Efficacy and safety of edoxaban in patients with chronic thromboembolic pulmonary hypertension: protocol for a multicentre, randomised, warfarin-controlled, parallel group trial - KABUKI trial

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ABSTRACT

Introduction Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of prior pulmonary thromboembolism (PE), caused by incomplete clot dissolution after PE. In patients with CTEPH, lifelong anticoagulation is mandatory to prevent recurrence of PE and secondary in situ thrombus formation. Warfarin, a vitamin K antagonist, is commonly used for anticoagulation in CTEPH based on historical experience and evidence. The anticoagulant activity of warfarin is affected by food and drug interactions, requiring regular monitoring of prothrombin time. The liability of anticoagulant effect often results in haemorrhagic and thromboembolic complications. Thus, lifelong warfarin is a handicap in terms of safety and convenience. Currently, the use of direct oral anticoagulants (DOACs) in CTEPH has increased with the advent of four DOACs. The safety of DOACs is superior to warfarin, with less intracranial bleeding in patients with non-valvular atrial fibrillation and venous thromboembolism. Edoxaban, the latest DOAC, also has proven efficacy and safety for those diseases in two large clinical trials; the ENGAGE-AF trial and HOKUSAI-VTE trial. The present trial seeks to evaluate whether edoxaban is non-inferior to warfarin in preventing worsening of CTEPH.

Methods and analysis The KABUKI trial is an investigator-initiated, multicentre, phase 3, randomised, single-blind, parallel-group, warfarin-controlled, non-inferiority trial to evaluate the efficacy and safety of edoxaban versus warfarin (vitamin K Antagonist) in subjects with chronic thromboembolic pulmonary hypertension taking warfarin (vitamin K antagonist) at baseline is designed to prove the non-inferiority of edoxaban to warfarin in terms of efficacy and safety in patients with CTEPH.

Ethics and dissemination This study is approved by the Institutional Review Board of each participating institution. The findings will be published in a peer-reviewed journal, including positive, negative and inconclusive results.

Trial registration number NCT04730037.

Strengths and limitations of this study

⇒ This study is the first multicentre randomised controlled trial comparing the efficacy and safety of edoxaban and warfarin in patient with chronic thromboembolic pulmonary hypertension (CTEPH).
⇒ The study is designed to prove non-inferiority of edoxaban to warfarin by evaluating the changes in catheter-based pulmonary vascular resistance in edoxaban and warfarin arms over 12 months.
⇒ The secondary efficacy and safety endpoints are the incidence of clinical worsening of CTEPH and the incidence of major bleeding and/or clinically relevant non-major bleeding.
⇒ The trial is conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines.
⇒ A limitation of this study is small sample size.

Protocol version This paper was written per the study protocol V.4.0, dated 29 January 2021.

INTRODUCTION

The KABUKI trial is an investigator-initiated, multicentre, phase 3, randomised, single-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of edoxaban versus warfarin (vitamin K Antagonist) in subjects with chronic thromboembolic pulmonary hypertension taking warfarin (vitamin K antagonist) at baseline is designed to prove the non-inferiority of edoxaban to warfarin in terms of efficacy and safety in patients with CTEPH.

CTEPH is a complication of prior pulmonary
thromboembolism (PE) and develops in approximately 4% of patients with PE.\(^1\)\(^2\) Although the pivotal pathogenesis of CTEPH is incomplete clot dissolution, once CTEPH is established, secondary pathogenic mechanisms including shear stress-induced microvascular arteriopathy in non-obstructed vascular regions and in situ thrombus formation due to blood flow disturbance cause disease progression.\(^3\) The annual incidence of CTEPH is reported to be 5.1 per 100,000 population in the USA, 3.3–5.0 in Europe and 1.9 in Japan,\(^4\) although the numbers of patients with CTEPH are increasing. Dedicated treatments such as pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA) and/or pulmonary vasodilators have improved the haemodynamics and the long-term survival in these patients.\(^3\)\(^9\) Meanwhile, anticoagulation is the most crucial treatment for CTEPH and is continued lifelong irrespective of the specific treatments. CTEPH per se is a risk for fatal PE, since large-vessel occlusion/stenosis and microvascular disease reduce the pulmonary circulatory reserve in these patients. Lifelong anticoagulation is therefore the mandatory treatment for CTEPH. Warfarin, a vitamin K antagonist (VKA), is the first-line anticoagulant used in CTEPH because of the abundant available data and historical experience for the prevention of recurrent PE and CTEPH exacerbation.\(^10\)\(^11\) In clinical practice, treatment with VKA is associated with several problems. VKA is slow acting, requiring bridging with parenteral anticoagulant in emergency situations. VKA has complicated mechanism of action in the coagulation cascade and interacts with food and drugs leading to lability of anticoagulant effect. Thus, regular monitoring of prothrombin time is required, which poses a significant burden on the patients. Direct oral anticoagulants (DOACs) have replaced VKA in several clinical situations, because of their favourable risk-benefit profile and practicability. DOACs are less susceptible to food and drug interactions, resulting in stable anticoagulant activity. DOACs can be administered in fixed doses without the need for routine blood monitoring. Four DOACs are currently available: dabigatran, rivaroxaban, apixaban and edoxaban. The safety and efficacy of the four DOACs in non-valvular atrial fibrillation and venous thromboembolism (VTE) have been established in several large clinical trials.\(^12\)\(^-{22}\) In these trials, DOACs show a lower risk of major bleeding, especially intracranial haemorrhages, compared with VKA. Meanwhile, the use of DOACs for the treatment of CTEPH has not been established.

