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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Statistical Analysis Plan

Version 1.0, Amendment 1.0

14DEC2020

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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

Approved by: _____ Date: ___/___/___

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List of Abbreviations

AE	adverse event
ATC	anatomical therapeutic chemical
BP	blood pressure
CI	confidence interval
CTEPH	chronic thromboembolic pulmonary hypertension
DSMB	data safety monitoring board
ECG	electrocardiogram
ERA	endothelin receptor antagonist
eCRF	electronic case report form
HR	heart rate
ICA	International CTEPH Association
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IRB	institutional review board
ITT	intent to treat
IWRS	interactive web response system
LVEDP	Left ventricular end-diastolic pressure
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
PPS	per-protocol set
PT	Preferred Term
PVR	pulmonary vascular resistance
QTcF	QT interval Fridericia correction
RHC	right heart catheterisation
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
sGC	soluble guanylate cyclase
SMQ	Standardised MedDRA Query
TEAE	treatment-emergent adverse event
tid	3 times a day
WHO	World Health Organization

1. Introduction

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). CTEPH 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.

Pulmonary endarterectomy (PEA) is the surgical procedure that removes the obstructing thromboembolic material, resulting in significant improvements (or normalisation) in pulmonary haemodynamics and right ventricular function. PEA 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 improve post-PEA (Cannon et al 2016). The perioperative mortality rate was 4.7% even from experienced centres (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).

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 CTEPH. Nonclinical studies indicated that riociguat is a NO-independent but haeme-dependent stimulator of the sGC and effective in several cardiopulmonary animal models. There were 9 clinical 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. 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 (Ghofrani et al 2013). Riociguat is effective in treating patients with inoperable and persistent CTEPH after PEA, as well as patients with pulmonary arterial hypertension (PAH). The adverse event (AE) profile observed in the patient populations tested was within the range expected in these chronically ill patient groups. Overall, riociguat was safe and well tolerated and did not present untoward side effects not already identified in the patient populations studied.

Riociguat is approved in patients with inoperable CTEPH or patients with persistent or recurring CTEPH after surgical treatment. The cumulative worldwide exposure to riociguat (Adempas®) since start of marketing authorisation until 31 AUG 2017 is estimated at 168,623 patient-months or approximately 14,052 patient years, excluding interventional clinical studies[1].

Improving pulmonary haemodynamics before surgery could potentially reduce the morbidity and mortality associated with PEA. To date there is no convincing evidence that preoperative treatment of technically operable CTEPH with endothelin receptor antagonists (ERAs), phosphodiesterase-5 (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.

This statistical analysis plan (SAP) describes the analyses and data presentations for PEA Bridging Study based on protocol Version 3 which was issued on 27Jul2017 (amended on 26Apr2018, Version 3.0). This document follows the principles of the international Guideline ICH E9. It contains definitions of analysis set, derived variables and statistical methods for the analysis of efficacy and safety. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and any data analysis for the final analysis. The SAP will be finalised before database lock and the breaking of the study blind. All statistical analyses detailed in this SAP will be conducted using SAS® software Version 9.3 or later (SAS Institute Inc, Cary, North Carolina).

