BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028831
Article Type:	Protocol
Date Submitted by the Author:	26-Dec-2018
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Keywords:	chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, riociguat

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Multicenter randomized comparative trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Rationale and design of the MR BPA study

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Acknowledgements: The study was funded by Bayer Yakuhin Ltd.

Keywords: Chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, riociguat

Abstract

Introduction: The management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) remains a clinical challenge. Medical treatment mainly involving pulmonary vasodilators (e.g. a soluble guanylate cyclase stimulator) is recommended for ameliorating their symptoms. More recently, balloon pulmonary angioplasty (BPA) has developed as alternative treatment modality for inoperable CTEPH. We aim to compare the efficacy and safety of BPA and riociguat, for the treatment of inoperable CTEPH.

Methods and Analysis: The study was designed as a multicenter randomized controlled trial for treatment of inoperable CTEPH. Subjects with inoperable CTEPH will be randomized (1:1) into either BPA or riociguat group, and observed for 12 months after treatment. The primary endpoint will be change in the mean pulmonary arterial pressure from baseline to 12 months. For the primary analysis, the least square mean difference in the change of pulmonary arterial pressure between BPA and riociguat group at 12 months and its 95% confidential interval will be estimated using an analysis of covariance (ANCOVA) model adjusted for allocation factors.

Ethics and Dissemination: This study was approved by the institutional review board of Keio University School of Medicine and each participating institution. Written informed consent will be obtained from all participants. Results of the study will be disseminated at medical conferences and journal publications.

Registration: This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (UMIN000019549).

Strengths and Limitations of the Study:

- This is the first randomized controlled trial to compare the efficacy and safety of BPA and riociguat in patients with inoperable CTEPH.
- This study evaluates the efficacy and safety of BPA and riociguat at 12 months after the start of the treatment, which is a relatively longer observation period than the usual RCTs.
- This is also the first study to compare the health insurance resource costs between BPA and riociguat.
- This study will be conducted at the expert BPA centers in Japan, and the CTEPH operability will be assessed by experienced PEA surgeon under blind circumstance.
- The limitation of this study is that this is open-label trial, and is expected to recruit a relatively small number of study subjects.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is an intractable disease in which an organized thrombus causes stenosis or occlusion of the pulmonary artery[1]. Unless early diagnosis and appropriate treatment are performed, which causes death due to right-sided heart failure[2]. Pulmonary endarterectomy (PEA) has been established as a method for operable CTEPH[3]. According to the AHA/ACC and ESC guidelines, PEA is recommended for patients with operable CTEPH as the first line therapy in class of recommendation I and level of evidence C[4-5]. However, riociguat as soluble guanylate cyclase stimulator is recommended for subjects with inoperable CTEPH[6-7], and is the first and only an approved medical treatment for inoperable CTEPH.

In 2014, a soluble guanylate cyclase stimulator (general name: riociguat), which is one of the pulmonary hypertension treatment agents, received insurance reimbursement approval for inoperable or persistent/recurrent CTEPH for the first time. This was based on the findings of a multicenter randomized clinical trial (CHEST-1)[6] and its extension study (CHEST-2)[7] indicating the efficacy of riociguat for subjects with inoperable CTEPH. Balloon pulmonary angioplasty (BPA), as catheter-based treatment, has also been reported to be effective for subjects with inoperable CTEPH[8-20].

As described above, the two main treatment options for inoperable CTEPH consist of riociguat or BPA. Although BPA is associated with a certain level of risk of complications such as procedure related pulmonary artery injury, it can provide marked improvement when the treatment finished. On the other hand, riociguat is the most effective pulmonary vasodilator and have low risk of serious adverse events. However, no reports have yet compared the treatment outcomes of these two treatment methods[8]. The present study was planned to compare the efficacy and safety of riociguat with BPA in the treatment of

inoperable CTEPH over the course of 12 months, to potentially aid in optimizing treatment selection and improving treatment outcomes.

Methods and Analysis

Study Design: The Multicenter Randomized controlled trial based on Balloon Pulmonary Angioplasty for chronic thromboembolic pulmonary hypertension (MR BPA) study will enroll subjects from January 15, 2016 to October, 31, 2019. The study is designed as a multicenter, prospective, randomized controlled trial. As shown in Figure 1, after acquiring consent, the subjects will undergo right heart catheterization and pulmonary angiography before provisional enrollment. An independent experienced PEA surgeon will determine if these subjects are eligible to undergo PEA under blind circumstance. Those who are judged to have inoperable CTEPH will be assigned into either BPA or riociguat group via an online assignment system and observed for 12 months. The observations will be made at screening, baseline, 0-4 months, 6 months, and 12 months. Table 1 shows the schedule of assessments performed at each visit for each treatment group, including mandatory and optional assessments.

Sample size calculation: Previously, BPA resulted in a reduction in mean pulmonary arterial pressure from 45.4±9.6 to 24.0±6.4 mm Hg in 24 months[9], while riociguat decreased the pulmonary arterial pressure by 4±7 mm Hg[7]. Based on these studies, the change in mean pulmonary arterial pressure from the start of treatment to 12 months later was assumed to be −15 mmHg for the BPA group and −4 mmHg for the riociguat group, and the standard deviation for each change was assumed to be 14 for the BPA group and 10 for the riociguat group. The minimum sample size required to achieve a significance of 0.05 for a two-sided test with a statistical power of 90% was determined to be 27 subjects for both groups,

indicating a total of 54 subjects. With the dropout rate estimated to be 10%, the planned enrollment was set at 30 subjects for each group, for a total of 60 subjects.

Eligibility criteria: *Inclusion criteria*: Patients meeting the following criteria will be included in the study: (a) patients who are diagnosed with CTEPH (based on the diagnostic criteria in the 2012 Japanese Circulation Society guidelines[21] with a WHO functional class II or III). (b) male and female aged ≥ 20 years and < 80 years. (c) patients with mean pulmonary arterial pressure of ≥25 mmHg to <60 mmHg and pulmonary artery wedge pressure of ≤15 mmHg. (d) patients who undergo appropriate anticoagulant therapy for at least three months prior to consent acquisition (if warfarin is used, prothrombin time-international normalized ratio should be 1.5 to 3.0). (e) patients who provide written consent form to participate in this study after full explanation of the study.

Exclusion criteria: Patients meeting any of the following exclusion criteria will be excluded from the trial: (a) patients with a history of BPA. (b) patients who underwent PEA within six months prior to consent acquisition. (c) patients who are using unapproved pharmaceutical products. (d) patients who used a pulmonary vasodilator within four weeks prior to the right heart catheterization after consent acquisition. (e) patients with co-existing etiology of pulmonary hypertension other than Group 4 in the Nice Pulmonary Hypertension Classification System. (f) patients who are pregnant or breastfeeding. (g) patients who met the contraindication for riociguat. (h) patients whose life expectancy is less than two years. (i) patients who are considered to be unsuitable for participation by investigators.

Recruitment and consent:

When subjects are determined to be able to participate in this study, the informed consent document is used to give them a sufficient explanation of this study and their written consent

is then obtained. When obtaining consent, it is also explained that data related to pulmonary angiography, right heart catheterization, and chest computed tomography (CT) scan from within three months prior to acquiring consent, as well as pulmonary ventilation-perfusion scintigraphy prior to acquiring consent, may be used for research purposes.

As a general rule, right heart catheterization and pulmonary angiography are performed after acquiring consent and investigators determine whether each subject can be definitively diagnosed with CTEPH. However, to reduce the burden on the subjects, data from within three months prior to consent acquisition for pulmonary angiography, right heart catheterization, and CT scan, as well as pulmonary ventilation-perfusion scintigraphy obtained in general practice prior to consent acquisition, can also be utilized.

Based on the imaging data of the subjects who give their consent, an independent experienced PEA surgeon who is not involved in this study will determine operability (whether the subjects are eligible to undergo PEA). The standards for this determination of operability will be based on the Guidelines for Treatment of Pulmonary Hypertension (2012 revised version)[21] and will be anatomically performed.

Random allocation: Random assignment will be performed centrally with stratification by mean pulmonary arterial pressure (<40 mmHg and ≥40 mmHg), and research institutions (Keio University, Okayama Medical Center, Kyusyu University, and Kobe University) by the minimization method with biased coin assignment.

Endpoints: Primary endpoint will be the change in mean pulmonary arterial pressure from baseline to 12 months. Secondary endpoints will include several clinical and quality of life parameters. These are detailed in Table 2.

Data collection: An electronic clinical testing data collection system, electric data capture system (EDC), will be used for data collection. In cases when the system is unavailable, a case report form, a specialized data collection form, will be used and the data later entered into the EDC. The investigators who will enter information into the EDC system will be responsible for ensuring accuracy and completeness of the information.

Data management and monitoring: The processes of data collection and management will be performed by third-party entities for data without bias. Data management in this study will be performed by Soiken Inc., Data Management Group (the Data Center). Data Center will prepare a "Procedure Manual for Data Management." The Data Center's approval is required prior to sending data related to the subjects in an electronic format. If transmitting data over an unsecured electronic network, the data must be encoded at the source. Linkable anonymization with central registration number will be used to identify the subjects. The investigators will be responsible for appropriately storing the correspondence table prepared by them to identify subjects in accordance with the procedures at the research institution. This correspondence table must be retained for up to five years after the completion of the study or three years after the final publication of the study, whichever comes later. For displaying and publicly disclosing all information related to the study, appropriate measures will be taken, such as encoding or deletion, to ensure that the subjects cannot be identified in accordance with applicable laws and regulations.

In this study, the Soiken Inc., Data Management Group will perform monitoring to manage and ensure quality. The monitoring manager will monitor the subjects in accordance with the manual on the monitoring procedure. For data quality management, the principal investigator and Central Committee will confirm the progress of the study, as necessary, through the Soiken Inc., Data Management Group to ensure that the study is being conducted in accordance with the protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014;

Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare).

Adverse events: Occurrence of any untoward medical events experienced by subjects, including the worsening of a pre-existing underlying disease or a complication, will be defined as adverse events. However, the worsening of efficacy evaluation indices will not be defined as an adverse event. Any concomitant symptoms or clinically significant abnormal fluctuations in test results will be investigated to determine whether there is a cause-and-effect relationship with BPA or riociguat and findings will be documented in the EDC system. As a general rule, adverse events will be followed up until normalization or recovery occurs to a level at which it is not considered to be an adverse event or in case of an irreversible adverse event (cerebral infarction, myocardial infarction etc.), until symptoms stabilize or no longer change.

Statistical Analysis:

The analyses of the primary and secondary efficacy endpoints will be performed using the full analysis set, which will include all patients who underwent randomization and received at least one dose of a study drug and had at least one assessment after baseline. Safety analysis will be conducted in the safety analysis population.

For the baseline variables, summary statistics will be constructed using frequencies and proportions for categorical data, and means and standard deviations for continuous variables. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact test for categorical endpoints, and Student's t-test for continuous variables, as appropriate.

For the primary analysis, the least square mean difference in the change of pulmonary arterial pressure between groups at 12 months and its 95% confidential interval will be

estimated using an analysis of covariance (ANCOVA) model adjusted for allocation factors. The secondary analysis will be performed in the same manner as the primary analysis. Adverse events will be evaluated during the safety analysis. The frequencies of adverse events will be compared using Fisher's exact test. All comparisons are planned, and all *p*-values will be two sided. *P*-values <0.05 will be considered statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The statistical analysis plan will be developed by the principal investigator and the biostatistician before completion of patient recruitment and data fixation.

Discussion

Early diagnosis and appropriate treatment for CTEPH are essential to prevent death due to right-sided heart failure. Riociguat as a pulmonary vasodilator is recommended for treatment of inoperable CTEPH[1]. As a result, riociguat is now covered by the Japanese health insurance system. The two main treatment options for inoperable CTEPH consist of riociguat or BPA, a form of catheter-based treatment. The present study was therefore planned to compare the efficacy and safety of riociguat with BPA in the treatment of inoperable CTEPH. This study will also compare healthcare costs for each of the therapies. Results from such a randomized trial will be important for optimizing the treatment selection and improving treatment outcomes.

Ethics and Dissemination: This study was approved by the institutional review board of Keio University School of Medicine and each participating institution and will be conducted in accordance with the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labor and Welfare in Japan, and other current legal regulations in Japan. Written informed consent will be obtained

from all participants after a full explanation of this study. Results of the study will be disseminated at medical conferences and journal publications.

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Author's Contributions:

TK and HM equally contributed in this study. TK and HM contributed to the conception and design of the study, drafted the protocol, and supervised the revision. MK, KA, SK, YS and TS provided intellectual input into improving the study design and revising the protocol. KF contributed to and supervised the conception and design of the study. All authors read and approved the final manuscript.

Funding statement:

This study was financially supported by Bayer Yakuhin, Ltd.

Competing interests statement:

SK has received honoraria for scientific lectures from Bayer Yakuhin, Ltd. KF has received scholarship grants from Bayer Yakuhin, Ltd. and MSD K.K. The other authors declare no conflict of interest.

Figure and Table Legends

Figure 1. Study outline and randomization schematic. After consent, and CTEPH diagnosis is confirmed, subjects will be randomized into either BPA or riociguat group for 12 months, and observation measurements taken at screening, baseline, 0-4, 6 and 12 months.

Table 1. Schedule of assessments for subjects enrolled into the study.

Table 2. Secondary endpoints that will be measured and/or compared at baseline and at 12 months.

Table 1: Schedule of assessments for subjects enrolled into the study.

Observation items	Screening	Baseline	observation period		
	~0M	0M	0~4M	6M+1M	12M+2M
Subjects' attributes	○	○	—	—	—
6-minute walk distance	—	○	—	○	○
Borg dyspnea index	—	○	—	○	○
WHO functional class	—	○	—	○	○
Right heart catheterization	○	—	—	○	○
Pulmonary angiography	○	—	—	—	—
Pulmonary function testing	—	○	—	○	○
Blood gas test[a]		○	—	○	○
Vital signs[a]		○	—	○	○
Echocardiography (cardiac ultrasound)	—	○	—	○	○
Chest X-ray		○	○[b]	○	○
Chest CT scan	○	—	○[b]	○	○
Oxygen therapy usage status	—	○	—	○	○
Adverse event onset [c]	—	—	←	○	→
Clinical worsening and time to clinical	—	—	←	○	→

worsening (TTCW) [c]							
Quality of Life parameters (EQ5D)	—	○	—		○		○
Health insurance	—	—		←	○	→	
BPA status[d]	—	—	○		—		—
Medication adherence[e]	—	—		←	○	→	

(a) Recommended to be implemented during right heart catheterization

(b) Required if BPA is performed

(c) Onset of adverse events and indices related to clinical worsening will be observed, as necessary, throughout the clinical study period

(d) Observation items for Group A (BPA group)

(e) Observation items for Group B (riociguat group)

Table 2: Secondary endpoints that will be studied and or compared at baseline and at 12 months.

Endpoint	
Change in 6-minute walk distance	
Change in Borg dyspnea index	
Change in hemodynamic variables	Includes pulmonary vascular resistance, mean right arterial pressure, cardiac output etc.
Change in WHO functional class	
Change in plasma brain natriuretic peptide levels	
Change in SaO_2 and PaO_2	
Change in usage volume of oxygen therapy	Includes commencing oxygen therapy due to the exacerbation of a primary disease or dosage change.
Change in pulmonary function test	
Change in echocardiography test parameter	
Frequency and severity of pulmonary artery injury	Assessed by chest X-ray and chest CT scan.
Frequency of Adverse Events	Bloody sputum/hemoptysis/pulmonary hemorrhage (vascular perforation, vascular dissection, vascular rupture, etc.), pneumothorax, hypotension, pulmonary congestion/pulmonary edema, late-onset lung disturbance, heart failure, pneumonia, headache, dizziness, peripheral edema, nausea/vomiting,

	retching, diarrhea, nasopharyngitis, upper respiratory inflammation, respiratory distress, coughing, fainting.
Clinical worsening during the observation period and time to clinical worsening	All-cause mortality, heart/lung transplant, salvage PEA due to worsening of primary disease, new or repeated implementation of BPA due to the worsening of a primary disease, hospitalization, new initiation of pulmonary vasodilators, worsening of 30% or greater from baseline in the 6-minute walk distance, persistent worsening in the WHO functional class from baseline due to the worsening of a primary disease.
Change in Quality of Life parameters (EQ5D)	
Health insurance resource costs	

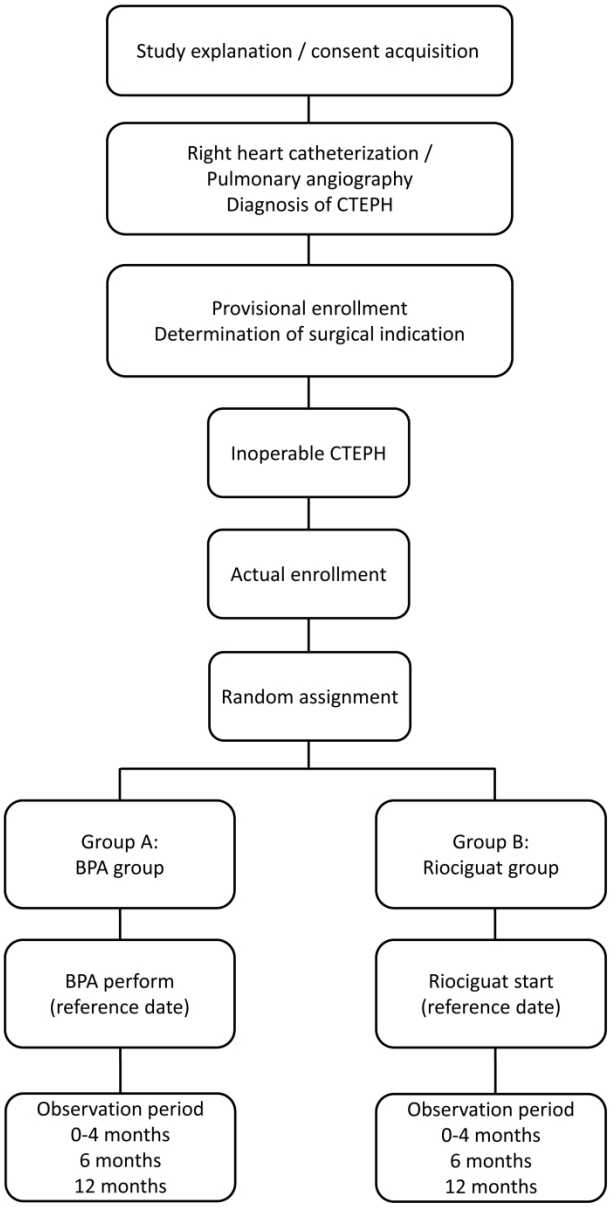

Figure 1. Study outline and randomization schematic. After consent, and CTEPH diagnosis is confirmed, subjects will be randomized into either BPA or riociguat group for 12 months, and observation measurements taken at screening, baseline, 0-4, 6 and 12 months.

