient must be either surgically sterile, postmenopausal (no menses for the previous 12 months), or must be practicing an effective method of birth control as determined by the investigator (eg, oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or male partner with vasectomy or complete abstinence)

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Has unstable disease in need of urgent PEA surgery as determined by the treating physician
2. Has known hypersensitivity, allergic, or adverse reactions to riociguat or any of the excipients comprising riociguat tablets
3. Has known active hepatitis A immunoglobulin M, hepatitis B surface antigen, or hepatitis C antibody
4. Is human immunodeficiency virus positive
5. Has pulmonary veno-occlusive disease
6. Has symptomatic hypotension
7. Has symptomatic carotid disease
8. Has significant coronary atherosclerotic disease in need of intervention
9. Has severe left heart disease in need of intervention
10. Has redo sternotomy
11. Has received any background therapy for PAH in the preceding 30 days before Visit 1 including ERAs, PDE5 inhibitors, or prostanoids
12. Is receiving nitrates, NO donors (eg, amyl nitrite), ERAs, prostanoids, specific PDE5 inhibitors, nonspecific phosphodiesterase inhibitors (eg, dipyridamole, theophylline)
13. Is receiving strong cytochrome P450 and P-glycoprotein/breast cancer resistance protein inhibitors
14. Is receiving strong cytochrome P450 3A inducers
15. Has creatinine clearance <15 mL/min or is on any form of dialysis
16. Has severe hepatic impairment classified as Child-Pugh B or C

17. Has received an investigational drug within the past 4 weeks before Visit 1

18. Is a lactating or pregnant (as demonstrated by a serum or urine dipstick pregnancy test) woman, or not willing to take measures not to become pregnant during the 3-month treatment study period and 1 month after the last dose of study drug administered

19. Has smoked or used tobacco in any form, including snuff or chewing within 3 months prior to Visit 1

20. Has idiopathic interstitial pneumonitis

4.2 Assessment of Exclusion Criteria

The exclusion criteria related to laboratory assessments:

- Has known active hepatitis A immunoglobulin M, hepatitis B surface antigen, or hepatitis C antibody;
- Is human immunodeficiency virus positive;
- Has creatinine clearance <15 mL/min or is on any form of dialysis

will be assessed from patient history when the last assessment of these criteria occurred not more than or equal to 180 days before Visit 1.
If the last assessment occurred more than 180 days ago, laboratory assessments for these criteria will be performed on V0. Patients will be instructed to either represent for V1 or, when V0 and V1 are held on the same day, to initiate study drug when the laboratory results are available and the patient eligibility has been confirmed. In the latter cases, eligibility will be communicated to the patient by telephone call.
Laboratory assessments of these criteria, and a serum pregnancy test (if applicable), will be performed as confirmation at Visit 1 in all cases.

4.3 Withdrawal of Patients From the Study

The duration of the study is defined for each patient as the date signed written informed consent is provided through the last follow-up visit 6 months after PEA. The approximate study duration is 1 year for each patient including a screening period of 3 months, double-blind treatment period of 3 months, and a safety follow-up period of 6 months.

4.3.1 Reasons for Withdrawal/Discontinuation

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep patients in the study. The reasons for patients not completing the study will be recorded. A patient may be withdrawn from the study for any of the following reasons:

1. Does not meet the protocol inclusion or exclusion criteria
2. Noncompliance with the protocol
3. A serious or intolerable AE that in the investigator's opinion requires withdrawal from the study
4. Laboratory safety assessments that reveal clinically significant haematological or biochemical changes from the baseline values
5. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal
6. Loss to follow-up
7. Other (eg, pregnancy, development of contraindications of use of study drug)
8. If the investigator believes that continued administration of the study drug is contrary to the best interests of the patient
9. The patient withdraws consent or the investigator or sponsor decides to discontinue the patient's participation in the study

The investigator will also withdraw a patient if International CTEPH Association (ICA) terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. If a patient is discontinued because of an AE, the event will be followed until it is resolved. Any patient may withdraw his or her consent at any time.

4.3.2 Handling of Withdrawals

Patients are free to withdraw from the study or study drug at any time upon request. Patient participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Patients who discontinue study drug or active participation in the study will no longer receive study drug. When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all patients who discontinue study drug or withdraw from the study prematurely will undergo 6-month safety follow-up visit (Visit 4) assessments. Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety follow-up procedures.

4.3.3 Replacements

A total of 88 patients will be randomly assigned in the study with a target of 80 patients completing the study with an assumption of a 10% dropout rate.

Therefore, drop out for any reason before the last follow-up visit (Visit 4) will be monitored continuously throughout the study, and patients that drop out will be replaced to make a total number of 88 randomised patients. In case of a high initial dropout rate, the DSMB and the sponsor will evaluate the reasons for drop out and decide in mutual agreement on potential extension of further randomisations.

5 Study Drugs

5.1 Method of Assigning Patients to Treatment Groups

Patients will be randomly assigned to receive riociguat or placebo using a 1:1 allocation ratio. An interactive web response system (IWRS) will be used to administer the randomisation schedule. Biostatistics will generate the randomisation schedule using SAS® software Version 9.3 or later (SAS Institute Inc, Cary, North Carolina) for IWRS, which will link sequential patient randomisation numbers to treatment codes. It will also use an appropriate block size, which will not be revealed.

5.2 Treatments Administered

Patients will initiate the treatment with either riociguat or matching placebo tablets orally tid for 3 months. The study drug will be initiated no later than 180 days after RHC (used for screening of patients) and within 90 days of planned RHC before PEA. Right heart catheterisation will be performed within 3 months of the initiation of treatment per site procedures no more than 1 week prior to PEA. The study drug will be initiated at 1 mg and the dosage can be increased by 0.5 mg at 2-week intervals based on tolerability (SBP) up to a maximum dose of 2.5 mg tid. The individual study drug dose of the next titration step will be determined every 2 weeks at home according to the peripheral SBP measured at trough before intake of the morning dose under consideration of the following algorithm:

- If trough SBP ≥95 mmHg, increase dose (+0.5 mg tid)
- If trough SBP <95 mmHg without symptoms of hypotension, maintain dose
- If any SBP <95 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, stop study drug; restart after 24 hours with reduced dose (-0.5 mg tid)

The BP measuring device will be supplied along with study drug to each patient to monitor BP at home. If the dose is interrupted for 3 or more days, restart the dose with 1 mg tid and follow the up-titration algorithm. The up titration will be monitored by study staff contacting the patient by telephone at home.

5.3 Identity of Investigational Product

Riociguat is a film-coated, round shaped with 6-mm diameter, immediate-release tablet of pale orange colour. The excipients include lactose, microcrystalline cellulose, crospovidone, magnesium stearate, hypromellose, and sodium lauryl sulfate.