2. 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

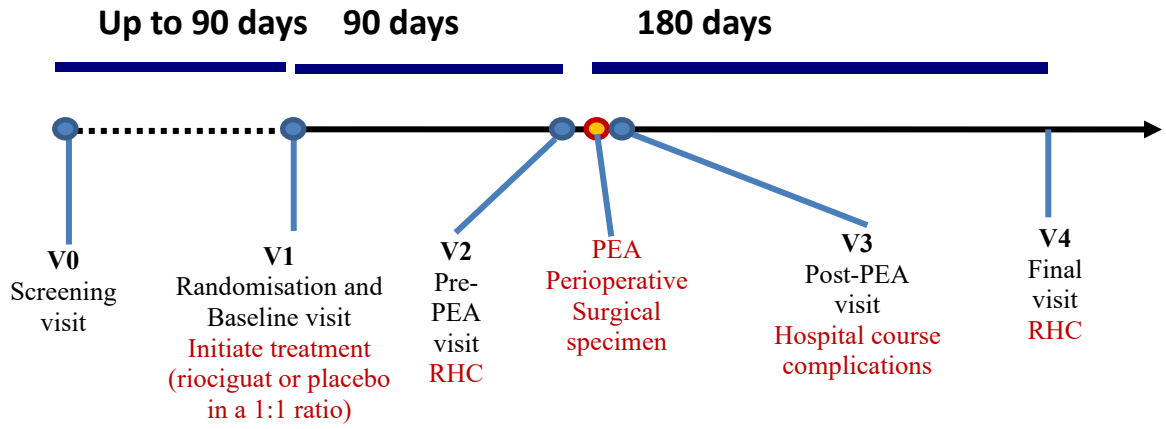
3. Investigational Plan

3.1. Overall Study Design and Plan

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 $dyn \cdot s \cdot cm^{-5}$). Eligible patients will be randomly assigned to riociguat or matching placebo 3 times a day (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 (systolic blood pressure [SBP]) up to a maximum dose of 2.5 mg tid based on the algorithm mentioned in Section 3.4. 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 (Appendix 13.1). The primary efficacy measure is the reduction in PVR. Additional efficacy measures include cardiac output, cardiac index, mean right atrial pressure (mRAP), mean pulmonary arterial pressure (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, 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 (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.

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

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

3.2.2. 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.
2. Composite clinical endpoints (6 months after PEA), including patients with any one of the following clinical endpoints, from randomisation to Visit 4.
    - All-cause death
    - PH-related hospitalisation
    - Need for PAH-targeted therapy
    - Functional class unchanged or worse
3. Perioperative findings at Visit 2:

- Circulatory arrest time
- Surgery-related complications (Appendix 13.3)

4. Surgical evaluation of specimen (difficulty to withdraw obstructive material):
   - Ease of dissection plane
   - Completeness of disease clearance
   - Clot and vessel wall
5. All-cause death
6. Withdrawal during randomised treatment phase

3.2.3. Exploratory Efficacy Endpoints

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 (mRAP) change from baseline at the preoperative visit (Visit 2) and at 6 months after PEA (Visit 4)
4. Mean pulmonary arterial pressure (mPAP) change from baseline at the preoperative visit (Visit 2) and at 6 months after PEA (Visit 4)
5. Pulmonary artery wedge pressure (PAWP) 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 from immediately after PEA to the 6-month visit (Visit 4)

3.2.4. 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.

3.3. Treatments

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.

Riociguat is a film-coated, round shaped with 6-mm diameter, immediate-release tablet of pale orange colour. Placebo tablets are identical in appearance to riociguat but do not have the active compound. 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

3.4. Dose Adjustment/Modifications

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 blood pressure (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.

4. General Statistical Considerations

- Data from all study centers will be combined for analysis.
- Statistical methods to be used will be mainly descriptive. Summary statistics will be tabulated and represented graphically, whenever appropriate.
- Continuous data will be summarised using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Besides presentation of absolute values, tabulation for differences to baseline by time will be provided, if appropriate. Categorical data will be summarised using the frequency counts and percentages. Time to event data will be analysed using the Kaplan-Meier method.

- For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999 it will be reported as ">0.999".
- When frequency counts are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. Percentages will be based on the total number of patients in the respective analysis set unless otherwise specified.
- Unless otherwise specified, statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% (2 sided) confidence intervals (CIs). Modelling techniques will be used in an exploratory sense. No adjustments for multiplicity are made.
- Partial dates will be imputed based on the rules specified in Appendix 13.4.
- All laboratory data will be reported by using the International System of Units.
- Unless otherwise specified, the baseline will be defined as the last valid assessment, including assessments from the unscheduled visit, prior to the study drug administration.
- A Visit 2 assessment is considered as valid only when the assessment is completed within 7 days prior to PEA. For assessments at Visit 4, the nominal visit collected in electronic case report form (eCRF) will be used in the analysis. This rule is applicable to all endpoints derived by the visit.
- By-patient listings will be created for each eCRF module for all screened patients. Patients will be identified in the listings by patient number. If data are to be summarised by visit, the visit name collected on the eCRF page will be used.
- All analyses will be conducted using SAS® software Version 9.3 or later (SAS Institute Inc, Cary, North Carolina).