Multicenter Randomized controlled trial based on Balloon Pulmonary Angioplasty for chronic thromboembolic pulmonary hypertension（MR BPA study）

Protocol

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Study execution period: January 2016–March 2021

Ver. 1.0 created: June 16, 2015
Ver. 2.0 created: November 17, 2015
Ver. 2.1 created: January 4, 2016
Ver. 3.0 created: March 25, 2016
Ver. 4.0 created: September 23, 2016
Ver. 5.0 created: October 16, 2017

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1. PROTOCOL OUTLINE AND SCHEMATIC

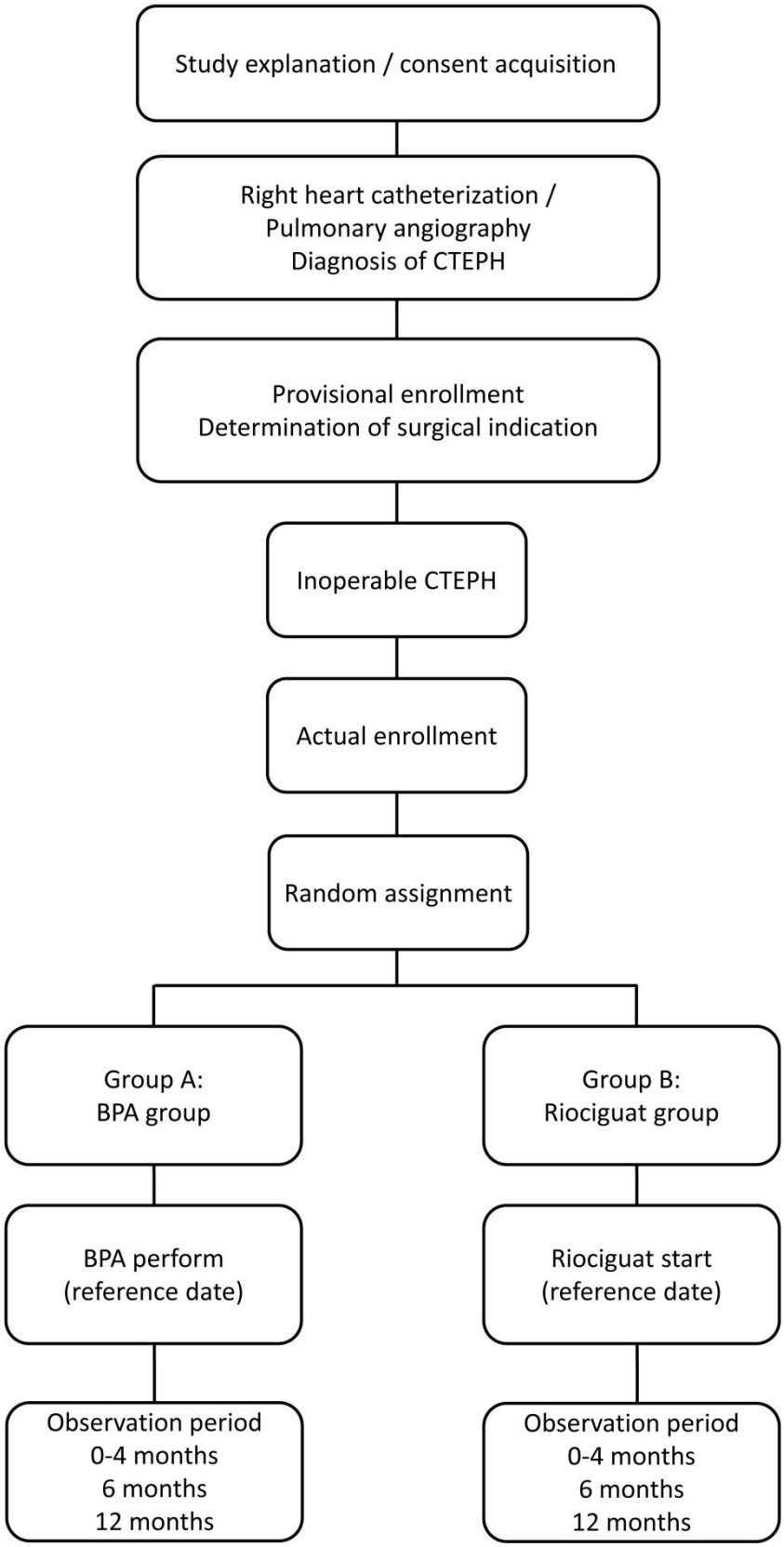
1.1. Protocol Outline

Title	Multicenter Randomized controlled trial based on Balloon Pulmonary Angioplasty for chronic thromboembolic pulmonary hypertension (MR BPA study)
Purpose	To compare the efficacy and safety of riociguat with balloon pulmonary angioplasty (BPA) in the treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) over the course of 12 months, to potentially aid in optimizing treatment selection and improving treatment outcomes
Study Design	Multicenter, prospective, randomized, controlled, open-label, two-arm, trial Subjects with inoperable CTEPH will be randomized (1:1) into either BPA (group A) or riociguat (group B), and observed for 12 months after treatment.
Inclusion Criteria	Patients meeting the following criteria will be included in the study. (a) patients who are diagnosed with CTEPH (based on the diagnostic criteria in the 2012 Japanese Circulation Society guidelines with a WHO functional class II or III). (b) male and female aged ≥ 20 years and < 80 years. (c) patients with mean pulmonary arterial pressure of ≥25 mmHg to <60 mmHg and pulmonary artery wedge pressure of ≤15 mmHg. (d) patients who undergo appropriate anticoagulant therapy for at least three months prior to consent acquisition (if warfarin is used, prothrombin time-international normalized ratio should be 1.5 to 3.0). (e) patients who provide written consent form to participate in this study after full explanation of the study.
Exclusion Criteria	Patients meeting any of the following exclusion criteria will be excluded from the trial. (a) patients with a history of BPA. (b) patients who underwent PEA within six months prior to consent acquisition.

	(c) patients who are using unapproved pharmaceutical products. (d) patients who used a pulmonary vasodilator within four weeks prior to the right heart catheterization after consent acquisition. (e) patients with co-existing etiology of pulmonary hypertension other than Group 4 in the Nice Pulmonary Hypertension Classification System. (f) patients who are pregnant or breastfeeding. (g) patients who met the contraindication for riociguat. (h) patients whose life expectancy is less than two years. (i) patients who are considered to be unsuitable for participation by investigators.
Primary Endpoint	Change in the mean pulmonary arterial pressure from baseline to 12 months
Secondary Endpoints	① Changes in the six-minute walk distance from baseline to 12 months ② Changes in the Borg dyspnea index from baseline to 12 months ③ Changes in hemodynamic variables, including pulmonary vascular resistance (PVR), mean right arterial pressure, and cardiac output] from baseline to 12 months ④ Changes in the WHO functional class ⑤ Changes in plasma brain natriuretic peptide (BNP) levels from baseline to 12 months ⑥ Changes in arterial oxygen saturation (SaO_2) and oxygen partial pressure (PaO_2) from baseline to 12 months ⑦ Changes in the usage volume of oxygen therapy from baseline to 12 months, including commencing oxygen therapy due to the exacerbation of a primary disease or dosage change. ⑧ Changes in pulmonary function test parameters from baseline to 12 months ⑨ Changes in echocardiography test parameters from baseline to 12 months ⑩ Frequency and severity of pulmonary artery injury

	assessed by chest X-ray and chest computed tomography (CT) scan ⑪ Frequency of adverse events ⑫ Clinical worsening during the observation period and time to clinical worsening (TTCW) ⑬ Change in Quality of Life (QOL) parameters (EQ5D) from baseline to 12 months ⑭ Health insurance resource costs over 12 months
Study execution period and observation points	Enrollment period: January 15, 2016, to October 31, 2019 (45 months) Study period: January 15, 2016, to March 31, 2021* (62 months) Observation period: 12 months (+2 months) Observation measurement: Screening, baseline, 0 to 4 months, 6 months (+1 month), 12 months (+2 months) (five observation measurements in total) *A period of five months is provided after the completion of subject observation to allow for the preparation of statistical and analytical data
Planned Enrollment of Subjects	Inoperable CTEPH: 60 subjects

1.2. Schematic



2. DEFINITIONS OF TERMS

Term	Definition
Subjects	Individuals who participate in the study (includes those who were asked to participate)
Responsible investigators	Physicians who are engaged in implementing the study and preside over duties related to this study at their affiliated research institution
Investigators	Attending physicians, the responsible investigators, and other people related to study implementation
Research institution	Medical institution at which the study is implemented. Exclude institution that receive a consignment to engage in part of the duties related to the study (Soiken Inc.)
Collaborating research institution	Refers to research institutions at which the study is jointly conducted in accordance with the protocol; includes institutions at which specimens and data are newly obtained from subjects for the study and then provided to other research institutions
Intervention	Actions that limit the presence or extent of factors that affect various health-related phenomena for research purposes
Institutional Review Board	Refers to a council body established to examine whether a study can be implemented or continued or other necessary matters related to the study from ethical and scientific viewpoints
Linkable anonymizing	A method of anonymization in which a correspondence table of symbols or numbers newly added to each individual's data is stored so that subjects can be identified if necessary
BPA	Balloon Pulmonary Angioplasty
BNP	Brain Natriuretic Peptide
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CRF	Case Report Form: a specialized data collection form for this study
EDC	Electric Data Capture System: an electronic clinical testing data collection system
EQ5D	EuroQol 5 Dimension: a comprehensive evaluation scale composed of five items; it was developed to measure health-related Quality of Life (QOL)
Inoperable	Not eligible for surgery

Operable	Eligible for surgery
PEA	Pulmonary Endarterectomy
QOL	Quality of Life
SDV	Source Data Verification: direct viewing of source materials
SAE	Serious Adverse Event: includes unexpected SAEs. In this study, any kind of SAE requires emergency reporting (Chapter 12.5).

3. STUDY BACKGROUND AND SIGNIFICANCE

Chronic thromboembolic pulmonary hypertension (CTEPH) is an intractable disease in which an organized thrombus causes stenosis or occlusion of the pulmonary artery. Unless early diagnosis and appropriate treatment are performed, which causes death due to right-sided heart failure. Pulmonary endarterectomy (PEA) has been established as a method for operable CTEPH. According to the AHA/ACC and ESC guidelines, PEA is recommended for patients with operable CTEPH as the first line therapy in class of recommendation I and level of evidence C. However, riociguat as soluble guanylate cyclase stimulator is recommended for subjects with inoperable CTEPH, and is the first and only an approved medical treatment for inoperable CTEPH.

In 2014, a soluble guanylate cyclase stimulator (general name: riociguat), which is one of the pulmonary hypertension treatment agents, received insurance reimbursement approval for inoperable CTEPH for the first time; this was based on the findings of a multicenter randomized clinical trial (CHEST-1) indicating the efficacy of riociguat for subjects with inoperable CTEPH[1)]. Balloon pulmonary angioplasty (BPA), as a catheter-based treatment, has also been reported to be effective for subjects with inoperable CTEPH[2)- 8)].

As described above, the two main treatment options for inoperable CTEPH consist of riociguat and BPA. Although BPA is associated with a certain level of risk of complications such as procedure related pulmonary artery injury, it can provide marked improvement when the treatment finished. On the other hand, riociguat is the most effective pulmonary vasodilator and have low risk of serious adverse events (SAEs). However, no reports have yet compared the treatment outcomes of these two methods[8)].

We planned the present study to compare the efficacy and safety of riociguat with BPA in the treatment of inoperable CTEPH over the course of 12 months, to potentially aid in optimizing treatment selection and improving treatment outcomes.

4. STUDY PURPOSE

To compare the efficacy and safety of riociguat with BPA in the treatment of inoperable CTEPH over the course of 12 months, to potentially aid in optimizing treatment selection and improving treatment outcomes

5. STUDY DESIGN AND PLANNED ENROLLMENT OF SUBJECTS

5.1. Study Design

This will be a multicenter, prospective, randomized, controlled, open-label, two-arm, trial.

Subjects with inoperable CTEPH will be randomized (1:1) into either BPA (group A) or riociguat (group B), and observed for 12 months after treatment.

5.2. Planned Enrollment of Subjects

The enrollment of 60 subjects with inoperable CTEPH (30 subjects × 2 groups) is planned.

Group A: BPA group (30 subjects)

Group B: Riociguat group (30 subjects)

*The rationale for the sample size is as described in "16. PLANNED ENROLLMENT OF SUBJECTS AND RATIONALE."

6. STUDY AGENT

General name: Riociguat

Brand name: Adempas® tablets (0.5 mg, 1.0 mg, and 2.5 mg) (riociguat tablets)

Manufactured and sold by: Bayer Yakuhin, Ltd.

BREEZE TOWER 2-4-9, Umeda, Kita-ku, Osaka 530-0001

Contraindications*:

⑴ Those with a history of hypersensitivity to an ingredient in this drug

⑵ Women who are or may be pregnant

⑶ Those with severe hepatic dysfunction (Child-Pugh class C)

⑷ Those with severe renal dysfunction (creatinine clearance below 15 mL/min) or subjects receiving dialysis

⑸ Those being administered a nitric acid agent or nitrogen monoxide (NO) donor (nitroglycerin, amyl nitrite, isosorbide dinitrate, nicorandil, etc.)

⑹ Those being administered a phosphodiesterase (PDE) type 5 inhibitor

⑺ Those being administered an azole-based antifungal agent (e.g., itraconazole and voriconazole) or an HIV protease inhibitor (e.g., ritonavir, lopinavir/ritonavir, indinavir, atazanavir, and saquinavir)

*Package insert revised in February 2015 (2nd version)

7. STUDY SUBJECTS

This study will investigate the advanced methods of treatment of CTEPH subjects. Due to the small number of CTEPH subjects being treated in Japan, care is taken to encourage the enrollment of as many subjects as possible. However, in consideration of subject safety, high-risk subjects are excluded. In addition, to more thoroughly examine subject eligibility requirements for treatment strategies, the judgment of a third party (physician to determine operability) is incorporated.

7.1. Inclusion Criteria

Patients meeting the following criteria will be included in the study.

(a) patients who are diagnosed with CTEPH (based on the diagnostic criteria in the 2012 Japanese Circulation Society guidelines with a WHO functional class II or III).

(b) male and female aged ≥ 20 years and < 80 years.

(c) patients with mean pulmonary arterial pressure of ≥25 mmHg to <60 mmHg and pulmonary artery wedge pressure of ≤15 mmHg.

(d) patients who undergo appropriate anticoagulant therapy for at least three months prior to consent acquisition (if warfarin is used, prothrombin time-international normalized ratio should be 1.5 to 3.0).

(e) patients who provide written consent form to participate in this study after full explanation of the study.

7.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria will be excluded from the trial.

(a) patients with a history of BPA.

(b) patients who underwent PEA within six months prior to consent acquisition.

(c) patients who are using unapproved pharmaceutical products.

(d) patients who used a pulmonary vasodilator within four weeks prior to the right heart catheterization after consent acquisition.
(e) patients with co-existing etiology of pulmonary hypertension other than Group 4 in the Nice Pulmonary Hypertension Classification System.
(f) patients who are pregnant or breastfeeding.
(g) patients who met the contraindication for riociguat.
(h) patients whose life expectancy is less than two years.
(i) patients who are considered to be unsuitable for participation by investigators.

8. ENDPOINTS

8.1. Primary Endpoint

Change in the mean pulmonary arterial pressure from baseline to 12 months later

8.2. Secondary Endpoints

① Changes in the six-minute walk distance (6MWD) from baseline to 12 months
② Changes in the Borg dyspnea index from baseline to 12 months
③ Changes in hemodynamic variables, including pulmonary vascular resistance (PVR), mean right arterial pressure, and cardiac output] from baseline to 12 months
④ Changes in the WHO functional class
⑤ Changes in plasma brain natriuretic peptide (BNP) levels from baseline to 12 months
⑥ Changes in arterial oxygen saturation (SaO_2) and oxygen partial pressure (PaO_2) from baseline to 12 months
⑦ Changes in the usage volume of oxygen therapy from baseline to 12 months, including commencing oxygen therapy due to the exacerbation of an primary disease or dosage change
⑧ Changes in pulmonary function test parameters from baseline to after 12 months
⑨ Changes in echocardiography test parameters from baseline to after 12 months
⑩ Frequency and severity of pulmonary artery injury assessed by chest X-ray and chest computed tomography (CT) scan
⑪ Frequency of adverse events
Bloody sputum/hemoptysis/pulmonary hemorrhage (vascular perforation, vascular dissection, vascular rupture, etc.), pneumothorax, hypotension,

pulmonary congestion/pulmonary edema, late-onset lung disturbance, heart failure, pneumonia, headache, dizziness, peripheral edema, nausea/vomiting, retching, diarrhea, nasopharyngitis, upper respiratory inflammation, respiratory distress, coughing, fainting, etc.

⑫ Clinical worsening during the observation period and time to clinical worsening (TTCW)

⑫-1 The following events are considered to indicate clinical worsening and are calculated as TTCW.

⑬ -2 Each clinical worsening item should be entered into the electric data capture system (EDC) only at initial onset.

⑫-3 As a general rule, follow-up observations should be continued.

List of TTCW events:

- All-cause mortality
- Heart-lung transplantation
- Salvage PEA due to the worsening of a primary disease
- New or repeated implementation of BPA due to the worsening of a primary disease*

  *Repeated implementation refers to performing BPA again (or additionally) on a subject in the BPA group due to worsening of a primary disease four months after the reference date or after all BPA sessions have been completed.
- Hospitalization due to the worsening of a primary disease
- New initiation of pulmonary vasodilators due to the worsening of a primary disease

(e.g., soluble guanylate cyclase stimulator, endothelin receptor antagonist, PDE type 5 inhibitor, and prostaglandin I_2)

- Worsening of 30% or greater from baseline in the 6MWD due to a primary disease
- Persistent worsening in the WHO functional class from baseline due to the worsening of a primary disease*

  *For subjects whose condition worsened as shown below according to the WHO functional class, as a general rule, confirm this a second time 14 days later (interview by telephone allowed) and check that the worsening is persistent.

  - Class II to class III
  - Class II to class IV

- Class III to class IV

⑭ Change in Quality of Life (QOL) parameters (EQ5D) from baseline to 12 months

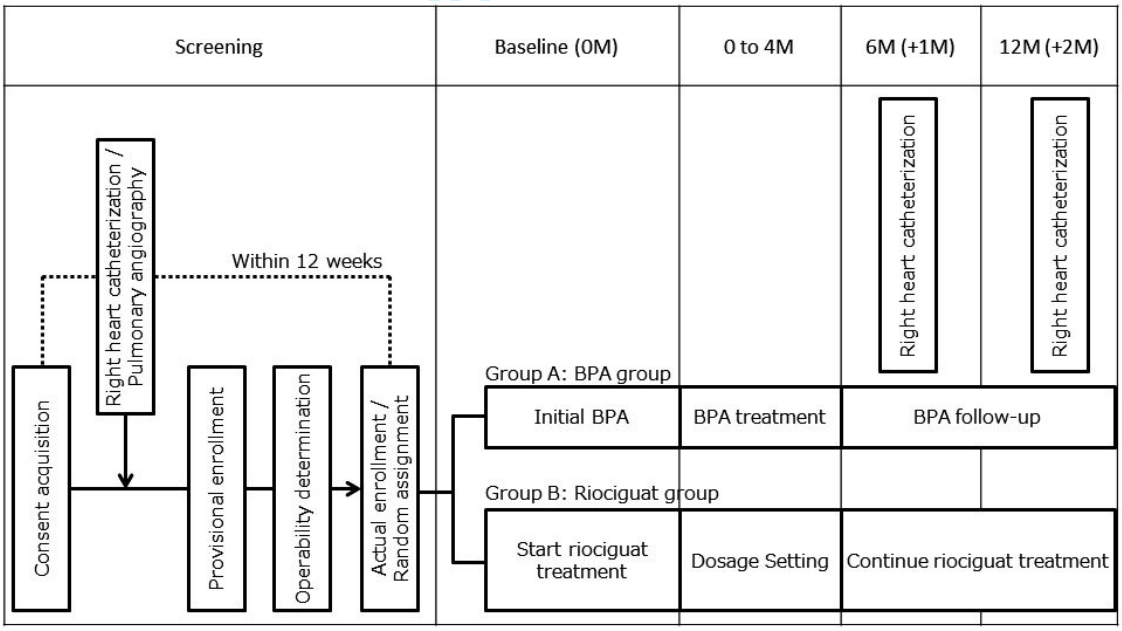
⑮ Health insurance resource costs over 12 months

9. STUDY METHODS

9.1. Study Outline

After acquiring consent, the subjects will undergo right heart catheterization and pulmonary angiography before provisional enrollment. An independent experienced PEA surgeon will determine if these subjects are eligible to undergo PEA under blind circumstance. Those who are judged to have inoperable CTEPH will be assigned into group A (BPA group) or group B (riociguat group) via an online assignment system, and observed for 12 months (Figure 1).