Placebo tablets are identical in appearance to riociguat but do not have the active compound. The excipients include lactose, microcrystalline cellulose, crospovidone, magnesium stearate, hypromellose, and sodium lauryl sulfate.

Study drug will be provided by the drug manufacturer to PPD (designated contract research organisation) for further distribution to sites.

The following drug supplies will be used in the study:

Product	Supplied as
Riociguat	0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg tablets
Placebo	Matching tablets

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Riociguat tablets and matching placebo tablets will be packed in high-density polyethylene bottles à 54 tablets and shipped by PPD Global Clinical Supplies or a third party vendor. Study drug will be packaged and labelled according to applicable local and regulatory requirements. Patients will receive sufficient bottles of randomised dosage for 3 months of treatment which will accommodate the uptitration procedure detailed in section 5.2.

Study drug must be stored in accordance with the manufacturer's instructions. The storage conditions and expiry date are indicated on the label. At the study site, study drug must be stored in a securely locked area and kept at a controlled room temperature not exceeding 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F).

The material's schedule will be prepared by an independent PPD statistician and provided to the IWRS and the packaging vendor. At the time of randomisation, the IWRS will assign each patient study drug bottles corresponding to the patient's assigned randomised treatment based on the drug supply inventory that is available at the study site. The bottles

will be identified by a unique bottle number that is separate from the patient randomisation numbers. On Day 1, the investigator will dispense the assigned study drug bottles to the patient as per the patient's randomisation schedule.

5.4.2 Test Article Accountability

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.4.3 Other Supplies

Upon site initiation, the PPD Central laboratory will provide initial supplies to the site. The BP measuring device will be provided to each patient.

These supplies include, but are not limited to the following:

- Laboratory manual
- Collection flow chart
- Courier contact sheet
- Specimen collection kits:
    - Prelabelled collection supplies and collection devices (needles, pipettes)
    - Prelabelled requisition form
- Shipping material (AWB# and shipping boxes)
- Study-specific material
    - Urine cups with lid

Further details of the collection of the samples and the supplies used can be found in the laboratory manual and the collection flow chart.

5.5 Overdose Management

An overdose is any dose of study drug given to a patient or taken by a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the PPD Drug Safety Centre. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

5.5.1 Treatment of Overdose

In cases of overdose, blood pressure should be closely monitored and supportive measures should be provided as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable. In case of pronounced hypotension, active cardiovascular support may be required.

5.6 Blinding

The clinical study will be performed in a double-blinded manner. The investigator, study coordinator(s), patients, and the sponsor study team and its representatives will be blinded to the identity of the randomised treatment assignment from the time of randomisation until database lock. Randomisation data will be kept in strict confidence by the statistician who will generate the randomisation schedule, the IWRS provider, and the vendor involved in the study drug labelling. The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labelling, schedule of administration, appearance, taste, and odour.

5.6.1 Breaking the Blind

A patient's treatment assignment will not be broken until the end of the study unless medical treatment of the patient depends on knowing the study drug the patient received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual patient's treatment allocation. As soon as possible, the investigator should first contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that patient. The treatment assignment will be unblinded through IWRS. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

5.7 Treatment Compliance

Patient compliance with study drug will be assessed by the investigator and/or study personnel at each visit using direct questioning and tablet counts. Deviations from the prescribed treatment regimen will be recorded on the source document and the patient's eCRF.

Compliance will be evaluated by calculating the number of tablets taken by the patient divided by the number of tablets expected to be used in the interval between visits.

5.8 Prior and Concomitant Therapy

Patients must be treated with anticoagulants. Drugs with the potential to reduce blood pressure should be used with caution in combination with riociguat, and no drugs named in the exclusion criteria may be administered to patients on riociguat therapy, including nitrates, NO donors, phosphodiesterase inhibitors (including PDE5 inhibitors), ERAs and prostanoids (see exclusion criteria Section 4.1.2).

All concomitant medications taken by the patient during the study, from the date of signature of the informed consent will be recorded in the appropriate section of the eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

6 Study Assessments and Procedures

Before any study procedures are performed, all potential patients will sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator will also sign the ICF.

Patients will undergo the procedures at time points specified in the Schedule of Events (Table 12-1).

6.1 Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics, including age, body weight (kg), height (cm), waist circumference, race, gender, and medical history will be collected at time points specified in the Schedule of Events (Table 12-1). The data of haemodynamic parameters at screening will be collected from the previous RHC.

6.2 Efficacy Assessments

6.2.1 Pulmonary Vascular Resistance

The resistance offered by the pulmonary circulation is known as the PVR. Pulmonary vascular resistance occurs when the pulmonary artery creates resistance against the blood flowing into it from the right ventricle. The resistance is naturally created by the arrangement of blood vessels in the lungs.

The change in pulmonary resistance from baseline will be measured at the pre-PEA visit (Visit 2) and at the 6-month follow-up visit (Visit 4) after PEA. The PVR value at screening will be collected from the medical history of the patient. The measurements prior to screening will be a prerequisite to confirm participation in study.

6.2.2 Death

The death of the patient irrespective of cause during the study will be reported.

6.2.3 Pulmonary Hypertension–Related Hospitalisation

The incidences of PH-related hospitalisation will be reported during the study for each patient.

6.2.4 Need for Pulmonary Arterial Hypertension–Targeted Medications

The need for PAH-targeted medications will be reported for each patient during the study.

6.2.5 WHO Functional Class

The change in WHO functional class from baseline will be noted at each visit.

WHO functional class is provided in Section 12.2 (Appendix 2).

6.2.6 Need for Other Medications

The need for medications other than PAH-targeted medications will be reported for each patient during the study.

6.2.7 Perioperative Findings

The circulatory arrest time in minutes and surgery-related complications during surgery as mentioned in Table 12-1 will be reported for each patient. Surgery-related complications are defined as the following:

- Bleeding and/or blood loss >1 L in 12 hours
- Airway bleed with need for extracorporeal membrane oxygenation
- Any use of extracorporeal membrane oxygenation for respiratory or haemodynamic support, specified as veno-venous or veno-arterial
- Prolonged ventilation >96 hours
- Need for tracheostomy
- Need for drainage of pericardial effusion
- Neurological complications, ie, stroke, cerebral, subdural bleeding
- Reintubation or noninvasive ventilation for reperfusion response
- Haemoptysis requiring any intervention
- Renal failure requiring dialysis

- Wound infections
- Pneumonia
- Prolonged need for inotropic support (≥ 5 days)

6.2.8 Surgical Evaluation of Specimen

The difficulty to withdraw the obstructive material will be measured as specified in Section 6.2.8.1, Section 6.2.8.2, and Section 6.2.8.3 scores as follows:

6.2.8.1 Ease of Dissection

The ease of dissection will be measured as a score of 1 to 3 with scores easier than normal (1), normal (2), and more difficult than normal (3).