Edoxaban, the test drug of the KABUKI trial, is a direct inhibitor of activated factor X (Xa). The drug is administered orally once daily, and a rapid onset of antithrombotic action has been proven. The efficacy and safety of edoxaban in patients with atrial fibrillation and those with VTE have been established in two large clinical trials; the ENGAGE-AF trial\(^14\) and HOKUSAI-VTE trial.\(^23\) Also, edoxaban has demonstrated efficacy in long-term prevention of recurrent VTE.\(^23\) However, it remains uncertain whether this drug can prevent in situ thrombosis, silent recurrent PE and incomplete clot dissolution that cause thrombotic progression in CTEPH (figure 1). To date, DOACs have not been approved for prevention of thrombotic progression in CTEPH worldwide. It is necessary to clarify whether

![Figure 1](https://example.com/figure1.png) Pathogenesis of CTEPH and potential targets of action of edoxaban. Large pulmonary thromboembolism and/or small recurrent asymptomatic pulmonary thromboembolism may cause the development of CTEPH. Incomplete clot dissolution causes persistent pulmonary circulation impairment and consequently leads to pulmonary hypertension. Turbulent and slow blood flow promotes clot formation at the organised thrombotic lesions and distal vessels (in situ thrombosis). In open vessels, excessive blood flow and compensatory blood flow impair small vessels. The KABUKI trial seeks to verify whether edoxaban prevents recurrent PE, incomplete clot dissolution and in situ thrombosis. CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary thromboembolism.

![Figure 2](https://example.com/figure2.png) Study flow diagram. After obtaining consent, the subjects undergo eligibility screening and right heart catheterisation including pulmonary vascular resistance measurement. Subjects will be randomly assigned to the edoxaban group or the warfarin group at 1:1 ratio. The investigators will carry out a 1 year observation that includes monthly or bimonthly visits. At the final visit, the subjects will again undergo right heart catheterisation to measure pulmonary vascular resistance.
DOAC is as effective and safe in patients with CTEPH as in patients with VTE. Despite a lack of scientific evidence, DOACs are increasingly being used for anticoagulation in patients with CTEPH in real-world clinical practice. Several large CTEPH registries including the Turkish national database (sample size; n=493) and the UK multicentre registry (sample size; n=1000) reported the use of DOACs in 21% and 36%, respectively, of patients with CTEPH who were treated with PEA.24 25 According to the Japanese multicentre registry that has enrolled more than 850 patients with CTEPH,26 DOACs and edoxaban are currently used by approximately 50% and 15%, respectively, of the patients. Moreover, the Turkish CTEPH database suggests that major bleeding rate is significantly higher in patients taking warfarin, while the UK CTEPH registry suggests a higher VTE recurrence rate in DOAC users.21 25 Several studies from Japan reported comparable pulmonary haemodynamics between warfarin and DOACs in patients with CTEPH.27 28 The KABUKI trial is the first randomised controlled trial aiming to prove the efficacy and safety of edoxaban for the prevention of thrombotic progression in patients with CTEPH.

METHODS AND ANALYSIS

Objectives

The primary objective of the KABUKI trial is to determine whether edoxaban is non-inferior to warfarin in preventing thrombotic progression in patients with CTEPH with WHO functional class I–III.

Trial design

This is an investigator-initiated, multicentre, phase 3, randomised, single-blind (participant-blind), parallel-group, warfarin-controlled, non-inferiority trial. The trial is conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and monitored by an independent clinical research organisation. A full list of trial personnel, including the investigators and trial committees, is provided in the online supplemental appendix. The required sample size is estimated according to the US Food and Drug Administration (FDA) guidance, to be described below under Statistical Considerations. The general flow of the study is shown in figure 2.

Patients and public involvement

There is no patient and public involvement in the development of the protocol.