Figure 1: Study outline



9.2. Study Execution Period

Enrollment period: January 15, 2016, to October 31, 2019 (45 months)

Study period: January 15, 2016, to March 31, 2021* (62 months)

Observation period: 12 months (+2 months)

Observation measurement: Screening, baseline, 0 to 4 months, 6 months (+1 month), 12 months (+2 months) (five observation measurements in total)

*A period of five months is provided after the completion of subject observation to allow for the preparation of statistical and analytical data.

9.3. Study Reference Dates

Following actual enrollment, the initial BPA implementation date will be the study reference date (observation point base calculation date) for group A (BPA group) and the riociguat administration start date will be the study reference date for group B (riociguat group).

9.4. Prohibited Concomitant Drugs

The following drugs may not be used during the observation period. However, if any of the following drugs are initiated during the observation period, the drug name, directions, and dosage should be input into the EDC and follow-up observation should be performed as much as possible. If a pulmonary vasodilator is used due to the worsening of a primary disease, calculate this as TTCW.

1. Pulmonary vasodilators
   Soluble guanylate cyclase stimulator, endothelin receptor antagonist, PDE type 5 inhibitor, and prostaglandin I_2

2. Others

- Nitric acid agent or nitrogen monoxide donor (nitroglycerin, isosorbide dinitrate, etc.)
- PDE type 5 inhibitors (sildenafil, vardenafil, tadalafil, etc.)
- Azole-based antifungal agents (itraconazole, voriconazole, etc.)
- HIV protease inhibitor (ritonavir, indinavir, atazanavir, saquinavir, etc.)

10. STUDY PROCEDURES

10.1. Acquisition of Consent

When subjects are determined able to participate in this study, the informed consent document is used to give them a sufficient explanation of this study and their written consent is then obtained. When obtaining consent, it is also explained that data related to pulmonary angiography, right heart catheterization, and chest CT scan from within three months prior to acquiring consent, as well as pulmonary ventilation-perfusion scintigraphy prior to acquiring consent, may be

used for research purposes. See “20.2 Informed Consent” for details on the methods of acquiring consent.

10.2. Screening, Provisional Enrollment

As a general rule, right heart catheterization and pulmonary angiography are performed after acquiring consent and investigators determine whether each subject can be definitively diagnosed with CTEPH. However, to reduce the burden on the subjects, data from within three months prior to consent acquisition for pulmonary angiography, right heart catheterization, and chest CT scan, as well as pulmonary ventilation-perfusion scintigraphy obtained in general practice prior to consent acquisition, can also be utilized. This information will be included on the informed consent document. Then, the subjects diagnosed with CTEPH are provisionally enrolled in the EDC after determining their eligibility based on the inclusion and exclusion criteria. During this assessment process, the subjects are assigned a number (central registration number) to identify them.

10.3. Determination of Operability

Based on the imaging data of the subjects who give their consent, an independent experienced PEA surgeon who is not involved in this study (physician to determine operability) will determine operability (whether the subjects are eligible to undergo PEA). The standards for this determination of operability will be based on the Guidelines for Treatment of Pulmonary Hypertension (2012 revised version) and will be anatomically performed.

The physician to determine operability in this study must meet one of the following criteria:

- Has performed PEA on more than 20 subjects per year in the year before starting to determine the eligibility of subjects in this study to undergo surgery
- Has performed PEA on over 40 subjects in the three years prior to starting to determine the eligibility of subjects in this study to undergo surgery

The determination of operability will be based on the above guidelines, as well as on the technical feasibility of surgery, taking the following into account:

- Ability to surgically reach the organized thrombus

- Conformity of a surgically reachable vascular occlusion site and PVR

The above guidelines should be used to determine whether the subject is operable or inoperable based on pulmonary angiography imaging test results.

See the next section for specific procedures.

Procedures for Determining Operability

① The investigators will submit the subjects' imaging data, attributes, and right heart catheterization data to the Data Center. Linkable anonymization with central registration number will be used to identify the subjects.

② The Data Center confirms the receipt of imaging data and forwards it to the surgeon to determine operability.

③ The surgeon determines operability based on subjects' imaging data, attributes, and right heart catheterization data sent from the Data Center in accordance with the Guidelines for Treatment of Pulmonary Hypertension (2012 revised version). In addition, the surgeon takes into account the two considerations previously described (whether the organized thrombus causes stenosis or occlusion of the pulmonary artery)

Based on these factors, a determination is made on subject suitability to undergo surgery (determination of operability). The surgeon determining operability will then promptly report the results to the Data Center. The data used for determination are as follows:

(Data to be submitted)

・Subjects' attributes

・Pulmonary angiography

・Right heart catheterization

・Chest CT scan

*If possible, the following data will also be submitted:

- Pulmonary ventilation-perfusion scintigraphy

10.4. Actual Enrollment and Allocation

① The Data Center will receive the results of the determination from the surgeon determining operability and will then officially enroll subjects using an online system in accordance with these results.

1) Subjects determined to have inoperable CTEPH will be enrolled and allocated into groups A or B.

② The Data Center will report the results of operability determinations and allocation to study groups (actual enrollment) to the investigators.

As a general rule, the period until actual enrollment will be within 12 weeks after obtaining informed consent.

10.5. Treatment and Observation

The investigators will perform the following treatment in accordance with the allocation results and begin observation:

① Treatment

Group A: BPA group

- BPA is performed after allocation to this group (initial date of implementation will be the reference date).
- Based on preoperative right heart catheterization and pulmonary angiography, the degree of pulmonary hypertension severity is assessed and the pulmonary lesion is morphologically evaluated. Diuretics are used to regulate a high right atrial pressure. When the pulse cardiac output is low, measures are taken, such as administering dobutamine, prior to surgery. When performing BPA, a long sheath will be inserted into the main trunk of the pulmonary artery using a 0.014-inch guidewire. The first choice is the right internal jugular vein approach; however, depending on the state of the internal jugular vein, the femoral vein approach may be considered by the surgeon. Diagnostic imaging devices (e.g., intravascular ultrasound or optical coherence tomography) may be used to confirm lesion shape, range, blood vessel diameter, etc. Depending on the lesion type, the pulmonary blood vessel is expanded with a balloon catheter. After BPA, a Swan-Ganz catheter is placed, if necessary, and chest CT and X-ray scan must be taken within 24 h after treatment to confirm the presence/absence and extent of postoperative lung impairment. Sequential images will be taken with the slice thickness set at 2 mm or below.
- As a general rule, BPA will be completed within four months of the reference date.

Group B: Riociguat group

- After allocation to this group, riociguat treatment will be initiated (the initial administration day will be the reference date).

- Riociguat will be initially administered three times per day at 1.0 mg per dose. Using systolic blood pressure (95 mmHg or higher) as a guide, the dose will be increased by 0.5 mg for each subject every two weeks with a thrice-daily administration of 2.5 mg/dose set as the maximum dosage. Dosage adjustment, including the maintenance dosage, is based on the judgment of the responsible investigators and investigators. Dosage adjustment will be completed within four months of the reference date.

② Observation

- The observation period is 12 months (+2 months). A total of five observations are made at five points: 1) screening, 2) baseline, 3) 0 to 4 months, 4) 6 months (+1 month), and 5) 12 months (+2 months). One month is considered to be 30 days.
- In group B, if the study agent is discontinued or treatment with another pulmonary vasodilator is started, the investigators should report this by inputting the date and reason for discontinuation into the EDC system. However, for the purpose of safety analysis, the observation will be continued for as long as possible.

11. OBSERVATION ITEMS AND SCHEDULE

11.1. Observation Items

①Common items

1) Subject attributes

Age, sex, height, BMI, weight, primary disease, medical history, complications, risk factors (Associated Medical Conditions), right heart catheterization after consent acquisition, information regarding drug usage (e.g., pulmonary vasodilators, anticoagulants, etc. used in the past), reason for the determination of operability/inoperability, and history of CTEPH treatment.

2) 6MWD

*Arterial oxygen saturation and pulse rate are measured. If oxygen inhalation is performed during the test, the oxygen inhalation volume will be measured.

3) Borg dyspnea index

4) WHO functional class

5) Right heart catheterization

Thermodilution is recommended. The Fick method is also allowed (performed

under room temperature and in the dorsal position).

- Right atrial pressure (mean), pulmonary arterial pressure (mean systolic and diastolic phase), pulmonary artery wedge pressure (mean), cardiac output, heart rate, cardiac index, PVR, mixed venous oxygen saturation, and hemoglobin level

6) Pulmonary angiography

7) Pulmonary ventilation-perfusion scintigraphy (optional)

8) Pulmonary function tests

VC、%VC、FVC、%FVC、FEV1、%FEV 1 、FEV1%、RV、%RV、TLC、%TLC、DLCO、% DLCO、DLCO/VA、%DLCO/VA、VA、%VA、Peak flow、MMF、%MMF、V75、%V75、V50、%V50、V25、%V25、V50/V25

9) Echocardiography (cardiac ultrasound)

10) Blood tests (recommended to be performed during right heart catheterization, performed under room temperature in the dorsal position)

Plasma BNP, Cr, CCr, eGFR, SaO_2, pH, PaO_2, $PaCO_2$, HCO_3^-, BE, A-aDO_2

11) Measuring vital signs (recommended prior to performing right heart catheterization under room temperature and in the dorsal position), blood pressure, and pulse rates

12) Chest X-ray (CXR) scan *Must be measured after BPA.

13) Chest CT (CT) scan *Must be measured after BPA.

14) Oxygen therapy usage status

Oxygen inhalation volume during resting and exertion is expressed as mean oxygen inhalation volume.

*If there is worsening of the primary disease resulting in the initiation of oxygen therapy or a change in the oxygen dosage, this should be reported as an adverse event.

*If SpO_2 is ≥95% or higher during resting or ≥90% during exertion and at night, this will be used as the basis for increasing or decreasing oxygen dosage.

15) Occurrence of adverse events

16) Clinical worsening during the observational period and TTCW

17) QOL parameters (EQ5D)

18) Health insurance expenses

The starting points for subjects' health insurance expenses (medical costs) will be (a) the first day when BPA is performed (hospitalization day if hospitalized for initial treatment) in the BPA group and(b) riociguat administration start date in the riociguat group. Data will be collected for 12 months from the start point.

② Group A: Observation items only in the BPA group

・Whether BPA was performed at months 0–4

③ Group B: Observation items only in the riociguat group

・Adherence to the study agent.

Confirm whether the subjects are taking the study agent at each observation point during the observational period via interviews conducted by the investigators.

11.2. Observation Schedule (one month is defined as 30 days).

Observation items	Screening	Baseline	Follow-up		
	~0M	0 M	0~4M	6M +1M	12M +2M
Subjects' attributes	○	○	—	—	—
6MWD	—	○	—	○	○
Borg dyspnea index	—	○	—	○	○
WHO functional class	—	○	—	○	○
Right heart catheterization	○	—	—	○	○
Pulmonary angiography	○	—	—	—	—
Pulmonary function testing	—	○	—	○	○
Blood tests(1)	○		—	○	○
Vital signs(1)	○		—	○	○
Echocardiography (cardiac ultrasound)	—	○	—	○	○
Chest X-ray	○		○(2)	○	○
Chest CT scan	○	—	○(2)	○	○
Pulmonary ventilation-perfusion scintigraphy	△	—	—	—	—
Oxygen therapy usage status	—	○	—	○	○
Adverse event onset (3)	—	—	← ○ →		
Clinical worsening and TTCW (3)	—	—	← ○ →		
QOL parameters (EQ5D)	—	○	—	○	○
Health insurance resource costs	—	—	← ○ →		
BPA implementation status(4)	—	—	○	—	—
Subjects' medication adherence(5)	—	—	← ○ →		

○・・・Required △・・・Optional

(1) Recommended to be implemented during right heart catheterization

(2) Required if BPA is performed

(3) Onset of adverse events and indices related to clinical worsening will be observed, as necessary, throughout the clinical study period

(4) Observation items for Group A (BPA group)

(5) Observation items for Group B (riociguat group)

12. ADVERSE EVENTS

12.1. Handling of Adverse Events

During the study period, the occurrence of any untoward medical events experienced by subjects, including the worsening of a pre-existing underlying disease, will be defined as adverse events. If complications worsen after starting the study, this will also be defined as an adverse event. However, the worsening of efficacy evaluation indices will not be treated as an adverse event.

If any concomitant symptoms or clinically significant abnormal fluctuations in test results are observed, a subject's disease condition, medical history, concomitant medications, and temporal relationship between medication and onset will be investigated. The investigators at each medical facility will subsequently determine whether there is a cause-and-effect relationship with BPA or riociguat and findings will be documented into the EDC system.

12.2. Response to Adverse Events

If a subject experiences an adverse event during the study period, the investigators will immediately take the appropriate medical action. In accordance with the procedures of each participating research institution, they will also generate a report to the responsible investigator and the head of the institution and enter the necessary information into the subject's medical record and the EDC system.

12.3. Recording of Adverse Events and Follow-up

If an adverse event occurs, in accordance with the classifications described below in section 12.3.1, symptoms or the clinical condition; objective findings; day of onset; extent and severity; whether medical treatment was provided and, if so, what treatment; outcome that was determined and day this was determined; and the relationship of adverse events to this study as well as the reasons for the occurrence of the adverse event should be entered into the subject's medical record and the EDC system. As a general rule, adverse events will be followed up until normalization or recovery occurs to a level at which it is not considered to be an adverse event or if damage (cerebral infarction, myocardial infarction etc.) causes an irreversible adverse event until symptoms stabilize or no longer change.

However, this is not required if the responsible investigator or investigator determines that there has been recovery or if it has been determined that there is no clear cause-and-effect relationship. The reasons for this determination will be entered into the EDC system.

12.3.1 Classification of Adverse Events

① Mild: Does not disrupt the activities of daily living of subjects
② Moderate: Impairs subjects' activities of daily living, but they can still engage in these activities if they endure a significant amount of discomfort.
③ Severe: Greatly impedes subjects' activities of daily living

12.3.2 Classification of Concomitant Symptoms

① Mild: Subjects can continue to participate with no treatment
② Moderate: Subject participation can be continued if some form of treatment is administered
③ Severe: Subject participation is or should be terminated

12.3.3 Cause-and-Effect Relationship with BPA or Riociguat

The cause-and-effect relationship will be determined based on the following criteria: assessing a subject's clinical condition, temporal relationship with treatment, and other potential associations. Adverse events which were judged to be (1) or (3) will be considered to be "adverse events in which a relationship with BPA or riociguat cannot be denied." Those judged as (2) will be considered to be "adverse events for which a relationship with this study can be denied."

① Related, ② Unrelated, and ③ Unknown

12.3.4 Classification of Outcomes

① Recovery: Normalization or recovery to a level at which it is no longer considered to be an adverse event
② Improvement: Not normalized, but symptoms have improved
③ Recovery (with after effects): Recovery, but residual dysfunction that impairs activities of daily living
④ Non-recovery: Not recovered at this point
⑤ Unknown: Outcome is unknown as subjects have stopped visiting the hospital
⑥ Death

12.3.5 Other Classifications

- Status of riociguat (1: continuation, 2: discontinuation)
- Repeat BPA (1: yes, 2: no)
- Were appropriate actions required? (1: yes, 2: no)

12.4. SAEs and Unexpected SAEs

Regardless of the cause-and-effect relationship with the clinical study drug, this section pertains to undesirable or unintended signs, symptoms and disorders that occur in subjects, as well as SAEs that meet the criteria described in "Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare; Chapter 1, Part 2)." Among SAEs, those that are not described in the clinical study protocol, drug agent package insert, or pharmaceutical interview form or those that are documented but for which properties or severity differs from the documentation will be treated as "unexpected SAEs."

Regardless of the cause-and-effect relationship with BPA or riociguat, if an SAE or unexpected SAE occurs during the study period, the investigators or responsible investigators will immediately offer appropriate treatment to the subject.

[SAEs]

1) SAEs resulting in death
2) Life-threatening SAEs
3) SAEs requiring hospitalization or extended hospitalization for treatment
4) SAEs causing permanent or marked impairment/dysfunction
5) SAEs causing a congenital anomaly in the offspring

12.5. Reporting (Immediate Reporting) of and Response to SAEs

- If an adverse event (SAE or unexpected SAE) requiring immediate reporting occurs during the study period, regardless of the cause-and-effect relationship with BPA or riociguat, the investigators must take necessary measures in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare)" and established procedures at the research institution: providing an explanation to the subjects and reporting the matter to the appropriate head of the institution with authority or to the Institutional Review Board. If this was an unexpected

SAE in which a cause-and-effect relationship with BPA or riociguat cannot be denied, it must be promptly reported to the Minister for Health, Labour and Welfare in accordance with procedure at the research institution

- Within 24 h of learning about an adverse event, investigators must report this to the Research Support Center. The Research Support Center will immediately gather relevant information and submit a report to the principal investigator and Safety Monitoring Committee. Similarly, the Research Support Center will report this to the responsible investigators at the collaborating research institutions.
- The principal investigator will consult with the Central Committee and the Safety Monitoring Committee and determine whether to continue the study or make any changes to the protocol. This will be reported to the collaborating research institutions, and necessary measures will immediately be taken. Moreover, if the principal investigator considers the event to be highly urgent, the principal investigator will take necessary measures without waiting for an evaluation by the Central Committee or the Safety Monitoring Committee.

12.6. Provision of New Information to Study Subjects

If investigators become aware of new information related to this clinical study, the investigators will provide follow-up explanations to subjects and, if necessary, revise the informed consent document/consent form.

13. TERMINATING SUBJECT PARTICIPATION OR DROPOUT

If, for the reasons listed below, the investigators determine that a subject can no longer continue to participate in the study, necessary measures such as discontinuing administration of the study drug will be immediately taken. Data on the subject will be handled as data of a “study termination case.” The date, time point in the study, reason for termination, and the subject’s course of the disease will be entered into the EDC system. Necessary tests will also be performed upon termination. The efficacy and safety of the subject`s treatment will be evaluated at this point. Moreover, even if the subject’s participation is terminated, excluding cases in which a request is made to withdraw informed consent, items to be evaluated will be followed up as much as possible for the purpose of analyzing safety. If informed consent was withdrawn, no data on the subject, including data that has already been collected, except for data related to study termination, such as the termination date or reason, will be used for analysis.

If it becomes difficult to follow-up subjects, their data will be treated as a “dropout case.”
Subjects who use contraindicated drugs will be handled as “study termination cases,” although follow-up observations will be continued.

① If the subject or their legal representative declines to participate in the study or requests the withdrawal of consent
② If the investigators determine that continuing the study would harm the health of the subject
③ If riociguat needs to be discontinued for some reason or administration is banned
④ If pregnancy is detected or breastfeeding has started
⑤ If the study itself is discontinued
⑥ If, for any reason, the investigators consider it appropriate to terminate study participation

14. DATA MANAGEMENT

14.1. Data Management

The processes of data collection and management will be performed by third-party entities for data without bias. Data management in this study will be performed by Soiken Inc., Data Management Group (Data Center). Before performing data management, the Data Center will prepare a “Procedure Manual for Data Management.”
Linkable anonymization with central number registration will be used to identify the subjects. The investigators will be responsible for appropriately storing the correspondence table prepared by them to identify subjects in accordance with the procedures at the research institution. This correspondence table must be retained for up to five years after the completion of the study or three years after the final publication of the study, whichever comes later.
For displaying and publicly disclosing all information related to the study, appropriate measures will be taken, such as encoding or deletion, to ensure that the subjects cannot be identified in accordance with applicable laws and regulations.
The Data Center’s approval is required prior to sending data related to the subjects in an electronic format. If transmitting data over an unsecured electronic

network, the data must be encoded at the source.