6.2.8.2 Completeness of Disease Clearance

The completeness of disease clearance will be measured as a score of 1 to 3 with scores better than expected (1), as expected (2), and worse than expected (3).

6.2.8.3 Evaluation of Clot and Vessel Wall

Both clot and vessel wall will be measured as a score of 1 to 3 with the following scores: more solid than usual (1), normal (2), more friable than usual (3).

6.2.9 Withdrawal During Randomised Treatment Phase

The withdrawal of the patient during the treatment phase after randomisation along with the reason for withdrawal will be reported.

6.2.10 Plasma Pro-Brain Natriuretic Peptide Concentration

The plasma NT-proBNP concentration will be measured at baseline, pre-PEA, and at the 6-month follow-up visit after PEA. The change in NT-proBNP concentration from baseline at the pre-PEA visit (Visit 2) and at the 6-month follow-up visit (Visit 4) will be reported.

6.2.11 Cardiac Index

Cardiac index is a cardiodynamic parameter measured by the amount of blood ejected by left ventricle into the systemic circulation in 1 minute divided by body surface area. The unit of measurement is litres per minute per square metre ($L/min/m^2$). The cardiac index will be measured at the pre-PEA visit (Visit 2) and at the 6-month follow-up visit after PEA (Visit 4). The cardiac index value at screening will be collected from the medical history of the patient. The measurement prior to screening will be a prerequisite to confirm participation in study. The method of measurement of cardiac output (thermodilution or Fick method) should be consistent for each patient. If thermodilution method is available, this should be recorded.

6.2.12 Mean Right Atrial Pressure

The mRAP will be measured at the pre-PEA visit (Visit 2) and at the 6-month follow-up visit after PEA (Visit 4). The mRAP value at screening will be collected from the medical history of the patient.

6.2.13 Mean Pulmonary Arterial Pressure

The mPAP will be measured at the pre-PEA visit (Visit 2) and at the 6-month follow-up visit after PEA (Visit 4). The mPAP value at screening will be collected from the medical history of the patient.

6.2.14 Pulmonary Artery Wedge Pressure

The PAWP will be measured at the pre-PEA visit (Visit 2) and at the 6-month follow-up visit after PEA (Visit 4). The PAWP value at screening will be collected from the medical history of the patient. If the PAWP measurement is not available prior to screening, the left ventricular end diastolic pressure will be used to record wedge pressure at screening.

6.2.15 Length of Stay in Hospital and Intensive Care Unit

The length of stay in hospital and ICU in days after PEA during Visit 3 will be reported for each patient.

6.2.16 Time on Mechanical Ventilation

The total time spent on mechanical ventilation from the start of the ICU stay until end of mechanical ventilation during Visit 3 will be reported for each patient.

6.3 Safety Assessments

Safety assessments include AEs, vital sign measurements, ECG measurements, physical examinations, clinical laboratory examinations, and pregnancy testing. During the double-blind treatment period, patients will visit the study site at baseline (Visit 1) and at time points specified in the Schedule of Events (Table 12-1).

6.3.1 Adverse Events

6.3.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the investigator at any time after randomisation if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardise the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

6.3.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the patient signs the ICF until exit from the study.

At every study visit, patients will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs identified from any study data (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF.

6.3.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, action taken with the study drug, and outcome of the event (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, or unknown). Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that meets SAE criteria (Section 6.3.1.1) must be reported to PPD pharmacovigilance immediately (ie, within 24 hours) after the time site personnel first learn about the event. The following contact information is to be used for SAE reporting:

PPD pharmacovigilance
SAE Hotline: + 44 1223 374 240
SAE Fax line: + 44 1223 374 102

6.3.1.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	An event usually transient in nature and generally not interfering with normal activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal activities.
Severe:	An AE that is incapacitating and prevents normal activities.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed.

6.3.1.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterised using the following classification and criteria:

Unrelated:	This relationship suggests that there is no association between the study drug and the reported event.
Possible:	This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is readministered.

6.3.1.6 Exceptions

The hospitalisation due to study-related procedures ie, for scheduled RHC and PEA will not be considered as an SAE for this study.

6.3.1.7 Adverse events of special interest

Adverse events of special interest will be separately analysed and closely monitored throughout the course of the study for safety reasons.

Adverse events of special interests are defined as myocardial infarction, haemorrhage, hypotension, haemoptysis, syncope and stroke.

6.3.1.8 Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

6.3.2 Vital Sign Measurements

Vital signs, including blood pressure, heart rate, respiration, and body temperature will be obtained with the patient in a supine or seated position after resting for approximately 5 minutes. Vital signs will be measured as mentioned in Table 12-1.

6.3.3 Electrocardiogram Measurements

Twelve-lead ECGs will be performed to calculate the HR, and PR, QRS, QT, and QT interval Fridericia correction (QTcF) will also be calculated. The ECGs will be obtained

with the patient in the supine position, prior to blood draws, and after the patient has been supine for at least 10 minutes. Electrocardiograms will be measured as mentioned in Table 12-1.

All standard 12-lead ECGs will be recorded and analysed locally at the site by the investigator.

6.3.4 Physical Examinations

A complete physical examination including assessments of the head, eyes, ears, nose, throat, skin, neck (including thyroid), lungs, cardiovascular system, abdomen, lymph nodes, and extremities will be obtained at screening. A physical examination including updates since the screening visit with focus on previously noted abnormalities in organ systems, including skin and hair, will be completed at time points specified in schedule of events (Table 12-1).

6.3.5 Clinical Laboratory Testing

Laboratory assessments, including clinical laboratory testing, serum pregnancy test, and hepatitis B virus, hepatitis A immunoglobulin M, hepatitis C antibody, and human immunodeficiency virus screen will be performed at time points specified in Schedule of Events (Table 12-1).

- Routine clinical laboratory testing will be performed by a central laboratory and will include the following:
    - Haematology: haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and absolute platelet count;

- Clinical chemistry: total protein, sodium, potassium, calcium, chloride, inorganic phosphate, albumin, fasting blood glucose, glycated haemoglobin, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, blood urea nitrogen, creatinine (and creatinine clearance by the Cockroft-Gault formula), uric acid, bilirubin (total and direct), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ glutamyltransferase, lactate dehydrogenase, creatine kinase, cardiovascular marker panel, and high-sensitivity C-reactive protein;

- Urinalysis: appearance, colour, pH, specific gravity, glucose, blood, bilirubin, leukocyte esterase, ketones, nitrates, urine protein, urine creatinine, protein/creatinine ratio. Microscopic urinalysis will be performed if urinalysis results are abnormal.