4.1. 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.

4.2. Randomisation, Stratification, and Blinding

Following completion of the screening period, eligible study patients will be randomly assigned into the study. An interactive web response system (IWRS) will be used to administer the randomisation schedule. In order to obtain a treatment group assignment for a patient, a site representative will access the IWRS. Patients will be randomly assigned on Day 1 to receive

either riociguat or matching placebo tid in a 1:1 allocation ratio for 3 months. No stratification of the randomisation schedule will be performed.

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.

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.

4.3. Analysis Set

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

4.3.1. Intent-to-Treat (ITT) Set

The ITT set will consist of all patients who received at least one dosage of randomised study drug. All analyses using the ITT set will group patients according to randomised treatment.

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

4.3.2. PEA Set

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

The PEA set will be used in efficacy analyses with assessments depending on the implementation of PEA.

4.3.3. Per Protocol Set (PPS)

The PPS will consist of all ITT patients 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 (from patient history) and Visit 2, and undergo PEA as planned. All analyses using the PPS will group patients according to treatment actually received. A blind review of data will identify which patients will be included in the PPS.

The PPS will be used in the primary and secondary efficacy analyses as supportive analyses.

4.3.4. Safety Set

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

The safety set will be used in safety analyses.

4.4. Subgroups

Safety analyses (see Section 9.1) will be performed for the following subgroups for AEs occurring between V0 and V2:

- Intake of concomitant DOACs or NOACs being reported during V0 to V2
- Intake of concomitant vitamin K antagonists being reported during V0 to V2
- Intake of concomitant ß-blockers being reported during V0 to V2

5. Patient Disposition

5.1. Disposition

Patient disposition will be summarised by treatment group for the ITT set, unless otherwise specified.

The number and percentage of patients in each analysis set defined in Section 4.3 will be tabulated. The number and percentage of patients entered each scheduled visit will also be tabulated.

Patients who completed the study, patients who discontinued from the study and reasons of discontinuation will be tabulated using the frequency counts and percentages.

The reasons for patients not completing the study will be recorded on eCRF with the following categories: Adverse Event, Death, Lack of Efficacy, Lost to Follow-up, Non-Compliance with Study Drug, Physician Decision, Pregnancy, Progressive Disease, Protocol Violation, Recovery, Trial Screen Failure, Study Terminated by Sponsor, Technical Problem, Withdrawal by Subject, and Other.

Patient enrollment data and reasons for screen failure will be presented in a listing. Patient disposition data, including reasons for study discontinuation, will also be provided in a listing.

5.2. 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 approval of the Institutional Review Board/Ethics Committee (IRB/IEC). 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.

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.

Protocol deviations will be reviewed in a blind data review meeting before database lock and patients with relevant protocol deviation will be excluded from the PPS (defined in Section 4.3.3). A list of patients include in the PPS will be finalised and documented before database lock and the breaking of the study blind.

The number and percentage of patients with significant deviations will be summarised in a table for the ITT set. All protocol deviations will be presented in a listing.

6. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics will be summarised for the ITT set. Individual by-patient listings will be provided to support the summary tables.

6.1. Demographics

The continuous variables include age (years), body weight (kg), height (cm), and body mass index (BMI) (kg/m^2), and waist circumference (cm) will be summarised using descriptive statistics. The categorical variables include gender, race and ethnicity will be summarised using frequency counts and percentages.

BMI (kg/m^2) is calculated as body weight in kg / (height in $m)^2$.

6.2. Tobacco Usage

Patient's tobacco usage data will be presented in a listing.