14.2. Handling of Data for the Determination of Operability

The investigators will store data necessary for determining the operability of the subjects on paper and electronic media (such as CD-R disks) without including any personal information and present it to the Data Center. The Data Center will save a backup of the data and present it to the surgeon determining operability. Feedback will be given to the investigators via the Data Center on whether the subject is suitable for undergoing surgery.

14.3. Handling of Subject Data

In this study, the EDC system will be used to collect clinical data. The clinical data for each subject will be accurately entered into the EDC system in accordance with the protocol of the investigators at the research institutions. The investigators who will enter required information for the study into the EDC system will be responsible for ensuring accuracy and completeness of the information.

If data that have already been submitted require revision, a “Fixed Data Change Request” or query is generated. When accessing the EDC system, each investigator must have a login ID and password.

Moreover, when direct input into the EDC system is difficult for reasons such as the IT environment of the EDC system at the research institution, a case report form (CRF) should be used. In this case, the CRF should also be submitted by the investigators to the Data Center.

The CT, CXR, and echocardiography data submitted to the Data Center for storage from each research institution should not contain personal information of the subject. The Data Center then forwards the data to the Core Laboratory.

14.4. Handling of EQ5D (QOL) Data

As a general rule, the QOL scores assessing the psychological state of the subjects are directly mailed by the subjects to the Data Center using a specialized QOL questionnaire (EQ5D). If subjects find it difficult to mail the questionnaire, the investigators will collect sealed questionnaires, which prevent the responses of the subjects from being seen, for submission to the Data Center. The Data Center enters the data into the EDC system and database for storage.

14.5. Creation of Data Sets

The Data Center will store all data collected for this study in an independent database. The Data Center will convert the data to fixed data in accordance with the standards determined by the Data Handling Committee before data fixation. The following three data sets will be created prior to analysis:

① Creation of the full analysis set (FAS) for analysis
② Creation of the per protocol set (PPS) for analysis
③ Creation of the Safety Evaluation Analysis data set

15. MONITORING

15.1. Monitoring

In this study, the Soiken Inc., Data Management Group will perform monitoring to manage and ensure quality. The monitoring manager will monitor the subjects in accordance with the manual on the monitoring procedure. For data quality management, the principal investigator and Central Committee will confirm the progress of the study, as necessary, through the Soiken Inc., Data Management Group to ensure that the study is being conducted in accordance with the protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare). Appropriate measures will be taken to prevent any deviation from the protocol and from regulatory and human subject guidelines. The monitoring manager will regularly generate monitoring reports for submission to the Central Committee.

The collaborating research institutions will manage and maintain the following information to respond to the requests form the monitoring in this study or the Institutional Review Board.

⑴ Source documents for EDC creation or CRF entry

*Medical records, nursing records, test data, medication records, etc.

⑵ Informed consent records showing that the subject consented to participate in this study

15.2. Source Document Verification (SDV)

When necessary, the monitoring manager will directly view records related to the study for SDV and confirm that the study is being appropriately implemented as

well as the reliability of the data. Head and responsible investigator in research institutions and collaborating research institutions will ensure that the direct viewing of records related to the study can be done in response to requests from the monitoring manager. The person performing SDV must do so under the following conditions: 1) permission has been received for this study from the head of the research institution and approval has been obtained from the Institutional Review Board and 2) SDV is conducted in accordance with procedure of the research site after confirming that appropriate consent has been received from the subjects.

16. PLANNED ENROLLMENT OF SUBJECTS AND RATIONALE

16.1. Planned Enrollment of Subjects

Total of 60 inoperable CTEPH subjects

Group A: BPA group: 30 subjects

Group B: Riociguat group: 30 subjects

16.2. Rationale for Planned Enrollment of Subjects

Previously, BPA resulted in a reduction in mean pulmonary arterial pressure from 45.4±9.6 to 24.0±6.4 mm Hg in 24 months[3)], while riociguat decreased the pulmonary arterial pressure by 4±7 mm Hg[1)]. Based on these studies, the change in mean pulmonary arterial pressure from the start of treatment to 12 months later was assumed to be −15 mmHg in the BPA group and −4 mmHg in the riociguat group, and the standard deviation for each change was assumed to be 14 for the BPA group and 10 for the riociguat group. The minimum sample size required to achieve a significance of 0.05 for a two-sided test with a statistical power at 90% is determined to be 27 subjects for both groups, indicating a total of 54 subjects. With the dropout rate estimated to be 10%, the planned enrollment was set at 30 subjects for both groups, for a total of 60 subjects.

17. STATISTICAL ANALYSIS

17.1. Allocation Factor

In aligning important subject background attributes between the two groups, the mean pulmonary arterial pressure and research institution will be used as allocation factors. Random assignment will be performed centrally with

stratification by mean pulmonary arterial pressure (<40 mmHg and ≥40 mmHg) and research institutions (Keio University, Okayama Medical Center, Kyusyu University, and Kobe University) by the minimization method with biased coin assignment.

17.2. General Approach for Analysis

The analyses of the primary and secondary efficacy endpoints will be performed using the full analysis set, which will include all patients who underwent randomization and received at least one dose of a study drug and had at least one assessment after baseline. Safety analysis will be conducted in the safety analysis population. All p-values will be two sided. P-values <0.05 will be considered statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The statistical analysis plan will be developed by the principal investigator and the biostatistician before completion of patient recruitment and data fixation.

17.3. Subject Background Analysis

Subject background data distribution and summary statistics will be calculated for both groups. The frequency distribution and proportion of nominal variables will be shown for both groups. The summary statistics (number of subjects, mean value, standard deviation, minimum value, median value, and maximum value) of the continuous variables will be calculated per group. For the comparison between the groups, Fisher's exact test will be used for nominal variables to determine whether the proportions for one variable are different among those of the other variable. For continuous variables, Student's *t*-test will be used.

17.4. Primary Endpoint Analysis

The primary endpoint for efficacy will be the change in the mean pulmonary arterial pressure from the baseline to 12 months. Comparisons will be made between the two groups. Comparisons will be made by testing the null hypothesis that the change will be equal in both groups. Using analysis of covariance with both groups as the fixed effect and the allocation adjustment factor (mean pulmonary arterial pressure before starting the study and the research institute) as the covariance, the null hypothesis that the degree of change in the mean pulmonary arterial pressure is identical between the two groups will be tested. The summary statistics of the change after 12 months (number of subjects, mean

value, standard deviation, minimum value, median value, and maximum value) will also be calculated.

For sensitivity analysis, changes in the mean pulmonary arterial pressure over time in both groups will be presented. With an unstructured correlation structure, chronologically measured data will be analyzed using the mixed effects model for repeated measures. In this case, the fixed-effect factors consist of treatment effects, effect timing, and correlation between treatment and timing. The random-effect factors are subjects who were nested with the group effect. However, if the correlation structure is unstructured and the calculation results cannot be converged, composite symmetry will be used.

17.5. Secondary Endpoint Analysis

For each secondary endpoint, the measurement values, change, and summary statistics (number of subjects, mean value, standard deviation, minimum value, median value, and maximum value) will be calculated at each measurement point and compared between the two groups. The chi-square test or Fisher's exact test will be used for nominal values and Student's *t*-test or Wilcoxon sum rank test will be used for continuous variables. In terms of safety, lists of all adverse events will be made for both groups. If necessary, inter-group comparisons will be conducted using Fisher's exact test. Lists will also be made of clinical worsening seen during the observation period in the two groups. If necessary, K-M plots will be prepared for each instance of clinical worsening, and inter-group comparisons will be performed using the log-rank test. The hazard ratio will be estimated with Cox regression.

17.6. Interim Analysis

No interim analysis will be conducted in this study.

18. PROTOCOL APPROVAL, STUDY INITIATION, AND PROTOCOL CHANGES

18.1. Protocol Approval

In preparing the protocol for this clinical study, a rough draft will be created by the Central Committee. During this process, members of the committee must agree to the aims of this study and prepare the protocol so that the study can be

smoothly executed. Following this step, a medical statistician and the Central Committee will examine the protocol. Once it has been approved by the principal investigator, the document will be considered as the official protocol. This protocol will be followed when conducting this study after receiving approval from the Institutional Review Board of the research institution (medical facility) to which the principal investigator belongs. See "18.3 Protocol Changes" regarding any changes to be made to the protocol after approval has been received.

Even at a collaborating research institution, the protocol, as well as other necessary materials, must be approved by the head and the Institutional Review Board of the collaborating research institution prior to participating in the study

When approval has been received from the Institutional Review Board of the collaborating research institution, a copy of the approval document will be sent to the Research Support Center for storage. Annual updates of the screening and approval by the Institutional Review Board regarding the protocol of this study will be conducted in accordance with the regulations at each research institution.

18.2. Study Initiation

This study will be initiated with the permission of the head of each research institution after approval has been received from the Institutional Review Board.

18.3. Protocol Changes

If necessary, the principal investigator will determine whether changes to the protocol are required.

If a change to the protocol is necessary, the principal investigator will amend* or revise** the protocol after discussion with the Central Committee. After amendment/revision, a report will be promptly made to the responsible investigators in the collaborating research institutions so that appropriate steps to implement this change can be initiated at the collaborating research institutions.

*A change to an item that could increase the risk to subjects or is related to the primary endpoint

**A change to an item that will not increase the risk to subjects and will not affect the primary endpoint

If a change is made to the protocol after the study is initiated, the Research Support Center will inform the collaborating research institutions of this change. If any major changes are made to the protocol, the clinical study may not be

restarted at the collaborating research institutions until approval has been received from the head and Institutional Review Board or an equivalent committee or organization of the collaborating research institution.

19. STUDY CLOSURE AND PREMATURE TERMINATION

19.1. Study Closure

Once this study has been completed, the principal investigator will report on the closure of the study to the responsible investigators at each collaborating research institution. The responsible investigators will then report on the closure of the study to the head and Institutional Review Board of the collaborating research institution.

19.2. Premature Study Termination

1) If the principal investigator determines that it is difficult to continue the study for an unavoidable reason, such as one of the reasons shown below, a discussion will be held with the Central Committee to decide whether the study can be continued. If a decision is made that it would be inappropriate to continue with the study, the principal investigator will communicate the premature termination, reasons, and how to respond to the needs of the subjects as quickly as possible to the responsible investigators in all collaborating research institutions and implement any necessary measures.

① If serious information related to the quality, safety, or efficacy of the study drug or medical material involved in the study is received

② If there is difficulty in recruiting subjects and achieving the enrollment target number is difficult

③ If the purpose of the study is achieved before reaching the planned enrollment number or the end of the planned study period

④ If a directive such as a change to the protocol is received and it is determined to be difficult to accept this change

⑤ If an event occurs that is judged to markedly detract from the appropriateness of implementing the study or the reliability of the study results

2) If the responsible investigators in the collaborating research institutions report this in writing to the head of the collaborating research institution or Institutional Review Board and the study is swiftly terminated prematurely,

appropriate measures, such as contacting the subjects, will be taken.

20. HUMAN RIGHTS AND INFORMED CONSENT OF SUBJECTS

20.1. Protection of Subjects and Rules Requiring Observance

All subjects involved in this study must obey the WMA Declaration of Helsinki (revised in 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare) as well as all applicable laws and regulations.

20.2. Informed Consent

When participating in this study, the investigators must offer explanations regarding the objectives of the study using informed consent document and consent form approved by the Institutional Review Board and obtain written consent based on sufficient subject understanding. If it is difficult to obtain informed consent from the subjects, they cannot be enrolled in the study as consent cannot be obtained via a proxy. To prevent potential subjects from being subjected to any disadvantages, the following points will be included in the informed consent document: (1) that participation in this study is based on their free will, (2) that consent can be withdrawn after it is provided, and (3) that care will be taken to prevent subjects from suffering any disadvantages as a result of discontinuing their participation. This should prevent any limitations from being placed on the subjects' rights to self-determination in choosing medical treatment. As this study will not exceed the range of normal medical treatment, this will not be mentioned on the form; however, if special instructions are received from the Institutional Review Board or medical facility director regarding the methodology or details of obtaining informed consent from the subjects, this limitation is not applicable.

The investigator who provides the explanation to a potential subject will create two copies of the consent forms with their signature or name, date, and seal. One copy will be given to the subject, while an original copy will be kept with the subject's medical records at the research institution. The consent forms will be appropriately stored at the research institution for five years after the study has been completed or three years after the final publication of this study, whichever comes later.

If a subject chooses to revoke his/her consent during the study, all existing data provided by the subject for this study will be destroyed.

Items recorded on the informed consent document:

① The study title and language that states that implementation has been approved by the head of the research institution
② The research institution title and responsible investigator's name
③ The study purpose and significance
④ The study methods including the purpose of obtaining specimens and information from the subjects and the study schedule
⑤ Reasons the subject is being selected
⑥ Period of study participation, the points that subjects must adhere to during the study, and cautionary notes
⑦ Burden and predicted risks and benefits for the subjects
⑧ That consent can be revoked by the subject at any time even after consenting to study participation or continuation (if there are situations in which it is difficult to execute the measures in accordance with the revocation of consent, these situations and reasons should be described)
⑨ No disadvantages will be suffered by the subject by not consenting to study participation or continuation or by revoking consent
⑩ Methods of disclosure of information related to the study
⑪ In response to a request by a subject, the protocol and materials related to the study methods can be obtained and viewed as long as this does not impede the protection of other subjects' personal information or the assurance of this study's originality (include the methods of acquisition/viewing)
⑫ Handling of personal information (anonymization)
⑬ Methods of specimen/information storage and disposal
⑭ The study's funding source, conflicts of interest related to the study facilities, and conflicts of interest related to the investigators (e.g., personal profits)
⑮ Response to consultations from subjects and other related parties and communication channels for inquiries
⑯ Existence of compensation for any health damage that occurs as a result of the study and details of such compensation
⑰ While protecting subject confidentiality, people engaged in monitoring and the Institutional Review Board will be able to view the specimens and data provided by the subjects as necessary

⑱ The research results will be made public after processing them in an appropriate manner so that the subjects cannot be identified
⑲ Entitlement to intellectual property and patent rights
⑳ Economic burden or any rewards to the participants and the details

20.3. Handling of Personal Information

All people involved in this study must obey all relevant laws, such as the "Act on the Protection of Personal Information," pertaining to all personal information obtained from the subjects and will not divulge any of this information without a valid reason. The same restriction applies even after parties involved in the study have left their post. When handling any source materials or consent forms related to this study, sufficient care must be taken to protect the confidentiality of the subjects. People not associated with the research institution must not be involved in the entering of information into the EDC system that could identify the subjects (e.g., names, addresses, phone numbers, or medical record numbers) or the recording of such information in CRFs or QOL score questionnaires.

When the Data Center makes inquiries to the research institutions, central record numbers are used. The investigators should use a subject differentiation management table (correspondence table) to identify the subject. The investigators should carefully and appropriately store the correspondence table at the research institute for five years after the study has been completed or three years after the final publication of this study is released, whichever comes later. The person responsible for managing personal information at each research institution is the responsible investigator.

While it is planned that the results obtained in this study will be presented at academic conferences and in medical journals, sufficient care will be taken to not include any information that could identify the subjects (e.g., subjects' names). Data from subjects obtained in this study will not be used for non-research purposes.

21. SUBJECT BURDENS, POTENTIAL RISKS AND BENEFITS, MEASURES TO MINIMIZE BURDENS AND RISKS, AND COMPREHENSIVE EVALUATION

21.1. Subject Burdens and Potential Risks

As all treatments in this study are covered by national health insurance, the

subjects will be subjected to a cost burden within the range of national health insurance applicability. Moreover, because most tests in this study are the same tests and treatment used in routine medical practice, there are no particular risks. As riociguat and BPA are currently routinely conducted for inoperable CTEPH subjects, no particular disadvantages are associated with this study, and it appears that the level of risk will not exceed that of normal medical treatment. The associated tests other than the QOL score questionnaires (EQ5D) of the subjects are all conducted in general clinical practice and will not cause any special burden to the subject.

21.2. Potential Benefits

As the subjects will receive the same treatment as that offered in routine clinical treatment, they will not receive any particular treatment benefits. However, the responsible investigators (investigators) will provide a 5,000 Quo card to each subject for their cooperation at baseline and at each observation point (a total of two times) during the 12 months.

21.3. Measures to Minimize Burdens and Risks

In this study, from the standpoint of protecting the subjects, the investigators as well as the surgeon determining operability will judge the treatment strategy for each subject to ensure the most appropriate treatment. The test items were reduced as much as possible to reduce the burden on the subjects.

As this study will be conducted using approved existing drugs and all treatments will be the general treatments performed in routine clinical practice, as a general rule, no special compensation will be offered for health damage caused by the study drug. Any damages will be treated in an identical manner as health damage or a medical accident that occurs during the course of routine clinical treatment. Any such compensation will be offered in accordance with the Relief System for Victims of Side Effects of a Drug of the Pharmaceuticals and Medical Devices Agency, the Product Liability Act, and completed operations liability insurance.

However, the principal investigator will represent the investigators and apply for clinical study insurance offered by an insurance company in case of any health damage not related to treatment that occurs as a result of the study design.

The investigators will carefully observe the subjects' symptoms and conditions and strive to reduce all burdens and risks, including discomfort and fatigue associated with testing during observations with measures, including breaks.

21.4. Comprehensive Evaluation

This study will place little burden on the subjects, and there are no foreseen risks exceeding those observed in routine clinical practice. Although there will be no direct benefits for the subjects, this study may contribute to improving the disease pathophysiology and further developing the field of medicine.

22. RESPONSDING TO REQUESTS FOR CONSULTATIONS FROM SUBJECTS AND RELATED PARTIES

If consultation requests regarding this study are received from subjects or other related parties, the investigators will respond rapidly and with sincerity. If the investigators find it difficult to respond, the responsible investigator should consult the principal investigator, Central Committee, or Research Support Center, after which rapid measures will be taken based on an investigation on determining how to respond. If necessary, the responsible investigators should also report on consultations with the subjects or related parties to collaborating research institutions and responsible investigators through the Research Support Center.

23. PROTOCOL FOR REPORTING TO HEADS OF RESEARCH INSTITUTIONS (CONTENT AND METHOD)

In accordance with the rules of the affiliated research institution, the investigators should directly report to the head of the research institution or through the Institutional Review Board for the following points mentioned below. Based on the content of such a report, the principal investigator will hold discussions with the Central Committee and the Safety Monitoring Committee and consider measures (e.g., premature termination of the study) as necessary.

- Progress of the study and findings related to efficacy and safety obtained at the time reporting
- Occurrence of any SAEs or unexpected SAEs
- Receipt of any serious complaints from the subjects or other events that could impede the continuation of the study
- Occurrence of any serious risks from the standpoint of respecting the subjects' human rights or implementation the study
- Any facts, information, or risks that detract from the appropriateness of implementing the study or the reliability of study results

・Changes to the protocol
・Report on study closure
・Any other instructions from the head of the research institution or Institutional Review Board

24. SPECIMEN AND DATA STORAGE AND DISPOSAL METHODS

The responsible investigators and investigators must appropriately store all necessary documents related to the implementation of the study [application form copies, written notifications from the heads of the research institutions, application and report copies, subject management table (correspondence table), consent forms, and other documents or records required to ensure the reliability of data] in a locked cabinet for five years after it is reported that the study has been completed or three years after the final publication of this study is released, whichever comes later. Following this period, the data must be destroyed in accordance with the procedure at the research institution.

The Data Center must also store necessary information and data sets related to this study in an electronic format. Data present after the storage period must be destroyed after implementing necessary measures to ensure that they cannot be recovered. No particular specimens need to be stored for this study. Blood samples and other data will be destroyed in accordance with the procedures of the research institution after the results are converted to raw data. As a general rule, data collected during this study cannot be used for research that has a completely different purpose. If the data are to be used in a new study, a new application must be made to the Institutional Review Board of the said research institution.