- Serum pregnancy testing will be performed for all women of childbearing potential as mentioned in Table 12-1.

6.3.6 Clinical Significance of Safety Assessments

Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, vital sign measurements, physical examinations), including those that worsen from baseline, and are felt to be clinically significant in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

If any of the laboratory parameters of interest show a significant shift from baseline, patients will then be scheduled for an interim visit within 2 weeks to have the laboratory measurements repeated.

6.3.7 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor or its representative of all SAEs and non-serious AEs occurring during a clinical trial is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

6.4 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported to PPD pharmacovigilance using pregnancy report form. To ensure patient safety, each pregnancy must be reported to ICA within 2 weeks of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the patient has completed the study, and considered by the investigator as possibly related to the study drug, must be promptly reported to ICA.

6.5 Safety Monitoring Committee

An unblinded, independent DSMB will periodically review safety data. The frequency of data review and DSMB processes are outlined in the DSMB charter. In brief, the DSMB will meet before study start, after approximately 8 subjects have completed at least 12 weeks of study drug treatment and undergone PEA, after approximately 20 subjects have completed at least 12 weeks of study drug treatment and undergone PEA and after approximately 20 subjects have completed the study. An optional meeting is scheduled after 30–40 patients have completed the study. The DSMB will periodically review unblinded study information during the conduct of the study. If necessary, unblinding of individual patient data and treatment groups may be done.

6.6 Sample Collections

All visits that include clinical laboratory safety assessments must be after an 8-hour fast. Sample collection, processing, and shipping should be performed according to the central/local laboratory requirements.

7 Statistical and Analytical Plan

Due to the investigative nature of this study, all statistical analyses will be exploratory. A clearly defined statistical analysis plan (SAP) will be generated separately to provide a more detailed description of the planned statistical analyses in order to meet the objectives of the registry. The SAP will be finalised before database lock and the breaking of the study blind. Further specific analyses for publications will be prespecified in separate plans or documents.

7.1 Primary Efficacy Endpoints

The primary efficacy endpoint is percent change from baseline in PVR immediately before PEA at Visit 2. Unless otherwise specified, the baseline will be defined as the last valid assessment, including assessments from the unscheduled visit, prior to the study drug.

The PVR assessment from Visit 2 needs to be within 7 days prior to PEA. Assessments out of the time frame will be considered invalid and be treated as missing. In the case of patients who do not undergo PEA, the PVR at Visit 2 will be treated as missing.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study are mentioned below.

1. PVR (6 months after PEA): percent change from baseline in PVR at Visit 4.

   PVR assessment at Visit 4 will use the nominal visit information collected in eCRF without considering the time window because PVR status is expected to be stable after PEA.

2. Composite clinical endpoints (6 months after PEA), including patients with any one of the following clinical endpoints, from immediately after PEA to Visit 4.

   - All-cause death

     All deaths that happen after randomisation until the date of Visit 4, 6 months after the PEA, will be included.

   - PH-related hospitalisation

All PH-related hospitalisation except the in-hospital care after PEA from randomisation until 6 months after PEA will be included.

- Need for PAH-targeted therapy

  All PAH-targeted therapy from randomisation until 6 months after PEA will be included.

- Functional class unchanged or worse

  When comparing the functional class assessment at Visit 1 with the functional class assessment at other visits, the same class will be defined as unchanged, and a higher class will be defined as worse. The worst case after treatment will be used.

3. Perioperative findings at Visit 2:

   - Circulatory arrest time
   - Surgery-related complications (Section 6.2.7)

4. Surgical evaluation of specimen (difficulty to withdraw obstructive material):

   - Ease of dissection plane, classed as easier than normal (1), normal (2), more difficult than normal (3)
   - Completeness of disease clearance, classed as better than expected (1), as expected (2), worse than expected (3)
   - Both clot and vessel wall will be measured as score of 1 to 3 with the following scores: more solid than usual (1), normal (2) more friable than usual (3).

Surgical evaluations of specimen are from perioperative measures. The data will be treated as an ordinal response. A higher score means a worse case.

5. All-cause death

All deaths that happen during the whole course of the study will be included.

6. Withdrawal during randomised treatment phase

Only withdrawals after randomisation but before PEA will be included.

7.3 Exploratory Efficacy Endpoints

A Visit 2 assessment is considered as valid only when the assessment is completed within 7 days prior to the PEA. For assessments at Visit 4, the nominal visit collected in eCRF will be used in the analysis. This rule is applicable to all endpoints derived by the visit. The exploratory efficacy endpoints are mentioned below.

1. NT-proBNP measurement concentration change from baseline at the preoperative visit (Visit 2) and at 6 months after PEA (Visit 4)

2. Cardiac index change from baseline at the preoperative visit (Visit 2) and at 6 months after PEA (Visit 4)

3. Mean right atrial pressure change from baseline at the preoperative visit (Visit 2) and at 6 months after PEA (Visit 4)

4. Mean pulmonary arterial pressure change from baseline at the preoperative visit (Visit 2) and at 6 months after PEA (Visit 4)

5. Pulmonary artery wedge pressure change from baseline at the preoperative visit (Visit 2) and at 6 months after PEA (Visit 4)

6. Hospital length of stay

   The hospital length of stay in days will be derived from the first date when the patient is hospitalised for PEA until the date when the patient is discharged from the hospital.

7. ICU length of stay in days

8. Time on mechanical ventilation, in hours, from start of ICU stay until end of mechanical ventilation

9. In-hospital mortality

   Only deaths that happen on or after PEA but before discharge from the hospital will be included.

10. Functional class at the preoperative visit (Visit 2) and at 6 months after PEA (Visit 4)

11. Need for PAH-targeted postoperative therapy at the 6-month visit (Visit 4)

7.4 Safety Endpoints

The safety endpoints are the assessment of the safety and tolerability of riociguat as measured by the nature and frequency of AEs and changes in vital sign measurements, 12-lead ECGs, physical examination findings, and clinical laboratory analyses.

7.5 Sample Size Calculations

A total of 88 patients, accounting for a 10% dropout rate, will be randomly assigned into riociguat or placebo groups at a ratio of 1:1 in the study. The sample size for this study is not based on the required statistical power to test any specific hypothesis but feasibility to initially assess the safety and efficacy of riociguat on preoperative pulmonary haemodynamics in patients with operable CTEPH.

7.6 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-treat (ITT) set: The ITT set will consist of all participants who received at least one dosage of randomised study drug. All analyses using the ITT will group participants according to randomised treatment.

PEA set: The PEA set will consist of all ITT participants who actually undergo PEA. All analyses using the PEA will group participants according to randomised treatment.