Ethics and dissemination

This study is approved by the Institutional Review Board (IRB) of each participating institution and registered at ClinicalTrials.gov. The investigators explain the details of this study to subjects according to the Informed Consent Form at the time of hospital visit. Participants are informed that participation is voluntary and may withdraw from the study at any time and that withdrawal of consent will not affect any subsequent clinical practice. All participants will sign the informed consent form before inclusion. The results of this study will be disseminated at medical conferences and published in a peer-reviewed journal, including positive, negative and inconclusive results.

Setting

The trial will be carried out at the departments of cardiovascular or pulmonary medicine of eight institutes in Japan: Tohoku University Hospital, Chiba University Hospital, The University of Tokyo Hospital, Kyorin University Hospital, Toho University Ohashi Medical Center, Nagoya University Hospital, Kobe University Hospital and Kyushu University Hospital. Interventions will be administered in both outpatient and inpatient settings. Follow-up will be conducted at the same institutions.

Eligibility criteria

The inclusion and exclusion criteria of the KABUKI trial are shown in table 1. The subjects are stable patients with CTEPH (WHO functional class I–III) between 20 and 85 years of age, who have been taking warfarin for at least 3 months prior to enrolment. For patients who have been treated with PEA, BPA or/and pulmonary vasodilators, they are eligible even when their mean pulmonary arterial pressure is lower than 25 mm Hg at enrolment. Standard care based on clinical guidelines,10 11 such as home oxygen therapy and pulmonary vasodilators, will be continued during the trial. PEA, BPA and starting or changing doses of pulmonary vasodilators are prohibited during the trial. If these additional interventions are required due to deterioration of CTEPH, they may correspond to clinical worsening of CTEPH according to the definition.

Randomisation

After obtaining written informed consent, baseline screening and evaluation including right heart catheterisation are conducted during the screening phase of up to 28 days. Patients who pass the inclusion/exclusion criteria are registered and randomly assigned to the edoxaban group or warfarin group in a 1:1 ratio by stratification by pulmonary vascular resistance (PVR) (<3.4 Woods unit or ≥3.4 Woods unit). The allocation is not informed to the trial participants. Right heart catheterisation is performed again 1 year after treatment with the assigned drug. The 1 year/baseline PVR ratios are compared between the edoxaban group and the warfarin group.

Study intervention

As shown in figure 3, after randomisation, warfarin is switched to warfarin placebo (dummy) in the edoxaban group or continued (using unlabeled warfarin) in the warfarin group. Prothrombin time-international normalised ratio (PT-INR) is measured in both groups at least once during the switching period. At the initiation of intervention, edoxaban is added to warfarin placebo in
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Hosokawa K, et al. BMJ Open 2022;12:e061225. doi:10.1136/bmjopen-2022-061225

the edoxaban group after confirming PT-INR below the therapeutic level and warfarin is continued and edoxaban placebo is added in the warfarin group after blood test in a double-dummy fashion. Subjects will visit the hospital monthly for the first three visits and then bimonthly until study completion, during which INR monitoring and medical interview are conducted (table 2). The dose of warfarin is adjusted according to PT-INR. Japanese guidelines recommend target PT-INR of 1.5–2.5 based on the experience of general Japanese clinical practice.10

Table 1 Inclusion and exclusion criteria in KABUKI trial

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Male and female patients ≥20 and ≤85 years of age.                                | Prior PEA <180 days or BPA <90 days or start/dose change of pulmonary vasodilators <90 days before eligibility screening. |
| Patient once diagnosed with CTEPH based on imaging study (VQ scan, CT pulmonary angiogram) and haemodynamic criteria (MPAP ≥25 mm Hg and PAWP ≤15 mm Hg). For patients who have been treated with PEA, BPA or/and vasodilators, they are eligible even when their MPAP <25 mm Hg at enrolment. | Severe lung disease (FEV1.0/FVC <60% or % TLC <60%) or renal dysfunction (Ccr 15 mL/min) or liver dysfunction (Child-Pugh B or C). |
| WHO functional class I–III                                                        | Comorbidities requiring vitamin K antagonist.                                        |
| Patient with 6-minute walking distance ≥150 m.                                    | Contraindicated for edoxaban.                                                        |
| Treatment with vitamin K antagonists for at least 3 months prior to study enrolment. | Female of reproductive age not using an acceptable form of contraception.            |
| Patient who meets (A) and (B) at 90 days before eligibility screening.             | Pregnant or breast feeding.                                                          |
| No addition, reduction or change of endothelin antagonists, soluble guanylate cyclase stimulants, phosphodiesterase-5 inhibitors, prostacyclin and its derivatives, or calcium antagonists. No BPA or PEA has been done. | Patient with advanced cancer.                                                       |
|                                                                                   | Life expectancy less than 1 year.                                                    |
|                                                                                   | Unable to provide informed consent.                                                  |

BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; FEV1.0, forced expiratory volume in 1 s; FVC, forced vital capacity; MPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PEA, pulmonary endarterectomy; TLC, total lung capacity; VQ, ventilation-perfusion.