6.3. Female Reproductive Status

The method of birth control used for women along with fertility status will be recorded at the screening visit and will be presented in a listing.

6.4. Medical History

6.4.1. General Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities® (MedDRA) Version 20.1 or higher. The number and percentage of patients with any medical history will be summarised by system organ class (SOC) and preferred term (PT) for each treatment group.

6.4.2. Disease-Specific History

The haemodynamic parameters at screening collected from the previous RHC will be summarised using descriptive statistics for following parameters:

- pulmonary vascular resistance (PVR, mmHg)
- mean right atrial pressure (mRAP, mmHg)
- mean pulmonary arterial pressure (mPAP, mmHg)
- cardiac output (L/min)
- cardiac index (L/min/m^2)
- pulmonary artery wedge pressure (PAWP, mmHg)

6.5. Inclusion and Exclusion Criteria

Patients will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

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. 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.

A prior medication is defined as any medication that is ended prior to the date of first dose of study drug. A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study drug. Imputation for partial medication start dates and stop dates can be found in Appendix 13.4. Medications with completely missing stop dates will be classified as concomitant.

Medications reported on the Concomitant medications eCRF page will be presented in data listings for prior medications and concomitant medications. Concomitant medications will be summarised by the following subgroups:

Intake of concomitant DOACs or NOACs being reported during V0 to V2: Yes/No;

Intake of concomitant vitamin K antagonists being reported during V0 to V2: Yes/No.

Intake of concomitant ß-blockers being reported during V0 to V2: Yes/No

7.2. Study Treatments

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 up to a maximum dose of 2.5 mg tid. Study treatment will be classified into two groups, riociguat and placebo, regardless of the dosing scheme. Study drug accountability (dispensed and returned) and administration will be presented in a listing.

7.2.1. Extent of Exposure

Treatment duration in days is defined as the total number of days a patient is exposed to the study drug:

- Treatment Duration (day) = Date of last dose - Date of first dose + 1.

Because study drug adjustment may occur during the treatment period, the exposure to study drug will also be characterized by average daily dose, which is defined as below:

- Average Daily Dose (mg/day) = Cumulative dose (mg) / Treatment duration (day)

The cumulative dose (mg) will be defined as the sum of doses taken by patients during the treatment period.

Descriptive statistics will be provided for treatment duration (day) and average daily dose (mg/day) by treatment group for the safety set and the PPS. The number and percentage of patients will also be summarised according to the maximum dose level (mg) received at the end of up-titration period.

By-patient listing will be provided to support the summary table.

7.2.2. Treatment Compliance

Patient compliance with study drug will be assessed by the investigator and/or study personnel at Visit 2 and during a telephone call using direct questioning and tablet counts. Deviations from the prescribed treatment regimen will be recorded on the source document and the patient's eCRF.

The overall treatment compliance (%) will be evaluated by calculating the number of tablets taken by the patient divided by the number of tablets expected to be used during the treatment period and multiplied by 100.

The number of tablets taken will be calculated by subtracting the number of tablets returned from the number of tablets dispensed. The number of tablets expected will be calculated by multiplying the total number of days of planned exposure to study drug (treatment duration) by the number of tablets planned per day (3 tablets per day).

The overall treatment compliance (%) will be summarised using descriptive statistics.

A patient is considered compliant if overall treatment compliance is greater than or equal to 80%. A categorical summary of whether patients were compliant (yes/no) will be present. The number and percentage of patients in compliance category of <80%, >=80 and <=120%, and >120% will also be presented.

By-patient listing will be provided to support the summary table.

8. Efficacy Analysis

The primary analysis will use ITT set, all analyses on perioperative endpoints will use PEA set only; all analyses on postoperative endpoints will use PEA set and PPS. For other endpoints, the analysis set to be used is specified in each subsection below. By-patient listings will be provided to support the summary tables.

8.1. Primary Efficacy Endpoint

As defined in Section 3.2.1, the primary efficacy endpoint is percent change from baseline in PVR immediately before PEA at Visit 2. 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.