Per-protocol set (PPS): The PPS will consist of all ITT participants who fulfil all inclusion/exclusion criteria, have at least 80% overall dose compliance with study drug, have not taken any prohibited medication, have no significant protocol deviations, have valid PVR assessments at baseline and Visit 2, and undergo PEA as planned. All analyses using the PPS will group participants according to treatment actually received. A blind data review of data will identify which participants will be included in the PPS.

Safety set: The safety set will consist of all participants who received any study drug. All analyses using the safety set will group participants according to treatment actually received.

The ITT set will be used as the primary efficacy analysis set including primary, secondary, and exploratory efficacy analyses.

The PPS will be used in the primary and secondary efficacy analyses as supportive analyses. The exploratory efficacy analyses may use PPS in a way more relevant to the specific question, which is specified in the SAP.

The safety set will be used in safety analyses.

7.7 Description of Subgroups to be Analysed

No subgroup analyses are planned. Any subgroup analysis of special interest is specified in the SAP.

7.8 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.3 or later.

Statistical methods to be used will be mainly descriptive. Summary statistics will be tabulated and represented graphically, whenever appropriate. Continuous variables will be summarised using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages. Data will be listed in data listings. Time to event data will be analysed using the Kaplan-Meier method.

Details of the statistical analyses, methods, and data conventions will be described in the SAP.

Unless otherwise specified, statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% (2-sided) CIs.

Modelling techniques will be used in an exploratory sense. No adjustments for multiplicity are made. Covariates may be defined in the SAP as appropriate.

7.8.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is percent change from baseline in PVR immediately before PEA at Visit 2.

The null hypothesis is that there is no difference between the treatment groups in percent change from baseline in PVR immediately before PEA at Visit 2, and the alternative is that the difference is not zero.

The difference in the percent change from baseline in PVR immediately before PEA at Visit 2 between riociguat and placebo will be tested using the 2-sample Wilcoxon rank-sum test. If the normality of the residuals can hold, as a supportive analysis, analysis of covariance with baseline value as the covariate will be employed to test the null hypothesis.

To check the effect of missing values on the robustness of the primary analysis, the primary analysis will be repeated using the baseline observation carried forward approach for missing PVR values immediately before PEA at Visit 2.

7.8.2 Analysis of Secondary Efficacy Endpoint

For the secondary endpoint, percent change from baseline in PVR at Visit 4, the same approach as in the primary analysis will be used.

Composite clinical endpoints at 6 months after PEA will be tabulated by treatment group containing the number and percentage of patients with an event as well as the number of event. The Fisher exact test will be utilised to test the proportion difference along with the Clopper-Pearson exact CI when applicable. For analysis based on the ordinal response of functional class, the row mean score from the Cochran-Mantel-Haenszel test will be used to test the response difference between groups.

Circulatory arrest time from perioperative findings will be tabulated by treatment group using the descriptive statistics. An analysis of variance may be employed to compare the mean difference between 2 groups. In case normality assumption cannot hold, the Wilcoxon rank-sum test should be considered.

Surgery-related complications from the perioperative findings will be tabulated by treatment group in a descriptive way, presenting the number and percentage of patients for each symptom.

For surgical evaluation of specimen endpoints, ease of dissection plane and completeness of disease clearance will be tabulated by treatment group containing the number and percentage of patients in each level. The Cochran-Mantel-Haenszel test will be used to test the ordinal response difference between groups if deemed necessary.

Clot and vessel wall friability, measured as more solid than usual, normal, or more friable than usual, will be tabulated by treatment group containing the number and percentage of

patients in each level. The Cochran-Mantel-Haenszel test will be used to test the ordinal response difference between groups if deemed necessary.

All-cause death during the whole study course and withdrawal during the randomised treatment phase will be tabulated by treatment group containing the number and percentage of patients with event. Time to death will be analysed using the Kaplan-Meier method.

7.8.3 Analyses of Exploratory Efficacy Endpoint

No formal assessment of difference between treatment groups will be performed for any of the exploratory efficacy endpoints. All exploratory efficacy endpoints will be presented mainly in a descriptive way. If deemed necessary, the difference between both treatment groups in exploratory efficacy endpoints will be estimated with 95% CIs to quantify the treatment effect.

7.8.4 Safety Analyses

Safety analysis except by-visit summarisations will be presented in 2 ways, one based on only the assessments during the double blind treatment phase, and another based on the assessments during the whole study.

Adverse events will be summarised by presenting for both treatment groups the number and percentage of patients having any AE, having an AE in each MedDRA primary system organ class, and having each individual AE (preferred term). Additionally, a summary of AEs by preferred term and severity will be performed using the worst severity grade.

All related AEs, AEs with outcome death, AEs leading to permanent discontinuation of treatment, SAEs, and related SAEs will be summarised by percentages and frequencies and listed including the investigator term, the preferred term, start and end dates of the AE, duration (days), severity, drug relationship, action taken, and outcome.

Treatment-related AEs are those rated by the investigator as "definite," "probable," or "possible." In case the relationship is unknown or missing, the worst case will be assumed and the AE will be considered to be drug related.

For laboratory data, the proportion of patients with clinically significant abnormal values as reported by the investigator will be provided by laboratory parameter, dose cohort, and scheduled visit.

For each laboratory parameter, shift tables of baseline categories based on normal ranges (below, within, above) versus categories at each postbaseline scheduled visit and the worst postbaseline value will be provided.

Summary statistics of values and changes from baseline over time will be computed for all safety laboratory parameters.

For vital sign measurements, supine or seated blood pressure and HR (absolute values and change from baseline) will be summarised by dose cohort and scheduled visit.

For ECGs, the proportion of patients with a clinically significant abnormal ECG result will be provided. A summary of shifts in 12-lead ECG abnormalities from baseline will be provided by scheduled visits.

Abnormal physical examination data will be summarised by treatment group and body system with number and percentage of patients.

Previous and concomitant treatments coded using the WHO Drug Dictionary and medical history coded using MedDRA will be summarised by treatment group number and percentage of patients at different coded terms.

7.8.5 Interim Analyses

A DSMB will review unblinded safety data throughout the study and make recommendations as appropriate. Further details are specified in the DSMB charter.

7.9 Data Quality Assurance

7.9.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and ECG strips.

PPD will supply the eCRF.

Investigative site personnel will enter patient data into electronic data capture using the Medidata Rave® (a web-based tool). The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse events and medical history will be coded using MedDRA.

Patient data reports will be generated by Medidata for the study after database lock. Each site will receive a compact disc (CD) and a master copy will be sent to sponsor.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an institutional review board (IRB)/independent ethics committee (IEC) before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favourable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Patient Information and Consent

A written informed consent in compliance with regulatory authority regulations shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for

review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrolment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and gouvernment standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the regulatory authorities, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 Code of Federal Regulations (CFR) Part 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the patient's disease.