25. METHODS OF DISCLOSURE OF STUDY-RELATED INFORMATION

Before the first subject is enrolled in this study, the details of the protocol must be registered on a public registration system (University Hospital Medical Information Network) and made public. The responsible investigators must implement updates, as necessary, because of changes in the protocol or the progress of the study; furthermore, they must register the results of the study without delay once it has been completed. The responsible investigators will make the results of this study public at a relevant academic society or in a report. Results should only be published after taking necessary measures to protect the human rights of the

subjects and related parties, as well as the rights and interests of those involved in implementing the study. Upon the final publication of the results, a report must be made to the head of the research institution without delay.

26. STUDY FUNDING AND CONFLICTS OF INTEREST

26.1. Funding Provider

This study will be funded by the company shown below in the form of research outsourcing contract.

Bayer Yakuhin, Ltd.
BREEZE TOWER 2-4-9, Umeda, Kita-ku, Osaka 530-0001

26.2. Conflicts of Interest

The implementation or results of this study will not be affected by any related parties or the funding provider. The study protocol, its implementation, and details will be determined by the principal investigator. The funding provider will not be involved in data analysis in any way, and no data will be provided to the funding provider. The funding provider may utilize the results of this study, including those related to safety; however, any funds not used in the research will be quickly returned to the funding provider after study closure.
In accordance with the regulations at the collaborating research institution, parties involved in this study will report on any necessary items to the Conflict of Interest Committee established at each research institution for screening prior to approval.

27. RULES REQUIRING OBSERVANCE

This study will be conducted in accordance with the WMA Declaration of Helsinki (revised in October 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare). The principal investigator and all other people involved in the study will protect the confidentiality of the subjects during the implementation of this study.

28. ORGANIZATIONAL STRUCTURE OF THE CLINICAL STUDY

28.1. Principal Investigator

Keiichi Fukuda (Professor, Department of Cardiology, Keio University School of Medicine)

28.2. Central Committee

The Central Committee will supervise this study from the medical, scientific, and ethical viewpoints and co-ordinate with the collaborating research institutions and other parties involved in the implementation of this study. Any clerical functions based on decisions made by the Central Committee will be conducted by the Research Support Center. Regular reports must also be submitted to the Research Support Center, which will be supervised. In addition, on implementing this study, the Central Committee will record study details (e.g., test items) and prepare a rough draft for the protocol, including relevant laws that need to be followed.

① Prepare the protocol for this study and subsequently review as necessary.
② Act as the organizing unit of this study by determining its progress and understanding problems and solutions.
③ If feedback is received that there is a problem related to safety and that countermeasures should be taken, the appropriate methods and implementing countermeasures should be investigated.
④ Confirm the progress of this study as necessary and contact the collaborating research institutions in this study as necessary.
⑤ Work with medical statisticians and decide on methods for statistical analysis.
⑥ Determine the procedures and details related to this study that can be made public and editing material after determining which items will be made public.
⑦ Supervise external support companies.

Chairperson:
Keiichi Fukuda (Professor, Department of Cardiology, Keio University School of Medicine)
Members:
Hiromi Matsubara (Director, Department of Cardiology, Okayama Medical Center)
Shun Kohsaka (Lecturer, Department of Cardiology, Keio University School of Medicine)

Masaharu Kataoka	(Specially appointed lecturer, Department of Cardiology, Keio University School of Medicine)
Takashi Kawakami	(Specially appointed lecturer, Department of Cardiology, Keio University School of Medicine)

28.3. Collaborating Research institutions *In Japanese alphabetical order

Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University	(Responsible investigator: Hiroyuki Tsutsui)
Department of Cardiology, Keio University School of Medicine	(Responsible investigator: Keiichi Fukuda)
Division of Cardiovascular Medicine/Department of Internal Medicine, Graduate School of Medicine, Kobe University	(Responsible investigator: Kenichi Hirata)
Department of Cardiology, Okayama Medical Center	(Responsible investigator: Hiromi Matsubara)

28.4. Physician to Determine Operability

This physician will determine the eligibility of the subjects sent from the collaborating research sites via the Data Center and then inform each study site of the assessment.

Motomi Ando (Head of Department of Cardiac Surgery, Cardiovascular Center, Daiyukai General Hospital)

28.5. Data and Safety Monitoring Board (DSMB)

This independent organization is composed of three members who will not participate in this study. Based on information regarding adverse events etc., this organization will offer appropriate advice and recommendations to the principal investigator in order to protect the interests of subjects, ensure their safety, and maintain the ethical and scientific validity of implementing the study. It will monitor safety. The principal investigator will take necessary measures in accordance with any reports received from the DSMB.

Chairperson:

Hiroshi Ito (Professor, Division of Biophysiological Sciences, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University)

Members:

Hitoshi Ogino (Professor and Chairperson, Department of Cardiovascular Surgery, School of Medicine, Tokyo Medical University)

Toru Satoh (Professor, Division of Cardiology, Department of Medicine, Kyorin University Hospital)

28.6. Clinical Event Committee (CEC)

This committee is composed of three people who are not participating in this study: one cardiologist and two pulmonary cardiologists. The CEC ensures the scientific validity of the study by blindly evaluating whether important events presented by the responsible investigators at each collaborating research institution meet the standards of the protocol and maintains consistency and objectivity in the evaluation of events.

Chairperson:

Nobuhiro Tanabe (Specially appointed lecturer, Department of Respirology, Graduate School of Medicine, Chiba University)

Members:

Fumio Sakamaki (Professor, Division of Respiratory Medicine, Department of Internal Medicine, School of Medicine, Tokai University)

Ken Kozuma (Professor, Department of Medicine, School of Medicine, Teikyo University)

28.7. Data Handling Committee

The Data Handling Committee blindly evaluates data that have deviated from the protocol and missing data prior to analysis and determines how all data will be handled. The members include the members of the Central Committee as well as the statistical analysis manager.

28.8. Biostatistician

The biostatistician will perform medical statistical discussions and analyses for this study and offer advice.

Biostatistician:

Yasunori Sato (Associate Professor, Department of Preventive Medicine and Public Health, Keio University School of Medicine)

28.9. Core Laboratory (CT, CXR)

Chest CT scan and CXR data should be submitted to the Core Laboratory and analyzed. Measurement results will be presented to Soiken Inc. (Data Center) using central registration numbers.

Core Laboratory (CT, CXR) managers:

Masahiro Jinzaki (Professor, Department of Diagnostic Radiology, Keio University School of Medicine)

Yoshitake Yamada (Assistant professor, Department of Diagnostic Radiology, Keio University School of Medicine)

28.10. Core Laboratory (Echocardiography)

Echocardiography (cardiac ultrasound) data will be presented to the Core Laboratory and analyzed. Measurement results will be presented to Soiken Inc. (Data Center) using central registration numbers.

Core Laboratory (Echocardiography) Manager:

Mitsushige Murata (Full-time lecturer, Department of Laboratory Diagnosis, Keio University School of Medicine)

28.11. Research Support Center (Data Center)

To implement this study, some duties will be outsourced to a Contract Research Organization. The Research Support Center will be responsible for executing the duties of overseeing this study in accordance with the instructions of the Central Committee. The Research Support Center will also conduct research office duties (e.g., computer allocation during registration) as well as monitor and handle data for each independent department.

Clinical Research Support Division, Soiken Inc.
4F, NBF Ogawa-machi Bldg. 1-3-1 Kanda Ogawa-machi, Chiyoda-ku, Tokyo 101-0052

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BMJ Open

Multicenter randomized controlled trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Protocol for the MR BPA study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028831.R1
Article Type:	Protocol
Date Submitted by the Author:	31-May-2019
Complete List of Authors:	Kawakami, Takashi; Keio University, School of Medicine, Cardiology Matsubara, Hiromi; Okayama Medical Center Abe, Kohtaro; Kyushu University Kataoka, Masaharu ; Keio University, School of Medicine Kohsaka, Shun; Keio University, School of Medicine Sato, Yasunori ; Department of Preventive Medicine and Public Health, Keio University School of Medicine, Shinke, Toshiro; Showa University Fukuda, Keiichi; Keio University, School of Medicine
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Cardiovascular medicine, Surgery
Keywords:	chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, riociguat

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Multicenter randomized controlled trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Protocol for the MR BPA study

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Acknowledgements: The study was funded by Bayer Yakuhin Ltd.

Keywords: Chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, riociguat

Abstract

Introduction: The management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) remains a clinical challenge. Medical treatment mainly involving pulmonary vasodilators (e.g. a soluble guanylate cyclase stimulator) is recommended for ameliorating their symptoms. More recently, balloon pulmonary angioplasty (BPA) has developed as alternative treatment modality for inoperable CTEPH. We aim to compare the efficacy and safety of BPA and riociguat, for the treatment of inoperable CTEPH.

Methods and Analysis: The study was designed as a multicenter randomized controlled trial for treatment of inoperable CTEPH. Subjects with inoperable CTEPH will be randomized (1:1) into either BPA or riociguat group, and observed for 12 months after treatment. The primary endpoint will be change in the mean pulmonary arterial pressure from baseline to 12 months. For the primary analysis, the least square mean difference in the change of pulmonary arterial pressure between BPA and riociguat group at 12 months and its 95% confidential interval will be estimated using an analysis of covariance (ANCOVA) model adjusted for allocation factors.

Ethics and Dissemination: This study was approved by the institutional review board of Keio University School of Medicine and each participating institution. Written informed consent will be obtained from all participants. Results of the study will be disseminated at medical conferences and journal publications.

Registration: This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (UMIN000019549).

Strengths and Limitations of the Study:

- This is the first randomized controlled trial to compare the efficacy and safety of BPA and riociguat in patients with inoperable CTEPH.
- This study evaluates the efficacy and safety of BPA and riociguat for relatively longer observation period (12 months).
- This is also the first study to compare the health insurance resource costs between BPA and riociguat.
- The limitation of this study is that this is open-label trial.
- Another limitation of this study is that this study will recruit a relatively small number of study subjects.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by which an organized thrombus causes stenosis and/or occlusion of the pulmonary arteries[1]. Unless early diagnosis and appropriate treatment are performed, which causes death due to right-sided heart failure[2]. Pulmonary endarterectomy (PEA) has been established as a curative treatment for operable CTEPH[3, 4]. According to the AHA/ACC[5], ESC/ERS[6], and JCS/JPCPHS[7] guidelines, PEA is recommended for patients with operable CTEPH as the first line therapy in class of recommendation I and level of evidence C.

In 2014, a soluble guanylate cyclase stimulator (general name: riociguat), which is the pulmonary vasodilator, received insurance reimbursement approval for inoperable or persistent/recurrent CTEPH for the first time. This was based on the findings of a multicenter randomized clinical trial (CHEST-1)[8] and its extension study (CHEST-2)[9] indicating the efficacy of riociguat for subjects with inoperable CTEPH. Balloon pulmonary angioplasty (BPA), as catheter-based treatment, has also been reported to be effective for subjects with inoperable CTEPH[10-22].

As described above, the two treatment modalities for inoperable CTEPH are riociguat and BPA. Riociguat and BPA are recommended for inoperable CTEPH patients in class of recommendation I and level of evidence B, and class of recommendation IIb and level of evidence C, respectively in 2015 ESC/ESR guidelines[6] and in class of recommendation I and level of evidence B, and class of recommendation I and level of evidence C, respectively in 2017 JCS/JPCPHS guidelines[7]. Although BPA is associated with a certain level of risk of complications such as procedure related pulmonary artery injury, it can provide marked improvement when the treatment finished. On the other hand, riociguat is the most effective pulmonary vasodilator and have low risk of serious adverse events. Although it has been reported that sequential treatment with riociguat and BPA for inoperable CTEPH patients

significantly improved the mean pulmonary arterial pressure and pulmonary vascular resistance[23], no reports have yet directly compared the treatment outcomes of these two treatment methods. A randomized controlled trial to compare riociguat and BPA (RACE study) is ongoing in France[24], which has been started at the almost same time with this study[25]. The present study was planned to compare the efficacy and safety of riociguat with BPA in the treatment of inoperable CTEPH over the course of 12 months, to potentially aid in optimizing treatment selection and improving treatment outcomes.

Methods and Analysis

Study Design: The Multicenter Randomized controlled trial based on Balloon Pulmonary Angioplasty for chronic thromboembolic pulmonary hypertension (MR BPA) study will enroll subjects from January 15, 2016 to October, 31, 2019. The study is designed as a multicenter, prospective, randomized controlled trial. As shown in Figure 1, the subjects will undergo right heart catheterization and pulmonary angiography before provisional enrollment. An independent experienced PEA surgeon will determine if these subjects are eligible to undergo PEA under blind circumstance. Those who are judged to have inoperable CTEPH will be assigned into either BPA or riociguat group via an online assignment system and observed for 12 months. In the BPA group, the degree of pulmonary hypertension severity and the pulmonary lesion is morphologically evaluated by preoperative right heart catheterization and pulmonary angiography. BPA is then conducted depending on the lesion type. In general, BPA will be completed within 4 months after the initial BPA procedure. In the riociguat group, riociguat will be initially administered three times per day at 1.0 mg per dose. Using systolic blood pressure (95 mmHg or higher) as a guide, the dose will be increased by 0.5 mg for each subject every two weeks with a thrice-daily administration of 2.5 mg/dose set as the maximum dosage. Dosage adjustment will be completed within 4

months after the first administration of riociguat, and the administration of riociguat will be continued for total 12 months. The observations will be made at screening, baseline, 0-4 months, 6 months, and 12 months. Table 1 shows the schedule of assessments performed at each visit for each treatment group, including mandatory and optional assessments.

Sample size calculation: Previously, BPA resulted in a reduction in mean pulmonary arterial pressure from 45.4±9.6 to 24.0±6.4 mmHg in 24 months[11], while riociguat decreased the pulmonary arterial pressure by 4±7 mmHg[9]. Based on these studies, the change in mean pulmonary arterial pressure from the start of treatment to 12 months later was assumed to be −15 mmHg for the BPA group and −4 mmHg for the riociguat group, and the standard deviation for each change was assumed to be 14 for the BPA group and 10 for the riociguat group. The minimum sample size required to achieve a significance of 0.05 for a two-sided test with a statistical power of 90% was determined to be 27 subjects for both groups, indicating a total of 54 subjects. With the dropout rate estimated to be 10%, the planned enrollment was set at 30 subjects for each group, for a total of 60 subjects.

Eligibility criteria: *Inclusion criteria*: Patients meeting the following criteria will be included in the study: (a) patients who are diagnosed with CTEPH (based on the diagnostic criteria in the 2012 Japanese Circulation Society guidelines[24] with a WHO functional class II or III). (b) male and female aged ≥ 20 years and < 80 years. (c) patients with mean pulmonary arterial pressure of ≥25 mmHg to <60 mmHg and pulmonary artery wedge pressure of ≤15 mmHg. (d) patients who undergo appropriate anticoagulant therapy for at least three months prior to consent acquisition (if warfarin is used, prothrombin time-international normalized ratio should be 1.5 to 3.0). (e) patients who provide written consent form to participate in this study after full explanation of the study.

Exclusion criteria: Patients meeting any of the following exclusion criteria will be excluded from the trial: (a) patients with a history of BPA. (b) patients who underwent PEA within six months prior to consent acquisition. (c) patients who are using unapproved pharmaceutical products. (d) patients who used a pulmonary vasodilator within four weeks prior to the right heart catheterization after consent acquisition. (e) patients with co-existing etiology of pulmonary hypertension other than Group 4 in the Nice Pulmonary Hypertension Classification System. (f) patients who are pregnant or breastfeeding. (g) patients who met the contraindication for riociguat. (h) patients whose life expectancy is less than two years. (i) patients who are considered to be unsuitable for participation by investigators.

Recruitment and consent:

When subjects are determined to be able to participate in this study, the informed consent document is used to give them a sufficient explanation of this study and their written consent is then obtained. When obtaining consent, it is also explained that data related to pulmonary angiography, right heart catheterization, and chest computed tomography (CT) scan from within three months prior to acquiring consent, as well as pulmonary ventilation-perfusion scintigraphy prior to acquiring consent, may be used for research purposes.

As a general rule, right heart catheterization and pulmonary angiography are performed after acquiring consent and investigators determine whether each subject can be definitively diagnosed with CTEPH. However, to reduce the burden on the subjects, data from within three months prior to consent acquisition for pulmonary angiography, right heart catheterization, and CT scan, as well as pulmonary ventilation-perfusion scintigraphy obtained in general practice prior to consent acquisition, can also be utilized.

Based on the imaging data of the subjects who give their consent, an independent experienced PEA surgeon who is not involved in this study will determine operability

(whether the subjects are eligible to undergo PEA). The standards for this determination of operability will be based on the Guidelines for Treatment of Pulmonary Hypertension (2012 revised version)[26] and will be anatomically performed.

Random allocation: Random assignment will be performed centrally with stratification by mean pulmonary arterial pressure (<40 mmHg and ≥40 mmHg), and research institutions (Keio University, Okayama Medical Center, Kyusyu University, and Kobe University) by the minimization method with biased coin assignment.

Endpoints: Primary endpoint will be the change in mean pulmonary arterial pressure from baseline to 12 months. Secondary endpoints will include several clinical and quality of life parameters. These are detailed in Table 2.

Data collection: An electronic clinical testing data collection system, electric data capture system (EDC), will be used for data collection. In cases when the system is unavailable, a case report form, a specialized data collection form, will be used and the data later entered into the EDC. The investigators who will enter information into the EDC system will be responsible for ensuring accuracy and completeness of the information.

Data management and monitoring: The processes of data collection and management will be performed by third-party entities for data without bias. Data management in this study will be performed by Soiken Inc., Data Management Group (the Data Center). Data Center will prepare a "Procedure Manual for Data Management." The Data Center's approval is required prior to sending data related to the subjects in an electronic format. If transmitting data over an unsecured electronic network, the data must be encoded at the source. Linkable

anonymization with central registration number will be used to identify the subjects. The investigators will be responsible for appropriately storing the correspondence table prepared by them to identify subjects in accordance with the procedures at the research institution. This correspondence table must be retained for up to five years after the completion of the study or three years after the final publication of the study, whichever comes later. For displaying and publicly disclosing all information related to the study, appropriate measures will be taken, such as encoding or deletion, to ensure that the subjects cannot be identified in accordance with applicable laws and regulations.

In this study, the Soiken Inc., Data Management Group will perform monitoring to manage and ensure quality. The monitoring manager will monitor the subjects in accordance with the manual on the monitoring procedure. For data quality management, the principal investigator and Central Committee will confirm the progress of the study, as necessary, through the Soiken Inc., Data Management Group to ensure that the study is being conducted in accordance with the protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare).

Adverse events: Occurrence of any untoward medical events experienced by subjects, including the worsening of a pre-existing underlying disease or a complication, will be defined as adverse events. However, the worsening of efficacy evaluation indices will not be defined as an adverse event. Any concomitant symptoms or clinically significant abnormal fluctuations in test results will be investigated to determine whether there is a cause-and-effect relationship with BPA or riociguat and findings will be documented in the EDC system. As a general rule, adverse events will be followed up until normalization or recovery occurs to a level at which it is not considered to be an adverse event or in case of an

irreversible adverse event (cerebral infarction, myocardial infarction etc.), until symptoms stabilize or no longer change.

Statistical Analysis:

The analyses of the primary and secondary efficacy endpoints will be performed using the full analysis set, which will include all patients who underwent randomization and received at least one dose of a study drug and had at least one assessment after baseline. Safety analysis will be conducted in the safety analysis population.

For the baseline variables, summary statistics will be constructed using frequencies and proportions for categorical data, and means and standard deviations for continuous variables. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact test for categorical endpoints, and Student's t-test for continuous variables, as appropriate.