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 primary efficacy analyses will be conducted using the ITT set. Similar analysis will be repeated for the PPS as the supportive analysis.

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.

Analysis of covariance (ANCOVA) with baseline value as the covariate will be employed to test the null hypothesis as a supportive analysis. Residuals for percent change form baseline in PVR will be generated by using PROC GLM procedure with baseline value as the covariate. A quantile-quantile (Q-Q) plot of residuals with p-value from Shapiro-Wilk test will be presented to test the normality of the residuals.

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.

The PVR will be measured at pre-PEA visit (Visit 2) and at the 6-month follow-up visit (Visit 4). Observed values, changes from baseline and percent change from baseline will be provided for PVR using descriptive statistics by treatment group and scheduled visit.

Boxplot will be used to present the percent change from baseline in PVR by treatment group and scheduled visit. The upper (lower) edge of the box represents the 75^{th} (25^{th}) percentile. A horizontal line in the box interior represents the median. Above the box a vertical line indicates the region from the 3rd quartile to the 95% percentile; below the box a vertical line indicates the region from the 1st quartile to the 5% percentile. Values outside the whiskers are displayed by a distinct marker.

8.2. Secondary Efficacy Endpoint

Secondary efficacy endpoints are defined in Section 3.2.2.

8.2.1. Pulmonary Vascular Resistance (PVR)

The difference in the percent change from baseline in PVR at Visit 4 between riociguat and placebo will be tested using the 2-sample Wilcoxon rank-sum test for the PEA set and the PPS.

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.

8.2.2. Composite Clinical Endpoints

Composite clinical endpoints from randomisation to Visit 4 will be tabulated by treatment group containing the number and percentage of patients with an event as well as the number of event for the PEA set and the PPS. 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.

Composite clinical endpoints include following clinical endpoints:

- 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.

8.2.3. Perioperative Findings

8.2.3.1. Circulatory Arrest Time

Circulatory arrest time (minute) at Visit 2 from perioperative findings will be tabulated by treatment group using the descriptive statistics for the PEA set. An analysis of variance (ANOVA) will be employed to compare the mean difference between 2 groups. P-value from Shapiro-Wilk test will also be presented in this table to indicate the normality of this variable. In case normality assumption cannot hold, the Wilcoxon rank-sum test should be considered.

8.2.3.2. Surgery-related Complications

Surgery-related complications at Visit 2 from the perioperative findings will be tabulated by treatment group in a descriptive way for the PEA set, presenting the number and percentage of patients for each symptom. The Fisher exact test will be utilised to test the proportion difference along with the Clopper-Pearson exact CI.

8.2.4. Surgical Evaluation of Specimen

Surgical evaluations of specimen, including ease of dissection, completeness of disease clearance, clot and vessel wall, are from perioperative measures (Visit 3).

Ease of dissection plane will be classed as easier than normal (1), normal (2), more difficult than normal (3); Completeness of disease clearance will be 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). The data will be treated as an ordinal response. A higher score means a worse case.

Surgical evaluations of specimen will be tabulated by treatment group for the PEA setcontaining 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.

8.2.5. All-cause Death

All-cause death on or after randomisation will be tabulated by treatment group containing the number and percentage of patients with event for the PEA set and the PPS. All-cause death

during the whole study course, include deaths occurred during the screening period, will be captured in safety analyses.

Time from randomisation to death (in days) will be analysed using the Kaplan Meier method. Median and quartiles in days and associated 95% CI will be calculated using the LOGLOG transformation. All patients who are withdrawn or lost to follow-up prior to the end of the study, or who are still alive at the end of the study will be censored at the time of last contact, defined as the last reported visit date.

8.2.6. Withdrawal during Randomised Treatment Phase

Withdrawal during the randomised treatment phase along with the reason for withdrawal will be tabulated by treatment group for the ITT set and the PPS containing the number and percentage of patients with event. Only withdrawals after randomisation but before PEA will be included.