9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form US Food and Drug Administration (FDA) 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of patients begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authorities with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorisation from the sponsor, but data and publication thereof will not be unduly withheld.

10 Study Management

The administrative structure will include following roles:

Role	Name
Sponsor	International CTEPH Association
Sponsor Signatory	Gérald Simonneau (ICA chairperson)
Sponsor Medical Officer	Dr David Jenkins (Principal investigator and ICA board member)
Contract Research Organisation	For Monitoring and Clinical Trial Management: PPD
Central Laboratory	PPD Highland Heights, Kentucky and Brussels, Belgium

10.1 Monitoring

10.1.1 External Data Monitoring Committee

No external data monitoring committee except DSMB will be used for this study.

10.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study

records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC and to Regulatory Authorities for approval before patients can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the patient without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.3).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

Although ICA has every intention of completing the study, ICA reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last visit (includes follow-up visit).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agencies as required by the applicable regulatory requirements. The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

11 Reference List

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12 Appendices

12.1 Appendix 1: Schedule of Events

Table 12-1 Schedule of Events

	Visit 0 Pretreatment / Screening	Visit 1 Randomisation & baseline visit	Visit 2 RHC visit (Pre-PEA)	Visit 3 Post-PEA	Visit 4 Follow-up visit incl. RHC
Time frame	**Day -89 to 1**	**Day 1**	**Day 90±30**	**Day 96[a]**	**Day 276±10**
Activity / Observation					
Written informed consent	X				
Inclusion/exclusion criteria review	X	(X)[b]			
Assessment of current tobacco use	X				
Demographic data including height and weight	X				
HIV test	(X)[b]	X			
Medical and treatment history	X	X			
Physical examination including WHO functional class	X	X	X	X	X
Vital sign measurements	X	X	X	X	X
Clinical laboratory assessments (haematology, clinical chemistry, and urinalysis)	(X)[b]	X	X	X	X
NT-proBNP measurement		X	X		X
Haemodynamics incl. PVR, mRAP, mPAP, cardiac index, pulmonary artery wedge pressure measurement	X[c]		X		X
12-lead ECG		X	X		X
Pregnancy test (if applicable)[d]	X	X	X		X
Randomisation/treatment assignment		X			
Administration of double-blind study drugs[e]		X	X		
Provision of patient diary	X				
Perioperative assessment (circulatory arrest time, surgery-related complications)			X[f]		

	Visit 0 Pretreatment / Screening	Visit 1 Randomisation & baseline visit	Visit 2 RHC visit (Pre-PEA)	Visit 3 Post-PEA	Visit 4 Follow-up visit incl. RHC
Time frame	**Day -89 to 1**	**Day 1**	**Day 90+30**	**Day 96[a]**	**Day 276±10**
Activity / Observation					
Surgical evaluation of specimen[g]			X[g]		
Hospital and ICU length of stay				X	
Time on mechanical ventilation				X	
PAH-targeted therapy assessment	X	X	X	X	X
PH-related hospitalisation		X	X	X	X
Adverse event monitoring	X	X	X	X	X
Concomitant medications		X	X	X	X
Return of patient diary				X	
Return of study drug				X	
Telephone call			X[h]		X[i]
Patient compliance check (study procedures and study drug)		X	X	X	X

Abbreviations: ECG, electrocardiogram; HIV, human immunodeficiency virus; ICU, intensive care unit; incl., including; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; WHO, World Health Organization

[a] The PEA will be conducted by the principal surgeon of the site within a week of RHC.

[b] When laboratory analysis results are required/available (see Section 4.2)

[c] Patients must have undergone an RHC ≤ 180 days before Visit 1. This procedure is considered a prerequisite for participation and not part of the study itself. If it was performed at a referring centre, it is at the investigators' discretion based on the quality of the RHC data and the experience of the referring site to enroll the patient.

[d] Urine dipstick or serum pregnancy testing will be performed at Visit 0. Serum testing will be performed for all other applicable visits.

[e] The study drug will be initiated no later than 180 days after RHC. At Visit 2, RHC will be performed within 90 days of the initiation of treatment per site procedures no more than 1 week prior to PEA.

[f] Perioperative measures.

[g] Difficulty to withdraw obstructive material, ease of dissection plane (easier than normal, normal, or more difficult than normal), completeness of disease clearance (better than expected, as expected, or worse than expected).

[h] The treating physician should contact the patient at least once by telephone during treatment period,

[i] The treating physician should contact the patient during follow-up at 186±10 day by telephone, where questions related to patient's well-being adverse events can be asked.

12.2 Appendix 2: World Health Organization Classification for Patients With Pulmonary Arterial Hypertension

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

12.3 Appendix 3: Detailed summary of protocol changes

12.3.1 Amendment 1

1. Section 4.1.2, Exclusion Criteria (page 35)

Old text

Is a lactating or pregnant (as demonstrated by a serum pregnancy test) woman, or not willing to take measures not to become pregnant during the 3-month treatment study period and 1 month after the last dose of study drug administered

New text

Is a lactating or pregnant (as demonstrated by a serum or urine dipstick pregnancy test) woman, or not willing to take measures not to become pregnant during the 3-month treatment study period and 1 month after the last dose of study drug administered

Rationale for change

To allow for faster assessment of pregnancy status, pregnancy tests can be performed as quick tests (urine dipstick) or by serum testing. Serum pregnancy testing will be performed for all applicable patients at Visit 1.

2. Appendix 1, Schedule of events (page 73–74)

Old text

	Visit 0 Pretreatment / Screening	**Visit 1 Randomisation & baseline visit**	**Visit 2 RHC visit (Pre-PEA)**	**Visit 3 Post-PEA**	**Visit 4 Follow-up visit incl. RHC**
Time frame	**Day -90 to 0**	**Day 1**	**Day 90+30**	**Day 96[a]**	**Day 276±10**
Activity / Observation					
Written informed consent	X				
Inclusion/exclusion criteria review	X				
Assessment of current tobacco use	X				
Demographic data including height and weight		X			
HIV test	X	X			
Medical and treatment history	X	X			