For the primary analysis, the least square mean difference in the change of pulmonary arterial pressure between groups at 12 months and its 95% confidential interval will be estimated using an analysis of covariance (ANCOVA) model adjusted for allocation factors. The secondary analysis will be performed in the same manner as the primary analysis. Adverse events will be evaluated during the safety analysis. The frequencies of adverse events will be compared using Fisher's exact test. All comparisons are planned, and all *p*-values will be two sided. *P*-values <0.05 will be considered statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The statistical analysis plan will be developed by the principal investigator and the biostatistician before completion of patient recruitment and data fixation.

Patient and Public Involvement

No patient involved.

Discussion

Guidelines for diagnosis and treatment for CTEPH in Western countries[5, 6] and Japan[7, 26] recommend riociguat and BPA for inoperable CTEPH patients. However, no reports have yet directly compared the treatment outcomes of these two treatment methods. Sequential treatment with riociguat and BPA for inoperable CTEPH patients significantly improved the mean pulmonary arterial pressure and pulmonary vascular resistance, suggesting more benefits of BPA[23]. Direct comparison of riociguat and BPA by a randomized controlled trial is also ongoing in France[24]. The present study was therefore planned to compare the efficacy and safety of riociguat with BPA in the treatment of inoperable CTEPH, and has started at almost same time with the RACE study (both started from January, 2016)[25]. Results from such randomized trials will be important for optimizing the treatment selection and improving treatment outcomes in inoperable CTEPH.

This study will complete BPA treatment in 4 months. This treatment period is almost as same as that under real-world condition in Japan. Also, this study will evaluate longer-term efficacy and safety of riociguat and BPA for 12 months after the start of the treatment. Furthermore, recent systematic review showed that the treatment outcomes of BPA were greater in Japan than those in Western countries[4, 27]. This study will be conducted in expert CTEPH centers in Japan. Therefore, this study will compare the treatment efficacy and safety of riociguat and the highest-quality BPA in Japan. In addition, the operability of PEA is determined under blind circumstance by an independent experienced PEA surgeon who belongs to independent institute. This will avoid bias on the subject enrollment. Furthermore, this study will also compare health insurance resource costs and patient-reported quality of life parameters for each of the therapies. These may contribute to optimize treatment strategy or further to amend treatment guidelines for inoperable CTEPH. These are the strengths of

this study. On the other hands, this study has several limitations. One limitation is that this is open-label trial. Because there is no distinct criterion for BPA implementation in each lesion, bias for BPA surgeons cannot be completely avoided. However, since this study will compare medical treatment and surgical intervention, it is difficult to use placebo or to mask patients and/or physicians. Another limitation is that relatively small number of patients will be enrolled in this study (30 subjects for each group, for a total of 60 subjects).

Ethics and Dissemination: This study was approved by the institutional review board of Keio University School of Medicine and each participating institution and will be conducted in accordance with the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labor and Welfare in Japan, and other current legal regulations in Japan. Written informed consent will be obtained from all participants after a full explanation of this study. Results of the study will be disseminated at medical conferences and journal publications.

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Author's Contributions:

TK and HM equally contributed in this study. TK and HM contributed to the conception and design of the study, drafted the protocol, and supervised the revision. MK, KA, SK, YS and TS provided intellectual input into improving the study design and revising the protocol. KF contributed to and supervised the conception and design of the study. All authors read and approved the final manuscript.

Funding statement:

This study was financially supported by Bayer Yakuhin, Ltd.

Competing interests statement:

SK has received honoraria for scientific lectures from Bayer Yakuhin, Ltd. KF has received scholarship grants from Bayer Yakuhin, Ltd. and MSD K.K. The other authors declare no conflict of interest.

Figure and Table Legends

Figure 1. Study outline and randomization schematic. After consent, and CTEPH diagnosis is confirmed, subjects will be randomized into either BPA or riociguat group for 12 months, and observation measurements taken at screening, baseline, 0-4, 6 and 12 months.

Table 1. Schedule of assessments for subjects enrolled into the study.

Table 2. Secondary endpoints that will be measured and/or compared at baseline and at 12 months.

Table 1: Schedule of assessments for subjects enrolled into the study.

Observation items	Screening	Baseline	observation period		
	~0M	0M	0~4M	6M+1M	12M+2M
Subjects' attributes	○	○	—	—	—
6-minute walk distance	—	○	—	○	○
Borg dyspnea index	—	○	—	○	○
WHO functional class	—	○	—	○	○
Right heart catheterization	○	—	—	○	○
Pulmonary angiography	○	—	—	—	—
Pulmonary function testing	—	○	—	○	○
Blood gas test[a]	○		—	○	○
Vital signs[a]	○		—	○	○
Echocardiography (cardiac ultrasound)	—	○	—	○	○
Chest X-ray	○		○[b]	○	○
Chest CT scan	○	—	○[b]	○	○
Oxygen therapy usage status	—	○	—	○	○
Adverse event onset [c]	—	—	←	○	→
Clinical worsening and time to clinical	—	—	←	○	→

worsening (TTCW) [c]							
Quality of Life parameters (EQ5D)	—	○	—		○		○
Health insurance	—	—		←	○	→	
BPA status[d]	—	—	○		—		—
Medication adherence[e]	—	—		←	○	→	

(a) Recommended to be implemented during right heart catheterization

(b) Required if BPA is performed

(c) Onset of adverse events and indices related to clinical worsening will be observed, as necessary, throughout the clinical study period

(d) Observation items for Group A (BPA group)

(e) Observation items for Group B (riociguat group)

Table 2: Secondary endpoints that will be studied and or compared at baseline and at 12 months.

Endpoint	
Change in 6-minute walk distance	
Change in Borg dyspnea index	
Change in hemodynamic variables	Includes pulmonary vascular resistance, mean right arterial pressure, cardiac output etc.
Change in WHO functional class	
Change in plasma brain natriuretic peptide levels	
Change in SaO_2 and PaO_2	
Change in usage volume of oxygen therapy	Includes commencing oxygen therapy due to the exacerbation of a primary disease or dosage change.
Change in pulmonary function test	
Change in echocardiography test parameter	
Frequency and severity of pulmonary artery injury	Assessed by chest X-ray and chest CT scan.
Frequency of Adverse Events	Bloody sputum/hemoptysis/pulmonary hemorrhage (vascular perforation, vascular dissection, vascular rupture, etc.), pneumothorax, hypotension, pulmonary congestion/pulmonary edema, late-onset lung disturbance, heart failure, pneumonia, headache, dizziness, peripheral edema, nausea/vomiting,

	retching, diarrhea, nasopharyngitis, upper respiratory inflammation, respiratory distress, coughing, fainting.
Clinical worsening during the observation period and time to clinical worsening	All-cause mortality, heart/lung transplant, salvage PEA due to worsening of primary disease, new or repeated implementation of BPA due to the worsening of a primary disease, hospitalization, new initiation of pulmonary vasodilators, worsening of 30% or greater from baseline in the 6-minute walk distance, persistent worsening in the WHO functional class from baseline due to the worsening of a primary disease.
Change in Quality of Life parameters (EQ5D)	
Health insurance resource costs	

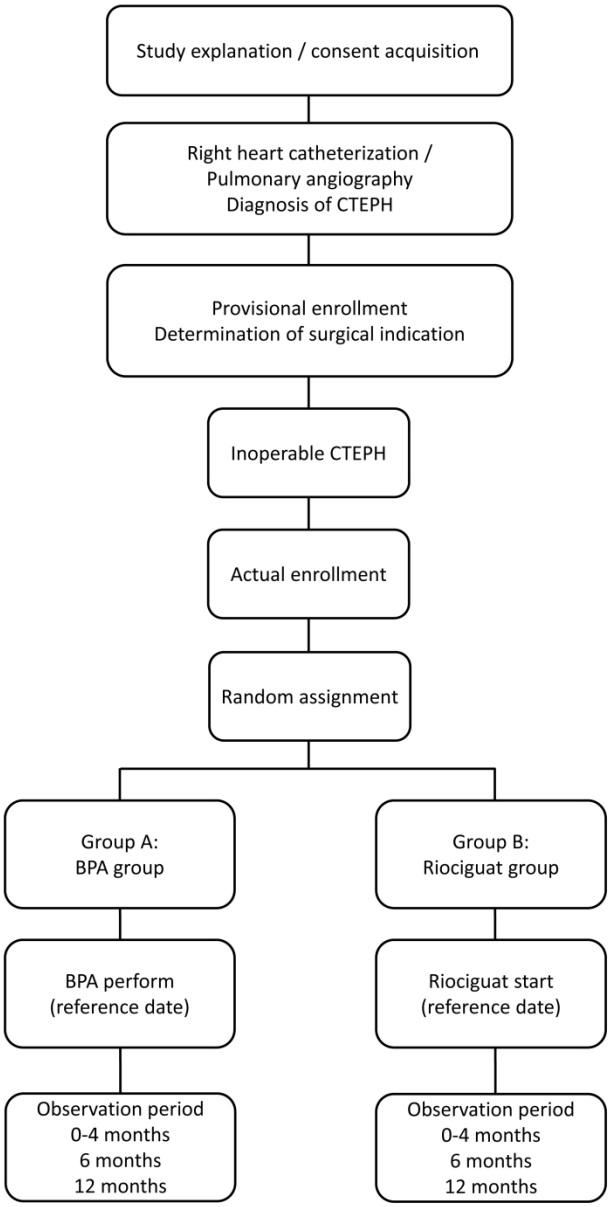

Figure 1. Study outline and randomization schematic. After consent, and CTEPH diagnosis is confirmed, subjects will be randomized into either BPA or riociguat group for 12 months, and observation measurements taken at screening, baseline, 0-4, 6 and 12 months.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/Item	Item No.	Description	Page in protocol	Page in protocol paper
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 5	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	42	3
	2b	All items from the World Health Organization Trial Registration Data Set	42	3
Protocol version	3	Date and version identifier	1	
Funding	4	Sources and types of financial, material, and other support	43	2, 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 43-47	1
	5b	Name and contact information for the trial sponsor	1	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	43	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	44-47	
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	11	3, 5
	6b	Explanation for choice of comparators	11	3, 5
Objectives	7	Specific objectives or hypotheses	5, 11-12	3, 5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 12	6
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	45	1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6, 13-14	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12, 16-24	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	28-29, 36	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	23-24	20
	11d	Relevant concomitant care and interventions that are permitted	17	

		or prohibited during the trial		
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7, 14-16	8, 21-22
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-24	6-8, 19-20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	31	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17-20	7-8
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	19-20	6-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16, 19-20	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16, 19-20	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18-19	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18-19	6
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	20-24	6-8, 19-20
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	28-29	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	29-31	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	32-34	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	32-34	10-11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	30-31	10-11

		imputation)		
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	46	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	34	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	25-28	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A	N/A
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	34-35	11-12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	35	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	36-39	7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	38-39	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	43	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	29-31	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	40	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	42	11-12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A	N/A
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	37-38	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Multicenter randomized controlled trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Protocol for the MR BPA study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028831.R2
Article Type:	Protocol
Date Submitted by the Author:	10-Oct-2019
Complete List of Authors:	Kawakami, Takashi; Keio University, School of Medicine, Cardiology Matsubara, Hiromi; Okayama Medical Center Abe, Kohtaro; Kyushu University Kataoka, Masaharu ; Keio University, School of Medicine Kohsaka, Shun; Keio University, School of Medicine Sato, Yasunori ; Department of Preventive Medicine and Public Health, Keio University School of Medicine, Shinke, Toshiro; Showa University Fukuda, Keiichi; Keio University, School of Medicine
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Cardiovascular medicine, Surgery
Keywords:	chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, riociguat

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Multicenter randomized controlled trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Protocol for the MR BPA study

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Acknowledgements: The study was funded by Bayer Yakuhin Ltd.

Keywords: Chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, riociguat

Abstract

Introduction: Management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) remains a clinical challenge. Currently, medical treatment involving pulmonary vasodilators (such as soluble guanylate-cyclase stimulators) is recommended, primarily for ameliorating symptoms. More recently, balloon pulmonary angioplasty (BPA) has been developed as alternative treatment for inoperable CTEPH. The present study aimed to compare the efficacy and safety of BPA and riociguat (a soluble guanylate-cyclase stimulator) as treatments for inoperable CTEPH.

Methods and analysis: The present study is a multicenter randomized controlled trial. Subjects with inoperable CTEPH will be randomized (1:1) into either a BPA or riociguat group, and observed for 12 months after initiation of treatment. The primary endpoint will be the change in mean pulmonary arterial pressure from baseline to 12 months after initiation of treatment. For primary analysis, we will estimate the least square-means difference and 95% confidential interval for the change of pulmonary arterial pressure between the groups at 12 months using analysis of covariance adjusted for allocation factors.

Ethics and dissemination: This study and its protocols were approved by the institutional review board of Keio University School of Medicine and each participating institution. Written informed consent will be obtained from all participants. Results will be disseminated at medical conferences and in journal publications.

Registration: This study is registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (UMIN000019549).

Strengths and limitations of the study:

- This is a randomized controlled trial comparing the efficacy and safety of BPA and riociguat in patients with inoperable CTEPH.
- This study evaluates the efficacy and safety of BPA and riociguat over a relatively long period (12 months).
- This is the first study to compare health insurance resource costs between BPA and riociguat.
- A limitation of this study is the open-label trial design.
- Another limitation of is that this study will recruit a relatively small number of subjects.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by stenosis and/or occlusion of pulmonary arteries caused by organized thrombi[1]. Early diagnosis and appropriate treatment are critical, as the condition is associated with a high rate of mortality due to right-sided heart failure[2]. Pulmonary endarterectomy (PEA) is an established curative treatment for operable CTEPH[3, 4]. According to the American Heart Association/American College of Cardiology (AHA/ACC)[5], European Society of Cardiology/European Respiratory Society (ESC/ERS)[6], and Japanese Circulation Society/the Japanese Pulmonary Circulation and Pulmonary Hypertension Society (JCS/JPCPHS)[7] guidelines, PEA is recommended for patients with operable CTEPH as the first-line therapy in the case of recommendation class I and level of evidence C.

In 2014, for the first time, a soluble guanylate-cyclase stimulator (riociguat, a pulmonary vasodilator) received approval for insurance reimbursement in the context of inoperable or persistent/recurrent CTEPH. This was based on the findings of a multicenter randomized clinical trial (CHEST-1)[8] and its extension study (CHEST-2)[9] which highlighted the efficacy of riociguat for patients with inoperable CTEPH. Balloon pulmonary angioplasty (BPA) is a catheter-based treatment which has also been reported to be effective for inoperable CTEPH[10-22]. Riociguat and BPA are recommended for patients with inoperable CTEPH in the case of recommendation class I and level of evidence B, or recommendation class IIb and level of evidence C, respectively, in the 2015 ESC/ESR guidelines[6], and in the case of recommendation class I and level of evidence B, and recommendation class I and level of evidence C, respectively, in the 2017 JCS/JPCPHS guidelines[7]. Although BPA is associated with the risk of complications such as procedure-related pulmonary artery injury, it can result in marked improvement of CTEPH. Riociguat is an effective pulmonary vasodilator and is associated with a low risk of serious adverse events. It has been reported that sequential

treatment with riociguat and BPA results in significant improvements in terms of mean pulmonary arterial pressure and pulmonary vascular resistance among patients with inoperable CTEPH[23], no reports to date have directly compared the treatment outcomes of these two treatment methods. A randomized controlled trial comparing riociguat and BPA (the RACE study) is conducted in France[24], aligning with the start of the present study[25]. The aim of the present study is to compare the efficacy and safety of riociguat and BPA for inoperable CTEPH over the course of 12 months. The results of this study may aid in optimizing treatment selection and improving patient outcomes.

Methods and Analysis

Study design and setting: This Multicenter Randomized controlled trial based on Balloon Pulmonary Angioplasty for chronic thromboembolic pulmonary hypertension (MR BPA) study will recruit subjects from January 15, 2016 to October, 31, 2019. The study is a multicenter, prospective, randomized controlled trial. As shown in Figure 1, subjects will undergo right-heart catheterization and pulmonary angiography before provisional enrollment. An independent experienced PEA surgeon will determine if subjects are eligible for PEA. Those who are judged to have inoperable CTEPH will be assigned into either a BPA or riociguat group via an online assignment system, and will be observed for 12 months. In the BPA group, the severity of pulmonary hypertension and morphology of the pulmonary lesion will be evaluated by preoperative right-heart catheterization and pulmonary angiography. Then, BPA will be conducted depending on the lesion type. If lesions of pulmonary artery are not suitable for BPA, the procedure will not be performed even if the patient is assigned to the BPA group. However, at least among the collaborative institutions included in this study, PEA-inoperable patients are very rarely considered unsuitable for BPA, because these institutes are expert BPA centers in Japan. In general, BPA will be completed

within 4 months of the first BPA procedure. In the riociguat group, 1.0 mg riociguat will be administered three times per day. When systolic blood pressure is 95 mmHg or higher, the dose will be increased by 0.5 mg every two weeks up to a maximum dosage of 2.5 mg thrice daily. Dosage adjustment will be completed within 4 months of the first administration of riociguat, and administration will be continued for a total of 12 months. Observations will be made at the time of screening; baseline; and at 0–4, 6, and 12 months after initial treatment. Table 1 shows the schedule of assessments performed at each visit for each treatment group, including mandatory and optional assessments.

Sample size calculation: Previously, BPA has been shown to result in reduced mean pulmonary arterial pressure from 45.4 ± 9.6 to 24.0 ± 6.4 mmHg (mean ± standard deviation) within 24 months[11], while riociguat has been reported to decrease pulmonary arterial pressure by 4 ± 7 mmHg[9]. Based on these studies, it was assumed that the change in mean pulmonary arterial pressure from the start of treatment to 12 months after treatment would be −15 mmHg for the BPA group and −4 mmHg for the riociguat group, with standard deviation of 14 and 10, respectively. The minimum sample size required to achieve a significance of 0.05 from a two-sided test with a statistical power of 90% was determined to be 27 subjects for both groups; a total of 54 subjects. We estimated the dropout rate to be 10%; thus, the planned enrollment was set at 60 subjects, with 30 in each group.

Eligibility criteria: *Inclusion criteria*: (a) Diagnosis with CTEPH with a World Health Organization (WHO) functional class II or III based on the diagnostic criteria of the 2012 Japanese Circulation Society guidelines[24], (b) age ≥20 years or < 80 years, (c) mean pulmonary arterial pressure of ≥25 to <60 mmHg and pulmonary artery wedge pressure of ≤15 mmHg, (d) administration of appropriate anticoagulant therapy for at least 3 months

prior to study enrollment (in the case of warfarin, the prothrombin time-international normalized ratio should be 1.5–3.0), and (e) provision of written informed consent to participate after full explanation of the study.

Exclusion criteria: (a) History of BPA, (b) PEA within six months prior to study enrollment, (c) use of unapproved pharmaceutical products, (d) use of a pulmonary vasodilator within 4 weeks prior to right-heart catheterization, (e) co-existing etiology of pulmonary hypertension (except for that classified as Group 4 in the Nice Pulmonary Hypertension Classification System), (f) pregnancy or breastfeeding, (g) contraindicated for riociguat, (h) life expectancy of less than two years, and (i) deemed to be unsuitable for participation by the investigators.

Recruitment and consent: The informed consent document is presented to potentially eligible subjects to provide a comprehensive explanation of this study. Written consent is then obtained.

As a general rule, right-heart catheterization and pulmonary angiography are performed after acquiring consent and the possibility of definitive diagnosis of CTEPH is determined by the investigators. However, to reduce the burden on the subjects, data from within three months prior to consent acquisition for pulmonary angiography, right-heart catheterization, and CT scan, as well as pulmonary ventilation-perfusion scintigraphy obtained in general practice within 3 months prior to the time of consent, can also be utilized. This is explained to subjects by investigators at the time of obtaining consent.

Once consent is obtained, an independent experienced PEA surgeon who is not involved in this study will determine operability (whether subjects are eligible for PEA) based on imaging data according to the Guidelines for Treatment of Pulmonary Hypertension (2012 revised version)[26].