8.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are defined in Section 3.2.3. No formal assessment of difference between treatment groups will be performed for any of the exploratory efficacy endpoints. The difference between treatment groups in exploratory efficacy endpoints will be estimated with 95% CIs to quantify the treatment effect.

Summary tables presenting observed values and changes from baseline for NT-proBNP measurement concentration (pg/mL), cardiac output (L/min), cardiac index (L/min/m^2), mRAP (mmHg), mPAP (mmHg), and PAWP (mmHg) will be provided for each treatment group by scheduled visits using descriptive statistics. The difference in the change from baseline between treatment groups with 95% CIs will be estimated non-parametrically using Hodges-Lehmann estimation of location shift in the tables. The analyses will be based on the PEA set and the PPS.

Hospital length of stay in days and ICU length of stay in days will be summarised using descriptive statistics. The difference between treatment groups with 95% CI will be estimated non-parametrically using Hodges-Lehmann estimation of location shift in the table. The analyses will be based on the PEA set.

Time from start of ICU stay to end of mechanical ventilation (in hours) will be analysed using the Kaplan Meier method. Median and quartiles in days and associated 95% CI will be calculated using the LOGLOG transformation. All patients stayed in ICU who do not have end date of mechanical ventilation will be censored at the time of discharged from the ICU. The analyses will be based on the PEA set.

Proportion of in-hospital mortality will be summarised using the frequency counts and percentages for the PEA set. Proportion difference between treatment groups along with the Clopper-Pearson exact CI will be provided

The proportion of patients who need PAH-targeted therapy immediately after PEA to Visit 4 will be summarised using the frequency counts and percentages for the PEA set and the PPS. Proportion difference between treatment groups along with the Clopper-Pearson exact CI will be provided.

WHO functional class will be summarised by scheduled visit for each treatment group. Shift table of baseline functional class versus functional class at each postbaseline scheduled visit will be provided. The analyses will be based on the PEA set and the PPS.

9. Safety Analysis

The purpose of this section is to define the safety analyses for the study. Safety assessments include adverse events, vital sign measurements, ECG measurements, physical examination, clinical laboratory examination, and pregnancy testing. Safety assessments will be performed at time points specified in Schedule of Events (Appendix 13.1). All summaries of safety data will be conducted using the safety set.

9.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Adverse events will be assessed from the time the patient signs the ICF until exit from the study. 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 defined as AEs and recorded appropriately. All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Adverse events will be coded using MedDRA (Version 20.1 or higher).

An overall summary of the number and percentage of patients having any treatment emergent adverse event (TEAE), serious TEAE, treatment-related TEAE, treatment-related serious TEAE, TEAE leading to permanent discontinuation of treatment, TEAE leading to study discontinuation, TEAE with outcome death, and TEAE of special interest will be provided by treatment group. All AEs will be listed including the investigator term, the preferred term, start and end dates of the AE, duration (days), severity, drug relationship, action taken, and outcome for all screened patients.

9.1.1. Incidence of Treatment Emergent Adverse Events

A treatment-emergent adverse event (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. If start date of an AE is missing after imputation, the corresponding AE will be included as TEAE if end date of AE is after the first dose of study drug or the end date is also missing. Imputation for partial AE start dates and end dates can be found in Appendix 13.4.

The number and percentage of patients with at least one TEAE will be summarised by MedDRA system organ class (SOC) and preferred term (PT). At each level of SOC or PT, a patient will be counted only once if the patient reported multiple events.

The above analysis will also be conducted for TEAEs occurred from V0 to V3 and by subgroups as defined in section 4.4.

9.1.2. Relationship of Adverse Events to Study Drug

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.

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 (definite) will be assumed and the AE will be considered to be drug related. TEAEs will be summarised by SOC, PT and relationship using the frequency counts and percentages.

The above analysis will also be conducted for TEAEs occurred from V0 to V3 for overall patients in the Safety set and by subgroups as defined in section 4.4.

9.1.3. Severity of Adverse Event

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.