	Visit 0 Pretreatment / Screening	Visit 1 Randomisation & baseline visit	Visit 2 RHC visit (Pre-PEA)	Visit 3 Post-PEA	Visit 4 Follow-up visit incl. RHC
Time frame	**Day -90 to 0**	**Day 1**	**Day 90+30**	**Day 96[a]**	**Day 276±10**
Activity / Observation					
Physical examination including WHO functional class	X	X	X	X	X
Vital sign measurements	X	X	X	X	X
Clinical laboratory assessments (haematology, clinical chemistry, and urinalysis)	X	X	X	X	X
NT-proBNP measurement		X	X		X
Haemodynamics incl. PVR, mRAP, mPAP, cardiac index, pulmonary artery wedge pressure measurement	X[b]		X		X
12-lead ECG		X	X		X
Serum pregnancy test (if applicable)		X	X		X
Randomisation/treatment assignment		X			
Administration of double-blind study drugs[c]		X	X		
Perioperative assessment (circulatory arrest time, surgery-related complications)			X[d]		
Surgical evaluation of specimen[e]			X[e]		
Hospital and ICU length of stay				X	
Time on mechanical ventilation				X	
PAH-targeted therapy assessment	X	X	X	X	X
PH-related hospitalisation		X	X	X	X
Adverse event monitoring	X	X	X	X	X
Concomitant medications		X	X	X	X
Return of study drug				X	
Telephone call			X[f]		X[g]
Patient compliance check (study procedures and study drug)		X	X	X	X

Abbreviations: ECG, electrocardiogram; HIV, human immunodeficiency virus; ICU, intensive care unit; incl., including; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; WHO, World Health Organization

[a] The PEA will be conducted by the principal surgeon of the site within a week of RHC.

[b] Patients must have undergone an RHC ≤ 180 days before Visit 1. This procedure is considered a prerequisite for participation and not part of the study itself. If it was performed at a referring centre, it is at the investigators' discretion based on the quality of the RHC data and the experience of the referring site to enroll the patient.

[c] The study drug will be initiated no later than 180 days after RHC. At Visit 2, RHC will be performed within 90 days of the initiation of treatment per site procedures no more than 1 week prior to PEA.

[d] Perioperative measures.

[e] Difficulty to withdraw obstructive material, ease of dissection plane (easier than normal, normal, or more difficult than normal), completeness of disease clearance (better than expected, as expected, or worse than expected).

[f] The treating physician should contact the patient at least once by telephone during treatment period,

[g] The treating physician should contact the patient during follow-up at 186±10 day by telephone, where questions related to patient's well-being adverse events can be asked.

New text

	Pretreatment / Screening	**Randomisation & baseline visit**	**RHC visit (Pre-PEA)**	**Post-PEA**	**Follow-up visit incl. RHC**
Time frame	**Day -89 to 1**	**Day 1**	**Day 90+30**	**Day 96[a]**	**Day 276±10**
Activity / Observation					
Written informed consent	X				
Inclusion/exclusion criteria review	X	(X)[b]			
Assessment of current tobacco use	X				
Demographic data including height and weight	X				
HIV test	(X)[b]	X			
Medical and treatment history	X	X			
Physical examination including WHO functional class	X	X	X	X	X
Vital sign measurements	X	X	X	X	X
Clinical laboratory assessments (haematology, clinical chemistry, and urinalysis)	(X)[b]	X	X	X	X
NT-proBNP measurement		X	X		X
Haemodynamics incl. PVR, mRAP, mPAP, cardiac index, pulmonary artery wedge pressure measurement	X[c]		X		X

	Pretreatment / Screening	Randomisation & baseline visit	RHC visit (Pre-PEA)	Post-PEA	Follow-up visit incl. RHC
Time frame	**Day -89 to 1**	**Day 1**	**Day 90+30**	**Day 96[a]**	**Day 276±10**
Activity / Observation					
12-lead ECG		X	X		X
Pregnancy test (if applicable)[d]	X	X	X		X
Randomisation/treatment assignment		X			
Administration of double-blind study drugs[e]		X	X		
Provision of patient diary	X				
Perioperative assessment (circulatory arrest time, surgery-related complications)			X[f]		
Surgical evaluation of specimen[g]			X[g]		
Hospital and ICU length of stay				X	
Time on mechanical ventilation				X	
PAH-targeted therapy assessment	X	X	X	X	X
PH-related hospitalisation		X	X	X	X
Adverse event monitoring	X	X	X	X	X
Concomitant medications		X	X	X	X
Return of patient diary				X	
Return of study drug				X	
Telephone call			X[h]		X[i]
Patient compliance check (study procedures and study drug)		X	X	X	X

Abbreviations: ECG, electrocardiogram; HIV, human immunodeficiency virus; ICU, intensive care unit; incl., including; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; WHO, World Health Organization

[a] The PEA will be conducted by the principal surgeon of the site within a week of RHC.

[b] When laboratory analysis results are required/available (see Section 4.2)

[c] Patients must have undergone an RHC ≤ 180 days before Visit 1. This procedure is considered a prerequisite for participation and not part of the study itself. If it was performed at a referring centre, it is at the investigators' discretion based on the quality of the RHC data and the experience of the referring site to enroll the patient.

[d] Urine dipstick or serum pregnancy testing will be performed at Visit 0. Serum testing will be performed for all other applicable visits.

[e] The study drug will be initiated no later than 180 days after RHC. At Visit 2, RHC will be performed within 90 days of the initiation of treatment per site procedures no more than 1 week prior to PEA.

[f] Perioperative measures.

[g] Difficulty to withdraw obstructive material, ease of dissection plane (easier than normal, normal, or more difficult than normal), completeness of disease clearance (better than expected, as expected, or worse than expected).

[h] The treating physician should contact the patient at least once by telephone during treatment period,

[i] The treating physician should contact the patient during follow-up at 186±10 day by telephone, where questions related to patient's well-being adverse events can be asked.

Rationale for change

CTEPH is an orphan disease and only a few expert centres world-wide are experienced in performing PEA. It is therefore expected that patients travel a long distance to the site. To minimise the burden on the patients, Visit 0 and Visit 1 can be held on the same day. For this, Visit 0 has been updated to occur on Day -89 to Day 1, the first pregnancy test can be a serum test or a urine dipstick test and eligibility on consideration of blood or urine markers (including HIV, hepatitis A, hepatitis B, creatinine clearance and hepatic impairment) will be assessed on patient history and confirmed by laboratory assessments at V1. If not available from patient history within 180 days prior to V1, laboratory tests will be performed and study drug intake can only occur once laboratory results are available.

The patient diary provision and collection has been added for clarity.

Assessment of patient demographics was moved to V0 for operational reasons.

3. Section 3.1 Study Design (page 30)

Old text

- **Screening Period (Day -90 to Day 0)**: The screening period of up to 90 days will be used to assess eligibility of patients and to allow for the washout of prohibited medications.

New text

- **Screening Period (Day -89 to Day 1)**: The screening period of up to 90 days will be used to assess eligibility of patients and to allow for the washout of prohibited medications. Screening visit (V0) and randomisation visit (V1) can occur on the same day.