Random allocation: Random assignment will be performed centrally with stratification by mean pulmonary arterial pressure (<40 mmHg and ≥40 mmHg), and research institutions (Keio University, Okayama Medical Center, Kyusyu University, and Kobe University) by biased-coin minimization.

Endpoints: The primary endpoint will be the change in mean pulmonary arterial pressure between baseline and 12 months. Secondary endpoints will include several clinical and quality-of-life parameters (detailed in Table 2).

Data collection: An electronic, clinical-test data collection system—electric data capture system (EDC) —will be used for data collection. In cases when the system is unavailable, a case report form—a specialized data collection form—will be used, and the data later entered into the EDC. The investigators who will enter information into the EDC system will be responsible for ensuring accuracy and completeness of information.

Data management and monitoring: Data collection and management will be carried out by third-party entities to avoid bias. Data management will be performed by Soiken Inc. Data Management Group (the Data Center). The Data Center will prepare a "Procedure Manual for Data Management". The Data Center's approval is required prior to sending any data related to the subjects in electronic format. If data is transmitted over an unsecured electronic network, the data must be encoded at the source. Linkable anonymization by central registration number will be used to identify the subjects. The investigators will be responsible for appropriate storage of the correspondence table prepared by them to identify subjects, in accordance with the procedures at the particular research institution. This correspondence table must be retained for five years after completion of the study or three years after final

publication, whichever is later. Appropriate measures, such as encoding or deletion, will be taken to ensure that the subjects cannot be identified in any display or public disclosure of information related to the study, in accordance with applicable laws and regulations.

The Soiken Inc. Data Management Group will monitor the present study to manage and ensure quality. The monitoring manager will monitor subjects in accordance with the manual on monitoring procedure. For data quality management, the principal investigator and Central Committee will confirm the progress of the study as necessary through the Soiken Inc. Data Management Group to ensure conformance with the protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare).

Adverse events: The occurrence of any untoward medical events, including complications or the worsening of pre-existing underlying diseases, will be defined as adverse events. Worsening of efficacy evaluation indices will not be defined as adverse events. Any concomitant symptoms or clinically significant abnormal fluctuations in test results will be investigated to determine whether there is a cause-and-effect relationship with BPA or riociguat, and findings will be documented in the EDC system. Adverse events will be followed up until normalization or recovery to a level not considered to be an adverse event; or, in the case of an irreversible adverse event (cerebral infarction, myocardial infarction, etc.), until symptoms stabilize.

Statistical analysis: Primary and secondary efficacy endpoints will be analyzed using the full study population, which will include all patients who were randomized into one of the intervention groups. However, patients who withdraw their consent, patients with severe

protocol violation, such as registration without consenting, or registration out of the enrollment period, or patients without any data related to the primary endpoint after the randomization, were excluded from the full study population. Safety analysis will be conducted in the safety analysis population, which will include all patients who were randomized into one of the intervention groups and either received at least one dose of riociguat or attended at least one BPA procedure (regardless of whether BPA was carried out or not).

Baseline variables are presented as frequencies and proportions for categorical data, and means and standard deviations for continuous data. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact test for categorical endpoints, and the Student's t-test for continuous variables.

For primary analysis, the least square-means difference and 95% confidence interval for change of pulmonary arterial pressure between groups at 12 months will be estimated using analysis of covariance (ANCOVA) adjusted for allocation factors. Secondary analysis will be performed in the same manner as primary analysis. Adverse events will be evaluated during safety analysis. The frequencies of adverse events will be compared using Fisher's exact test. All comparisons are planned, and all *p*-values will be two sided. We consider *p*-values of <0.05 to be statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Statistical analysis plan will be developed by the principal investigator and biostatistician before completion of patient recruitment and data fixation.

Patient and public involvement: There is no patient involvement.

Discussion

Guidelines for the diagnosis and treatment for CTEPH in Western countries[5, 6] and Japan[7, 26] recommend riociguat and BPA for patients with inoperable CTEPH. However, there are no reports directly comparing treatment outcomes of these two approaches. The primary endpoint of this study will be the change in mean pulmonary arterial pressure from baseline to 12 months, as this is an important prognostic factor of CTEPH. Other outcomes often used in studies on CTEPH, such as the 6-minute walk distance and pulmonary vascular resistance, are secondary endpoints in the present study. Sequential treatment with riociguat and BPA for patients with inoperable CTEPH has been shown to significantly improve mean pulmonary arterial pressure and pulmonary vascular resistance, highlighting the benefits of BPA[23]. A randomized controlled trial directly comparing riociguat and BPA is conducted in France[24]; the present study was therefore planned to compare the efficacy and safety of riociguat and BPA for treatment of inoperable CTEPH. The present study and the RACE study both began in January 2016[25]. Results from randomized trials such as these will be critical for optimizing treatment selection and improving outcomes of inoperable CTEPH.

In the present study, BPA treatment will be completed in 4 months, which is equivalent as real-world conditions in Japan. This study will also evaluate the long-term efficacy and safety of riociguat and BPA by continuing evaluations for 12 months after initiation of treatment. A recent systematic review has shown that treatment outcomes of BPA are better in Japan than in Western countries[4, 27]. The present study will be conducted in expert CTEPH centers in Japan, and will therefore compare the treatment efficacy and safety of riociguat and the highest-quality BPA in Japan. In addition, the operability of PEA will be determined by an independent experienced PEA surgeon who belongs to independent institute and is the most experienced PEA surgeon in Japan, having performed 49 PEAs in the last 3 years (320 PEAs in total). This will avoid recruitment bias and guarantee reliability in the present study. Furthermore, this study will compare the costs to health insurance resources and patient-

reported quality-of-life parameters for each therapy. These factors may contribute to optimizing treatment strategies or amending treatment guidelines for inoperable CTEPH. While these are the strengths of this study, there are several limitations which should be acknowledged. One limitation is that this is an open-label trial. Because there is no distinct criterion for BPA in each lesion, surgeons are aware of the mean pulmonary arterial pressure (the primary endpoint in this study), and they might be incentivized to continue BPA. Thus, bias for the BPA surgeons cannot be completely avoided. However, since this study will compare medical and surgical treatment, it is difficult to use a placebo or mask patients and/or physicians. Another limitation is that a relatively small number of patients will be enrolled (30 subjects per group, a total of 60 subjects).

Ethics and dissemination: This study and its protocols were approved by the institutional review board of the Keio University School of Medicine, and by each participating institution. The study will be conducted in accordance with the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan, and other current legal regulations in Japan. Written informed consent will be obtained from all participants after full explanation of this study. Results of the study will be disseminated at medical conferences and in journal publications.

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Author contributions:

TK and HM contributed to the conception and design of the study, drafted the protocol, and supervised the revision. MK, KA, SK, YS and TS provided intellectual input to improve the study design and revise the protocol. KF contributed to and supervised the conception and design of the study. All authors read and approved the final manuscript.

Funding statement:

This study was financially supported by Bayer Yakuhin, Ltd.

Competing interests statement:

SK received honoraria for scientific lectures from Bayer Yakuhin, Ltd. KF received scholarship grants from Bayer Yakuhin, Ltd. and MSD K.K. The other authors declare no conflict of interest.

Figure and table legends

Figure 1. Flow diagram of study recruitment and randomization. After obtaining consent and diagnosis of chronic thromboembolic pulmonary hypertension is confirmed, subjects will be randomized into either the balloon-pulmonary-angioplasty or riociguat group, to receive treatment for 12 months. Observations will be recorded at the time of screening; baseline; an at 0–4, 6, and 12 months after the initiation of treatment. Abbreviations: BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension.

Table 1. Schedule of assessments for enrolled subjects.

Table 2. Secondary endpoints that will be measured and/or compared at baseline and at 12 months after initiation of treatment.

Table 1: Schedule of assessments for enrolled subjects.

Observation items	Screening	Baseline	Observation period		
	~0M	0M	0–4M	6M + 1M	12M + 2M
Subjects' attributes	○	○	—	—	—
6-minute walk distance	—	○	—	○	○
Borg dyspnea index	—	○	—	○	○
WHO functional class	—	○	—	○	○
Right-heart catheterization	○	—	—	○	○
Pulmonary angiography	○	—	—	—	—
Pulmonary function	—	○	—	○	○
Blood gas test[a]		○	—	○	○
Vital signs[a]		○	—	○	○
Echocardiography (cardiac ultrasound)	—	○	—	○	○
Chest X-ray		○	○[b]	○	○
Chest CT scan	○	—	○[b]	○	○
Oxygen therapy usage status	—	○	—	○	○
Adverse event onset[c]	—	—	←	○	→
Clinical worsening and time to clinical	—	—	←	○	→

worsening[c]					
Quality-of-life parameters (EQ5D)	—	○	—	○	○
Health insurance	—	—	←	○	→
BPA status[d]	—	—	○	—	—
Medication adherence[e]	—	—	←	○	→

Notes: (a) Recommended during right-heart catheterization, (b) required if balloon pulmonary angioplasty is performed, (c) onset of adverse events and indices related to clinical worsening will be observed as necessary throughout the clinical study period, (d) observational items for the balloon-pulmonary-angioplasty group, (e) observational items for the riociguat group. Abbreviations: BPA, balloon pulmonary angioplasty; CT, computed tomography; WHO, World Health Organization.

Table 2: Secondary endpoints that will be measured and/or compared at baseline and at 12 months after initiation of treatment.

Endpoint	
Change in 6-minute walk distance	
Change in Borg dyspnea index	
Change in hemodynamic variables	Including pulmonary vascular resistance, mean right arterial pressure, cardiac output, etc.
Change in WHO functional class	
Change in plasma brain natriuretic peptide levels	
Change in SaO_2 and PaO_2	
Change in usage volume of oxygen therapy	Including commencing oxygen therapy due to exacerbation of primary disease or dosage change.
Change in pulmonary function	
Change in echocardiography parameter	
Frequency and severity of pulmonary artery injury	Assessed by chest X-ray and chest CT scan.
Frequency of adverse events	Bloody sputum/hemoptysis/pulmonary hemorrhage (vascular perforation, vascular dissection, vascular rupture, etc.), pneumothorax, hypotension, pulmonary congestion/pulmonary edema, late-onset lung disturbance, heart failure, pneumonia, headache, dizziness, peripheral edema, nausea/vomiting, retching, diarrhea, nasopharyngitis, upper respiratory

	inflammation, respiratory distress, coughing, fainting.
Clinical worsening during the observation period and time to clinical worsening	All-cause mortality, heart/lung transplant, salvage PEA due to worsening of primary disease, new or repeated implementation of BPA due to the worsening of a primary disease, hospitalization, new initiation of pulmonary vasodilators, worsening of 30% or greater from baseline in the 6-minute walk distance, persistent worsening in the WHO functional class from baseline due to the worsening of a primary disease.
Change in quality-of-life parameters (EQ5D)	
Health insurance resource costs	

Abbreviations: BPA, balloon pulmonary angioplasty; CT, computed tomography; PaO_2, partial pressure of oxygen; PEA, pulmonary endarterectomy; SaO_2, saturation of arterial blood; WHO, World Health Organization.

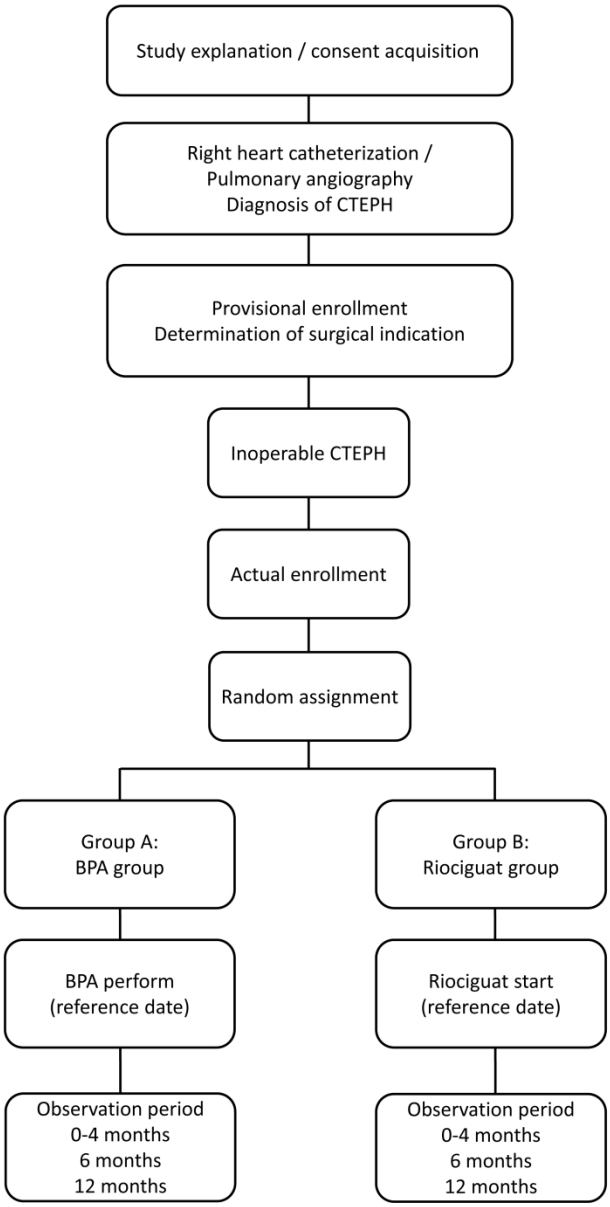

Figure 1. Study outline and randomization schematic. After consent, and CTEPH diagnosis is confirmed, subjects will be randomized into either BPA or riociguat group for 12 months, and observation measurements taken at screening, baseline, 0-4, 6 and 12 months.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/Item	Item No.	Description	Page in protocol	Page in protocol paper
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 5	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	42	3
	2b	All items from the World Health Organization Trial Registration Data Set	42	3
Protocol version	3	Date and version identifier	1	
Funding	4	Sources and types of financial, material, and other support	43	2, 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 43-47	1
	5b	Name and contact information for the trial sponsor	1	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	43	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	44-47	
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	11	3, 5
	6b	Explanation for choice of comparators	11	3, 5
Objectives	7	Specific objectives or hypotheses	5, 11-12	3, 5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 12	6
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	45	1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6, 13-14	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12, 16-24	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	28-29, 36	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	23-24	20
	11d	Relevant concomitant care and interventions that are permitted	17	

		or prohibited during the trial		
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7, 14-16	8, 21-22
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-24	6-8, 19-20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	31	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17-20	7-8
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	19-20	6-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16, 19-20	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16, 19-20	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18-19	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18-19	6
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	20-24	6-8, 19-20
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	28-29	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	29-31	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	32-34	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	32-34	10-11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	30-31	10-11

		imputation)		
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	46	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	34	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	25-28	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A	N/A
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	34-35	11-12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	35	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	36-39	7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	38-39	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	43	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	29-31	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	40	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	42	11-12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A	N/A
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	37-38	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Multicenter randomized controlled trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Protocol for the MR BPA study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028831.R3
Article Type:	Protocol
Date Submitted by the Author:	20-Dec-2019
Complete List of Authors:	Kawakami, Takashi; Keio University, School of Medicine, Cardiology Matsubara, Hiromi; Okayama Medical Center Abe, Kohtaro; Kyushu University Kataoka, Masaharu ; Keio University, School of Medicine Kohsaka, Shun; Keio University, School of Medicine Sato, Yasunori ; Department of Preventive Medicine and Public Health, Keio University School of Medicine, Shinke, Toshiro; Showa University Fukuda, Keiichi; Keio University, School of Medicine
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Cardiovascular medicine, Surgery
Keywords:	chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, riociguat

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Multicenter randomized controlled trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Protocol for the MR BPA study

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Acknowledgements: The study was funded by Bayer Yakuhin Ltd.

Keywords: Chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, riociguat

Abstract

Introduction: Management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) remains a clinical challenge. Currently, medical treatment involving pulmonary vasodilators (such as soluble guanylate-cyclase stimulators) is recommended, primarily for ameliorating symptoms. More recently, balloon pulmonary angioplasty (BPA) has been developed as alternative treatment for inoperable CTEPH. The present study aimed to compare the efficacy and safety of BPA and riociguat (a soluble guanylate-cyclase stimulator) as treatments for inoperable CTEPH.

Methods and analysis: The present study is a multicenter randomized controlled trial. Subjects with inoperable CTEPH were randomized (1:1) into either a BPA or riociguat group, and observed for 12 months after initiation of treatment. The primary endpoint will be the change in mean pulmonary arterial pressure from baseline to 12 months after initiation of treatment. For primary analysis, we will estimate the least square-means difference and 95% confidential interval for the change of pulmonary arterial pressure between the groups at 12 months using analysis of covariance adjusted for allocation factors.

Ethics and dissemination: This study and its protocols were approved by the institutional review board of Keio University School of Medicine and each participating institution. Written informed consent was obtained from all participants. Results will be disseminated at medical conferences and in journal publications.

Registration: This study is registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (UMIN000019549).

Strengths and limitations of the study:

- This is a randomized controlled trial comparing the efficacy and safety of BPA and riociguat in patients with inoperable CTEPH.
- This study evaluates the efficacy and safety of BPA and riociguat over a relatively long period (12 months).
- This is the first study to compare health insurance resource costs between BPA and riociguat.
- A limitation of this study is the open-label trial design.
- Another limitation of is that this study recruited a relatively small number of subjects.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by stenosis and/or occlusion of pulmonary arteries caused by organized thrombi[1]. Early diagnosis and appropriate treatment are critical, as the condition is associated with a high rate of mortality due to right-sided heart failure[2]. Pulmonary endarterectomy (PEA) is an established curative treatment for operable CTEPH[3, 4]. According to the American Heart Association/American College of Cardiology (AHA/ACC)[5], European Society of Cardiology/European Respiratory Society (ESC/ERS)[6], and Japanese Circulation Society/the Japanese Pulmonary Circulation and Pulmonary Hypertension Society (JCS/JPCPHS)[7] guidelines, PEA is recommended for patients with operable CTEPH as the first-line therapy in the case of recommendation class I and level of evidence C.

In 2014, for the first time, a soluble guanylate-cyclase stimulator (riociguat, a pulmonary vasodilator) received approval for insurance reimbursement in the context of inoperable or persistent/recurrent CTEPH. This was based on the findings of a multicenter randomized clinical trial (CHEST-1)[8] and its extension study (CHEST-2)[9] which highlighted the efficacy of riociguat for patients with inoperable CTEPH. Balloon pulmonary angioplasty (BPA) is a catheter-based treatment which has also been reported to be effective for inoperable CTEPH[10-22]. Riociguat and BPA are recommended for patients with inoperable CTEPH in the case of recommendation class I and level of evidence B, or recommendation class IIb and level of evidence C, respectively, in the 2015 ESC/ESR guidelines[6], and in the case of recommendation class I and level of evidence B, and recommendation class I and level of evidence C, respectively, in the 2017 JCS/JPCPHS guidelines[7]. Although BPA is associated with the risk of complications such as procedure-related pulmonary artery injury, it can result in marked improvement of CTEPH. Riociguat is an effective pulmonary vasodilator and is associated with a low risk of serious adverse events. It has been reported that sequential

treatment with riociguat and BPA results in significant improvements in terms of mean pulmonary arterial pressure and pulmonary vascular resistance among patients with inoperable CTEPH[23], no reports to date have directly compared the treatment outcomes of these two treatment methods. A randomized controlled trial comparing riociguat and BPA (the RACE study) is conducted in France[24], aligning with the start of the present study[25]. The aim of the present study is to compare the efficacy and safety of riociguat and BPA for inoperable CTEPH over the course of 12 months. The results of this study may aid in optimizing treatment selection and improving patient outcomes.