In case the severity is unknown or missing, the worst case (severe) will be assumed in the summary tables. A summary of TEAEs by SOC, PT and severity will be performed using the worst severity grade.

The above analysis will also be conducted for TEAEs occurred from V0 to V3 for overall patients in the Safety set and by subgroups as defined in section 4.4.

9.1.4. Serious Adverse Events

A serious adverse event (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. The

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

The serious TEAEs, treatment-related serious TEAEs will be summarised by SOC and PT using the frequency counts and percentages. All serious AEs will be presented in a listing.

The above analysis will also be conducted for TEAEs occurred from V0 to V3 for overall patients in the Safety set and by subgroups as defined in section 4.4.

9.1.5. TEAEs Leading to Treatment Discontinuation/Study Discontinuation

TEAEs leading to permanent discontinuation of treatment and TEAEs leading to study discontinuation will be summarised by SOC and PT using the frequency counts and percentages respectively.

The above analysis will also be conducted for TEAEs occurred from V0 to V3 for overall patients in the Safety set and by subgroups as defined in section 4.4.

9.1.6. TEAEs Leading to Death

TEAEs with outcome death will be summarised by SOC and PT using the frequency counts and percentages.

All-cause of death during the whole study course will be presented in a listing.

The above analysis will also be conducted for TEAEs occurred from V0 to V3 for overall patients in the Safety set and by subgroups as defined in section 4.4.

9.1.7. TEAEs of Special Interest

The following TEAEs of special interest will be defined and included in summary tables by treatment group:

MedDRA coding

- “Myocardial infarction” and “Acute myocardial infarction” as preferred term;
- “Haemorrhage” will be assessed by using the standardised MedDRA query (SMQ);
- “Hypotension”, “haemoptysis”, “syncope” will be assessed as preferred term;
- “Stroke” will be assessed by using the preferred terms “haemorrhagic stroke”, “ischaemic stroke” and “embolic stroke”.

The TEAEs of special interest will be summarized by group: Myocardial infarction, Haemorrhage, Hypotension, Haemoptysis, Syncope, Stroke and also by study period V0 to V2, V0 to V4, medication of interest subgroup as defined in Section 4.4. The number of patients along with number of events in each level of summary will be provided.

9.2. Clinical Laboratory Evaluations

Laboratory assessments include clinical laboratory testing, pregnancy test, and hepatitis B virus, hepatitis A immunoglobulin M, hepatitis C antibody, and human immunodeficiency virus screen. 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.

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.

Pregnancy testing will be performed for all women of childbearing potential. Urine dipstick or serum pregnancy testing will be performed at Visit 0. Serum pregnancy testing will be performed for all other applicable visits.

Summary tables presenting observed values and changes from baseline over time will be presented for continuous laboratory parameters by treatment group. Categorical laboratory parameters will be summarised using the frequency counts and percentages.

All relevant laboratory parameters will be classified as Low, Normal, and High according to the normal ranges if applicable. Shift tables of baseline categories versus categories at each postbaseline scheduled visit and the worst postbaseline value will be provided. Worst postbaseline value is the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold. If a patient has a value below the threshold and above the threshold, the value furthest from the threshold will be chosen.

All laboratory data with normality status will be presented in a listing.

9.3. Vital Sign Measurements

Vital signs, including blood pressure (mmHg), heart rate (BEATS/MIN), respiration (BREATHS/MIN), and body temperature (°C) will be obtained with the patient in a supine or seated position after resting for approximately 5 minutes.

Observed values and changes from baseline will be provided for vital signs parameters using descriptive statistics by treatment group and scheduled visit.

All vital sign measurements will be presented in a listing.

9.4. Electrocardiogram

Twelve-lead ECGs will be performed to calculate the heart rate (HR, BEATS/MIN), PR Interval (msec), QRS Duration (msec), QT Interval (msec), and QT interval Fridericia correction (QTcF, msec). The ECGs will be obtained with the patient in supine position. All standard 12 lead ECGs will be recorded and analysed locally at the site by the investigator.