Rationale for change

Please refer to the rationale for change for Appendix 1, Schedule of Events

4. Section 4.2 Assessment of Exclusion Criteria (page 35)

Old text

Not applicable

New text

The exclusion criteria related to laboratory assessments:

- Has known active hepatitis A immunoglobulin M, hepatitis B surface antigen, or hepatitis C antibody;
- Is human immunodeficiency virus positive;
- Has creatinine clearance <15 mL/min or is on any form of dialysis

will be assessed from patient history when the last assessment of these criteria occurred not more than or equal to 180 days before Visit 1.
If the last assessment occurred more than 180 days ago, laboratory assessments for these criteria will be performed on V0. Patients will be instructed to either represent for V1 or, when V0 and V1 are held on the same day, to initiate study drug when the laboratory results are available and the patient eligibility has been confirmed. In the latter cases, eligibility will be communicated to the patient by telephone call.
Laboratory assessments of these criteria, and a serum pregnancy test (if applicable), will be performed for confirmation at Visit 1 in all cases.

Rationale for change

Please refer to the rationale for change for Appendix 1, Schedule of Events

5. Section 7.6 Analysis set (page 57)

Old text

The ITT set will consist of all participants who were randomly assigned to receive double-blind study drug.

New text

Intent to treat (ITT) set : The ITT set will consist of all participants who received at least one dosage of randomised study drug. All analyses using the ITT will group participants according to randomised treatment.

Rationale for change

Study drug intake can only occur once all inclusion and exclusion criteria are confirmed. In a minortiy of instances, patients may be randomised while laboratory assessments are ongoing. In the interest of an unbiased ITT population, only patients with at least one study drug dosage will be included in the ITT analysis set.

6. Administrative changes

Section 5.4.1, Study Drug Packaging and Storage (page 39)

Old text

Riociguat tablets and matching placebo tablets will be packed in aluminium foil blisters in cartons and shipped by PPD Global Clinical Supplies.

New text

Riociguat tablets and matching placebo tablets will be packed in high-density polyethylene bottles and shipped by PPD Global Clinical Supplies.

Section 7.3, Exploratory Efficacy Endpoints (page 57)

Old text

Need for PAH-targeted preoperative therapy at the 6-month visit (Visit 4)

New text

Need for PAH-targeted postoperative therapy at the 6-month visit (Visit 4)

Section 6.3.2 and 7.8.4, Vital signs (pages 50 and 61)

Old text

Vital signs, including blood pressure, pulse rate, respiration, and body temperature will be obtained with the patient in a seated position after resting for approximately 5 minutes.

For vital sign measurements, supine blood pressure and HR (absolute values and change from baseline) will be summarised by dose cohort and scheduled visit.

New text

Vital signs, including blood pressure, pulse rate, respiration, and body temperature will be obtained with the patient in a supine or seated position after resting for approximately 5 minutes.

For vital sign measurements, supine or seated blood pressure and HR (absolute values and change from baseline) will be summarised by dose cohort and scheduled visit.

Section 10.2.1, Modification of the Protocol (page 69)

Old text

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients can be enrolled into an amended protocol.

New text

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC and to Regulatory Authorities for approval before patients can be enrolled into an amended protocol.

Section 5.4.1, Study Drug Packaging and Storage

Old text

Riociguat tablets and matching placebo tablets will be packed in high-density polyethylene bottles and shipped by PPD Global Clinical Supplies.

New text

Riociguat tablets and matching placebo tablets will be packed in high-density polyethylene bottles à 54 tablets and shipped by PPD Global Clinical Supplies or a third party vendor.

Study drug supply

Study drug will be provided per bottle rather than per kit to allow adaption of study drug supply to the patient's individual schedule. This has been amended throughout the protocol.

Study contacts

Sean Egan has been appointed as project manager.

12.3.2 Amendment 2

12.3.2.1 Protocol synopsis and Section 4.1.2, Exclusion Criteria

Old text

Not applicable.

New text

1. Has unstable disease in need of urgent PEA surgery as determined by the treating physician

20. Has idiopathic interstitial pneumonitis

Rationale for change

In the interest of patient safety, patients whose severity criteria require intervention in a shorter period of time are excluded from participation. In light of recent results from the RISE-IIP study (Nathan S, Behr J, Collard HR, et al. RISE-IIP: Riociguat for the treatment of pulmonary hypertension associated with idiopathic interstitial pneumonia. Eur Resp J 2017;50:OA1985. 2017) and recommendations from the EMA (EMA/396864/2016), idiopathic interstitial pneumonitis is added as an exclusion criterion.

12.3.2.2 Section 6.5, Safety Monitoring Committee (page 52)

Old text

An unblinded, independent DSMB will periodically review safety data. The frequency of data review and DSMB processes are outlined in the DSMB charter. The DSMB will periodically review unblinded study information during the conduct of the study. If necessary, unblinding of individual patient data and treatment groups may be done.

New text

An unblinded, independent DSMB will periodically review safety data. The frequency of data review and DSMB processes are outlined in the DSMB charter. In brief, the DSMB will meet before study start, after approximately 8 subjects have completed at least 12 weeks of study drug treatment and undergone PEA, after approximately 20 subjects have completed at least 12 weeks of study drug treatment and undergone PEA and after approximately 20 subjects have completed the study. An optional meeting is scheduled after 30–40 patients have completed the study. The DSMB will periodically review unblinded study information during the conduct of the study. If necessary, unblinding of individual patient data and treatment groups may be done.

Rationale for change

Following the request from health authorities, the scheduled DSMB meeting frequency is reflected in the protocol.

12.3.2.3 Section 6.3.1.7, Adverse events of special interest (page 49)

Old text

Not applicable.

New text

Adverse events of special interest will be separately analysed and closely monitored throughout the course of the study for safety reasons.

Adverse events of special interests are defined as myocardial infarction, haemorrhage, hypotension, haemoptysis, syncope and stroke.

Rationale for change

In order to increase the safety monitoring for this study, adverse events of special interest are defined.

12.3.2.4 Protocol synopsis and Section 3.1, Study Design (pages 13 and 29)

Old text

At Visit 2, RHC will be performed per site procedures no more than 1 week prior to PEA, which will be conducted by the principal surgeon of the site. The study drug will be discontinued once PEA is performed and the patient will remain hospitalised per the investigator's discretion.

New text

At Visit 2, RHC will be performed per site procedures no more than 1 week prior to PEA, which will be conducted by the principal surgeon of the site. The study drug will be discontinued once PEA is performed. The last study dose will be given on the morning of PEA surgery. The patient will remain hospitalised per the investigator's discretion.

Rationale for change

The exact time frame for the last study dose is specified in the interest of improving comparability between sites.

12.3.2.5 Section 5.3, Identity of Investigational Product (page 38)

Old text

Riociguat is a white to almost-white film-coated, round shaped with 6-mm diameter, immediate-release tablet.

New text

Riociguat is a film-coated, round shaped with 6-mm diameter, immediate-release tablet of pale orange colour.

Rationale for change

The tablet colour is corrected.