Methods and Analysis

Study design and setting: This Multicenter Randomized controlled trial based on Balloon Pulmonary Angioplasty for chronic thromboembolic pulmonary hypertension (MR BPA) study recruited subjects from January 15, 2016 to October, 31, 2019. The study is a multicenter, prospective, randomized controlled trial. As shown in Figure 1, subjects willing to consider enrolment were consented prior to invasive evaluation. Subjects underwent right-heart catheterization and pulmonary angiography for definitive diagnosis of CTEPH by the standard practice in Japan. The identified CTEPH patients were provisionally enrolled in the study. An independent experienced PEA surgeon determined if subjects were eligible for PEA. If the subjects were deemed technically operable, they were excluded from the study. Those who were judged to have inoperable CTEPH were assigned into either a BPA or riociguat group via an online assignment system, and will be observed for 12 months. In the BPA group, the severity of pulmonary hypertension and morphology of the pulmonary lesion were evaluated by preoperative right-heart catheterization and pulmonary angiography. Then, BPA will be conducted depending on the lesion type. If lesions of pulmonary artery are not suitable for BPA, the procedure will not be performed even if the patient is assigned to the

BPA group. However, at least among the collaborative institutions included in this study, PEA-inoperable patients are very rarely considered unsuitable for BPA, because these institutes are expert BPA centers in Japan. In general, BPA will be completed within 4 months of the first BPA procedure. In the riociguat group, 1.0 mg riociguat will be administered three times per day. When systolic blood pressure is 95 mmHg or higher, the dose will be increased by 0.5 mg every two weeks up to a maximum dosage of 2.5 mg thrice daily. Dosage adjustment will be completed within 4 months of the first administration of riociguat, and administration will be continued for a total of 12 months. Observations will be made at the time of screening; baseline; and at 0–4, 6, and 12 months after initial treatment. Table 1 shows the schedule of assessments performed at each visit for each treatment group, including mandatory and optional assessments.

Sample size calculation: Previously, BPA has been shown to result in reduced mean pulmonary arterial pressure from 45.4 ± 9.6 to 24.0 ± 6.4 mmHg (mean ± standard deviation) within 24 months[11], while riociguat has been reported to decrease pulmonary arterial pressure by 4 ± 7 mmHg[9]. Based on these studies, it was assumed that the change in mean pulmonary arterial pressure from the start of treatment to 12 months after treatment would be −15 mmHg for the BPA group and −4 mmHg for the riociguat group, with standard deviation of 14 and 10, respectively. The minimum sample size required to achieve a significance of 0.05 from a two-sided test with a statistical power of 90% was determined to be 27 subjects for both groups; a total of 54 subjects. We estimated the dropout rate to be 10%; thus, the planned enrollment was set at 60 subjects, with 30 in each group.

Eligibility criteria: *Inclusion criteria*: (a) Diagnosis with CTEPH with a World Health Organization (WHO) functional class II or III based on the diagnostic criteria of the 2012

Japanese Circulation Society guidelines[24], (b) age ≥20 years or < 80 years, (c) mean pulmonary arterial pressure of ≥25 to <60 mmHg and pulmonary artery wedge pressure of ≤15 mmHg, (d) administration of appropriate anticoagulant therapy for at least 3 months prior to study enrollment (in the case of warfarin, the prothrombin time-international normalized ratio should be 1.5–3.0), and (e) provision of written informed consent to participate after full explanation of the study.

Exclusion criteria: (a) History of BPA, (b) PEA within six months prior to study enrollment, (c) use of unapproved pharmaceutical products, (d) use of a pulmonary vasodilator within 4 weeks prior to right-heart catheterization, (e) co-existing etiology of pulmonary hypertension, (f) pregnancy or breastfeeding, (g) contraindicated for riociguat, (h) life expectancy of less than two years, and (i) deemed to be unsuitable for participation by the investigators.

Recruitment and consent: The informed consent document was presented to potentially eligible subjects to provide a comprehensive explanation of this study. Written consent was then obtained.

As a general rule, subjects willing to consider enrolment were consented prior to right-heart catheterization and pulmonary angiography for definitive diagnosis of CTEPH by the standard practice in Japan. However, to reduce the burden on the subjects, suitable patients that had undergone comprehensive evaluation including right-heart catheterization and pulmonary angiography within 3 months prior to the consenting could also be enrolled to the study. This was explained to subjects by investigators at the time of obtaining consent.

Once consent was obtained, an independent experienced PEA surgeon who is not involved in this study determined operability (whether subjects were eligible for PEA) based on imaging data according to the Guidelines for Treatment of Pulmonary Hypertension (2012 revised version)[26].

Random allocation: Random assignment were performed centrally with stratification by mean pulmonary arterial pressure (<40 mmHg and ≥40 mmHg), and research institutions (Keio University, Okayama Medical Center, Kyusyu University, and Kobe University) by biased-coin minimization.

Endpoints: The primary endpoint will be the change in mean pulmonary arterial pressure between baseline and 12 months. Secondary endpoints will include several clinical and quality-of-life parameters (detailed in Table 2).

Data collection: An electronic, clinical-test data collection system—electric data capture system (EDC) —is used for data collection. In cases when the system is unavailable, a case report form—a specialized data collection form—is used, and the data later entered into the EDC. The investigators who enter information into the EDC system are responsible for ensuring accuracy and completeness of information. The information of the health insurance resource costs are collected from Diagnosis Procedure Combination/Pre-Diem Payment system.

Data management and monitoring: Data collection and management is carried out by third-party entities to avoid bias. Data management is performed by Soiken Inc. Data Management Group (the Data Center). The Data Center prepared a "Procedure Manual for Data Management". The Data Center's approval is required prior to sending any data related to the subjects in electronic format. If data is transmitted over an unsecured electronic network, the data must be encoded at the source. Linkable anonymization by central registration number is used to identify the subjects. The investigators are responsible for appropriate storage of the

correspondence table prepared by them to identify subjects, in accordance with the procedures at the particular research institution. This correspondence table must be retained for five years after completion of the study. Appropriate measures, such as encoding or deletion, are taken to ensure that the subjects cannot be identified in any display or public disclosure of information related to the study, in accordance with applicable laws and regulations.

The Soiken Inc. Data Management Group monitors the present study to manage and ensure quality. The monitoring manager monitors subjects in accordance with the manual on monitoring procedure. For data quality management, the principal investigator and Central Committee confirms the progress of the study as necessary through the Soiken Inc. Data Management Group to ensure conformance with the protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Dec. 22, 2014; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare) and the Clinical Trials Act (April. 14, 2017; Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare).

Adverse events: The occurrence of any untoward medical events, including complications or the worsening of pre-existing underlying diseases, is defined as adverse events. Worsening of efficacy evaluation indices are be defined as adverse events. Any concomitant symptoms or clinically significant abnormal fluctuations in test results are investigated to determine whether there is a cause-and-effect relationship with BPA or riociguat, and findings will be documented in the EDC system. Adverse events are followed up until normalization or recovery to a level not considered to be an adverse event; or, in the case of an irreversible adverse event (cerebral infarction, myocardial infarction, etc.), until symptoms stabilize.

Statistical analysis: Primary and secondary efficacy endpoints will be analyzed using the full study population, which will include all patients who were randomized into one of the intervention groups. However, patients who withdraw their consent, patients with severe protocol violation, such as registration without consenting, or registration out of the enrollment period, or patients without any data related to the primary endpoint after the randomization, were excluded from the full study population. Safety analysis will be conducted in the safety analysis population, which will include all patients who were randomized into one of the intervention groups and either received at least one dose of riociguat or attended at least one BPA procedure (regardless of whether BPA was carried out or not).

Baseline variables are presented as frequencies and proportions for categorical data, and means and standard deviations for continuous data. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact test for categorical endpoints, and the Student's t-test for continuous variables.

For primary analysis, the least square-means difference and 95% confidence interval for change of pulmonary arterial pressure between groups at 12 months will be estimated using analysis of covariance (ANCOVA) adjusted for allocation factors. Secondary analysis will be performed in the same manner as primary analysis. Adverse events will be evaluated during safety analysis. The frequencies of adverse events will be compared using Fisher's exact test. All comparisons are planned, and all *p*-values will be two sided. We consider *p*-values of <0.05 to be statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Statistical analysis plan will be developed by the principal investigator and biostatistician before completion of patient recruitment and data fixation.

Patient and public involvement: Patients nor public are not involved in the study, including the planning, execution, analysis and evaluation..

Discussion

Guidelines for the diagnosis and treatment for CTEPH in Western countries[5, 6] and Japan[7, 26] recommend riociguat and BPA for patients with inoperable CTEPH. However, there are no reports directly comparing treatment outcomes of these two approaches. The primary endpoint of this study will be the change in mean pulmonary arterial pressure from baseline to 12 months, as this is an important prognostic factor of CTEPH. Other outcomes often used in studies on CTEPH, such as the 6-minute walk distance and pulmonary vascular resistance, are secondary endpoints in the present study. Sequential treatment with riociguat and BPA for patients with inoperable CTEPH has been shown to significantly improve mean pulmonary arterial pressure and pulmonary vascular resistance, highlighting the benefits of BPA[23]. A randomized controlled trial directly comparing riociguat and BPA is conducted in France[24]; the present study was therefore planned to compare the efficacy and safety of riociguat and BPA for treatment of inoperable CTEPH. The present study and the RACE study both began in January 2016[25]. Results from randomized trials such as these will be critical for optimizing treatment selection and improving outcomes of inoperable CTEPH.

In the present study, BPA treatment will be completed in 4 months, which is equivalent as real-world conditions in Japan. This study will also evaluate the long-term efficacy and safety of riociguat and BPA by continuing evaluations for 12 months after initiation of treatment. A recent systematic review has shown that treatment outcomes of BPA are better in Japan than in Western countries[4, 27]. The present study is conducted in expert CTEPH centers in Japan, and will therefore compare the treatment efficacy and safety of riociguat and the highest-quality BPA in Japan. In addition, the operability of PEA were determined by an independent

experienced PEA surgeon who belongs to independent institute and is the most experienced PEA surgeon in Japan, having performed 49 PEAs in the last 3 years (320 PEAs in total). This avoided recruitment bias and guarantee reliability in the present study. Furthermore, this study will compare the costs to health insurance resources and patient-reported quality-of-life parameters for each therapy. These factors may contribute to optimizing treatment strategies or amending treatment guidelines for inoperable CTEPH. While these are the strengths of this study, there are several limitations which should be acknowledged. One limitation is that this is an open-label trial. Because there is no distinct criterion for BPA in each lesion, operators are aware of the mean pulmonary arterial pressure (the primary endpoint in this study), and they might be incentivized to continue BPA. Thus, bias for the BPA operators cannot be completely avoided. However, since this study will compare medical and surgical treatment, it is difficult to use a placebo or mask patients and/or physicians. Another limitation is that a relatively small number of patients will be enrolled (30 subjects per group, a total of 60 subjects).

Ethics and dissemination: This study and its protocols were firstly approved by the institutional review board of each participating institution; Keio University School of Medicine an Ethical Committee, Ethics Committee of Okayama Medical Center, Clinical trial ethical review committee of Kyusyu University Graduated School of Medicine, and Medical Ethical committee of Kobe University Graduated School of Medicine, according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan. Because of the dispense of the Clinical Trials Act in April, 2017, this study and its protocols were again inspected and approved by the Certified Review Board of Keio, which had obtained certification from the Minister of Health, Labour and Welfare in Japan. The study is conducted in accordance with the

Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan, the Clinical Trials Act, and other current legal regulations in Japan. Written informed consent was obtained from all participants after full explanation of this study. Results of the study will be disseminated at medical conferences and in journal publications.

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Author contributions:

TK and HM contributed to the conception and design of the study, drafted the protocol, and supervised the revision. MK, KA, SK, YS and TS provided intellectual input to improve the study design and revise the protocol. KF contributed to and supervised the conception and design of the study. All authors read and approved the final manuscript.

Funding statement:

This study was financially supported by Bayer Yakuhin, Ltd. Bayer Yakuhin, Ltd. is not involved in this study, including the planning, execution, data management, statistical analysis, evaluation, or write-up.

Competing interests statement:

SK received honoraria for scientific lectures from Bayer Yakuhin, Ltd. KF received scholarship grants from Bayer Yakuhin, Ltd. and MSD K.K. The other authors declare no conflict of interest.

Figure and table legends

Figure 1. Flow diagram of study recruitment and randomization. After obtaining consent and diagnosis of chronic thromboembolic pulmonary hypertension is confirmed, subjects will be randomized into either the balloon-pulmonary-angioplasty or riociguat group, to receive treatment for 12 months. Observations will be recorded at the time of screening; baseline; an at 0–4, 6, and 12 months after the initiation of treatment. Abbreviations: BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension.

Table 1. Schedule of assessments for enrolled subjects.

Table 2. Secondary endpoints that will be measured and/or compared at baseline and at 12 months after initiation of treatment.

Table 1: Schedule of assessments for enrolled subjects.

Observation items	Screening	Baseline	Observation period		
	~0M	0M	0–4M	6M + 1M	12M + 2M
Subjects' attributes	○	○	—	—	—
6-minute walk distance	—	○	—	○	○
Borg dyspnea index	—	○	—	○	○
WHO functional class	—	○	—	○	○
Right-heart catheterization	○	—	—	○	○
Pulmonary angiography	○	—	—	—	—
Pulmonary function	—	○	—	○	○
Blood gas test[a]		○	—	○	○
Vital signs[a]		○	—	○	○
Echocardiography (cardiac ultrasound)	—	○	—	○	○
Chest X-ray		○	○[b]	○	○
Chest CT scan	○	—	○[b]	○	○
Oxygen therapy usage status	—	○	—	○	○
Adverse event onset[c]	—	—	←	○	→
Clinical worsening and time to clinical	—	—	←	○	→

worsening[c]					
Quality-of-life parameters (EQ5D)	—	○	—	○	○
Health insurance	—	—		← ○ →	
BPA status[d]	—	—	○	—	—
Medication adherence[e]	—	—		← ○ →	

Notes: (a) Recommended during right-heart catheterization, (b) required if balloon pulmonary angioplasty is performed, (c) onset of adverse events and indices related to clinical worsening will be observed as necessary throughout the clinical study period, (d) observational items for the balloon-pulmonary-angioplasty group, (e) observational items for the riociguat group. Abbreviations: BPA, balloon pulmonary angioplasty; CT, computed tomography; WHO, World Health Organization.

Table 2: Secondary endpoints that will be measured and/or compared at baseline and at 12 months after initiation of treatment.

Endpoint	
Change in 6-minute walk distance	
Change in Borg dyspnea index	
Change in hemodynamic variables	Including pulmonary vascular resistance, mean right arterial pressure, cardiac output, etc.
Change in WHO functional class	
Change in plasma brain natriuretic peptide levels	
Change in SaO_2 and PaO_2	
Change in usage volume of oxygen therapy	Including commencing oxygen therapy due to exacerbation of primary disease or dosage change.
Change in pulmonary function	
Change in echocardiography parameter	
Frequency and severity of pulmonary artery injury	Assessed by chest X-ray and chest CT scan.
Frequency of adverse events	Bloody sputum/hemoptysis/pulmonary hemorrhage (vascular perforation, vascular dissection, vascular rupture, etc.), pneumothorax, hypotension, pulmonary congestion/pulmonary edema, late-onset lung disturbance, heart failure, pneumonia, headache, dizziness, peripheral edema, nausea/vomiting, retching, diarrhea, nasopharyngitis, upper respiratory

	inflammation, respiratory distress, coughing, fainting.
Clinical worsening during the observation period and time to clinical worsening	All-cause mortality, heart/lung transplant, salvage PEA due to worsening of primary disease, new or repeated implementation of BPA due to the worsening of a primary disease, hospitalization, new initiation of pulmonary vasodilators, worsening of 30% or greater from baseline in the 6-minute walk distance, persistent worsening in the WHO functional class from baseline due to the worsening of a primary disease.
Change in quality-of-life parameters (EQ5D)	
Health insurance resource costs	

Abbreviations: BPA, balloon pulmonary angioplasty; CT, computed tomography; PaO_2, partial pressure of oxygen; PEA, pulmonary endarterectomy; SaO_2, saturation of arterial blood; WHO, World Health Organization.

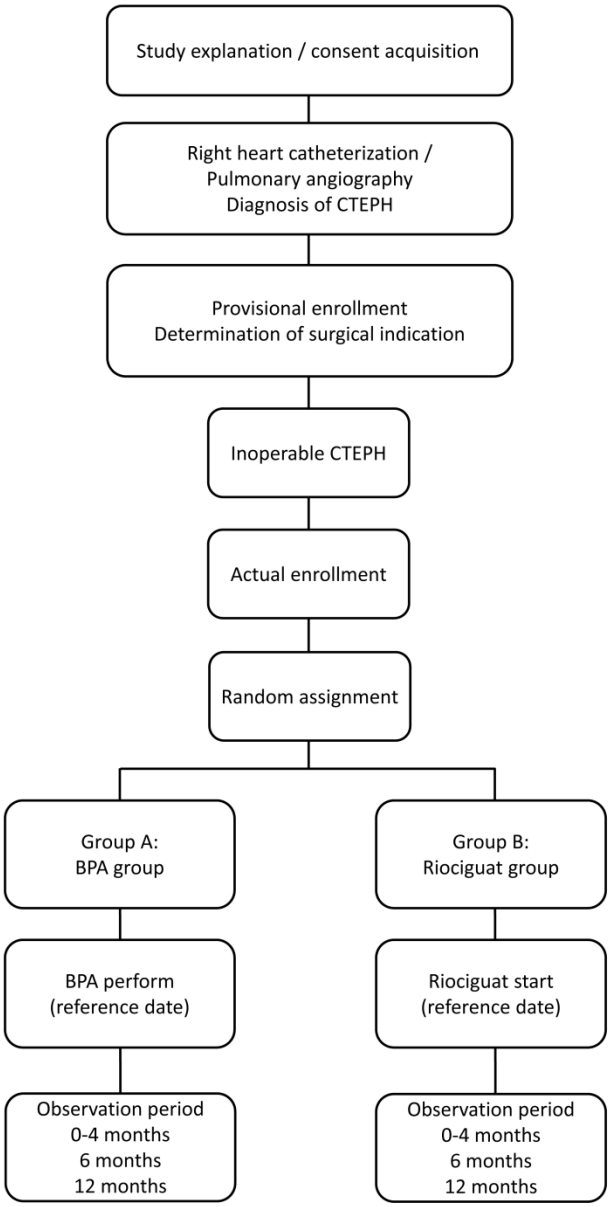

Figure 1. Study outline and randomization schematic. After consent, and CTEPH diagnosis is confirmed, subjects will be randomized into either BPA or riociguat group for 12 months, and observation measurements taken at screening, baseline, 0-4, 6 and 12 months.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/Item	Item No.	Description	Page in protocol	Page in protocol paper
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 5	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	42	3
	2b	All items from the World Health Organization Trial Registration Data Set	42	3
Protocol version	3	Date and version identifier	1	
Funding	4	Sources and types of financial, material, and other support	43	2, 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 43-47	1
	5b	Name and contact information for the trial sponsor	1	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	43	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	44-47	
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	11	3, 5
	6b	Explanation for choice of comparators	11	3, 5
Objectives	7	Specific objectives or hypotheses	5, 11-12	3, 5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 12	6
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	45	1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6, 13-14	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12, 16-24	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	28-29, 36	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	23-24	20
	11d	Relevant concomitant care and interventions that are permitted	17	

		or prohibited during the trial		
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7, 14-16	8, 21-22
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-24	6-8, 19-20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	31	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17-20	7-8
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	19-20	6-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16, 19-20	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16, 19-20	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18-19	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18-19	6
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	20-24	6-8, 19-20
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	28-29	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	29-31	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	32-34	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	32-34	10-11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	30-31	10-11

		imputation)		
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	46	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	34	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	25-28	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A	N/A
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	34-35	11-12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	35	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	36-39	7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	38-39	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	43	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	29-31	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	40	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	42	11-12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A	N/A
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	37-38	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.