Observed values and changes from baseline will be provided for ECG parameters using descriptive statistics by treatment group and scheduled visit.

The proportion of patients with a clinically significant abnormal ECG result will be provided by treatment group and scheduled visit.

A summary of shifts in 12-lead ECG abnormalities from baseline will be provided by scheduled visits.

ECG results for all patients will be presented in a listing.

9.5. Physical Examination

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.

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

Physical examination results for all patients will be presented in a listing.

10. Interim Analysis

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

11. Changes in the Planned Analysis

The changes for the statistical analyses from the protocol to this SAP are stated below:

1. The analysis set to be used for perioperative endpoints (Circulatory Arrest Time, Surgery-related Complications, Surgical Evaluation of Specimen, PEA hospital length of stay, PEA ICU length of stay, Time on mechanical ventilation, In-hospital mortality) have been updated to PEA set only, with the consideration that these endpoints are peri-PEA surgery related endpoints and it makes more sense to narrow down the patients to those who have undergone PEA surgery only.

2. The analysis sets to be used for postoperative endpoints (Percent Change in PVR from baseline to Visit 4, Composite clinical endpoint from baseline to Visit 4, NT-proBNP, cardiac output , cardiac index, mRAP, mPAP, PAWP change from baseline to Visit 4, Functional class at Visit 4, All-cause death, Need for PAH-targeted postoperative therapy at Visit 4) have been updated to PEA set and PPS, with the consideration that the endpoints are post-PEA surgery endpoints, and it makes more sense to restrict the analysis to patients who undergone PEA surgery; PPS will be used since those per-protocol patients need to be considered as a complementary analysis set.

3. The analysis defined in the protocol “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.” Will be removed since it is confirmed by central labs that the data on ‘clinically significant/non-clinically significant” will not be obtained.

4. The observation period for composite endpoints as now defined in section 8.2.2 has been changed to ‘from randomisation to Visit 4’ instead of ’from PEA to Visit 4’ since it is of more interest to investigate the endpoints from randomization;

5. The exploratory endpoint ‘Need for PAH-targeted postoperative therapy at the 6-month visit (Visit 4)‘ in the protocol has been changed to ‘Need for PAH targeted postoperative therapy from immediately after PEA to Visit 4’ since it is of more interest to see if PAH targeted therapy occurs from PEA till Visit 4.

The surgical evaluation of specimen is from perioperative measurement (Visit 3), according to the new text of Appendix 1 in Protocol Amendment 1.

12. References

1. Investigator's Brochure V18.0 23Feb18, Section "5.4.2 Exposure Information".

13. Appendices

13.1. 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				

	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					
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 Protocol 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.

13.2. 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

13.3. Surgery-related complications

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)

13.4. Adverse Events/ Prior or Concomitant Medications Date Imputation

Incomplete Start Date:

Missing day and month

- If the year is the same as the first dose of study drug, then the date of the first dose of study drug will be assigned to the missing fields.
- If the year is before the year of first dose of study drug, then December 31 will be assigned to the missing fields.
- If the year is after the year of first dose of study drug, then January 1 will be assigned to the missing fields.

Missing day only

- If the year is the same as the year of the first dose of study drug
  - If the month is before the month of the first dose of study drug, then the last day of the month will be assigned to the missing day.
  - If the month is the same as the month of the first dose of study drug, then the day of the first dose of study drug will be assigned to the missing day.
  - If the month is after the month of the first dose of study drug, then "01" will be assigned to the missing day.
- If the year is before the year of the first dose of study drug, then the last day of the month will be assigned to the missing day.
- If the year is after the year of the first dose of study drug, then "01" will be assigned to the missing day.

If year is missing, start date will not be imputed. If the end date is complete, and the imputed start date is after the end date, the start date will be imputed by the end date.

Incomplete End Date:

Missing day and month

- December 31 will be assigned to the missing fields.

Missing day only

- The last day of the month will be assigned to the missing day.

If imputed end date is later than death date if available, the death date will be used as the imputed end date.