The target PT-INR adopted in this trial is 2.0–2.5, in consideration of both Japanese and European guidelines.10,11 Time in therapeutic ranges of both INR 1.5–2.5 and 2.0–3.0 for warfarin will be assessed,29 corresponding to the two guidelines.10,11 The standard dose of edoxaban is 60 mg one time per day, but the dose is reduced to 30 mg one time per day for patients who meet at least one of the following dose adjustment criteria: moderate or severe renal impairment (creatinine clearance <50 mL/min), low body weight ≤60 kg and concomitant use of other drugs.

Figure 3 Study time course. After screening for eligibility, warfarin used at baseline is switched to warfarin placebo (dummy, edoxaban group) or unlabeled warfarin (warfarin group) in the period of switching to test drug. At the commencement of intervention, the edoxaban group starts edoxaban while continuing warfarin placebo after confirming prothrombin time-international normalised ratio below the therapeutic level, and the warfarin group continues warfarin with additional edoxaban placebo, in a double-dummy fashion. The black and red ellipses indicate warfarin (or warfarin placebo) tablet and edoxaban (or edoxaban placebo) tablet, respectively. After 1 year observation, the subjects will undergo right heart catheterisation. CTEPH, chronic thromboembolic pulmonary hypertension; WHO-FC, WHO functional class.

Table 2 Inclusion and exclusion criteria in KABUKI trial
following P-glycoprotein inhibitors: ciclosporin, drone-darone, erythromycin and ketoconazole.

Endpoints
The primary endpoint for efficacy is the change in catheter-based PVR at 1 year compared with baseline (1 year/baseline PVR ratio). The secondary endpoints are the incidence of clinical worsening of CTEPH, change in 6-minute walk distance, change in WHO functional class and change in N-terminal pro-brain natriuretic peptide at 1 year compared with baseline. Clinical worsening of CTEPH is a composite endpoint defined by the following criteria:

1. All-cause mortality, and/or
2. CTEPH-related hospitalisation or PEA, BPA or start/addition of pulmonary vasodilator, and/or
3. ≥15% reduction in 6-minute walk distance accompanied by worsening of WHO functional class.

Safety outcome is assessed by a composite endpoint of the incidence of major bleeding and clinically relevant non-major bleeding (CRNMB). The definitions of major bleeding and CRNMB are according to the International Society on Thrombosis and Haemostasis (ISTH) definitions.30 31 ISTH major bleeding in non-surgical patients is defined as:

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical region or organ, such as intracranial, intraspinal, intraocular, retropitoneal, intra-articular or pericardial or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.

CRNMB in non-surgical patients is defined as any sign or symptom of haemorrhage (such as more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: requiring medical intervention by a healthcare professional, leading to hospitalisation or increased level of care, prompting a face-to-face (ie, not just a telephone or electronic communication) evaluation.

Changes during the COVID-19 pandemic
In 2020, due to the COVID-19 pandemic, provision of outpatient service was changed periodically in Japan. During the pandemic emergency period, online video or telephone consultation was recommended instead of hospital visit. We thus should prepare the protocol with possible future changes due to the pandemic in mind. In the case of pandemic emergency, although data will be collected as much as possible, some clinical data will not be possible from all the participants because of the restrictions of non-urgent hospital visits. Blood sampling and 6-minute walk test will not be possible in virtual visits. Right heart catheterisation, which is necessary for evaluating the primary endpoint, will be performed as early as the situation permits.

Table 2 Schedule of examinations in KABUKI trial

|                        | Baseline screening | Switching period | Observation period |
|------------------------|-------------------|------------------|--------------------|
|                        |                   |                  | Monthly visits 2, 3, 4 | Bimonthly visits 5, 6, 7, 8 | Final visit 9 |
| Eligibility            | X                 | X                | X                  | X                  | X         |
| Height, weight         | X                 | X                | X                  | X                  |           |
| BP, PR, SpO₂,         | X                 | X                | X                  | X                  | X         |
| WHO functional class   | X                 | X                | X                  | X                  | X         |
| Blood test (haemoglobin, creatinine, PT-INR, D-dimer) | X | X | X | X | X |
| NT-proBNP             | X                 | X (visits 5, 7)  | X                  | X                  |           |
| 6-minute walk test     | X                 | X (visits 5, 7)  | X                  | X                  |           |
| ECG                    | X                 | X (visits 5, 7)  | X                  | X                  |           |
| Right heart catheterisation | X         | X (visits 5, 7)  | X                  | X                  |           |
| Medical interview (clinical worsening of CTEPH, bleeding events) | X | X | X | X |
| Adverse events         | X                 | X                | X                  | X                  |           |

BP, blood pressure; CTEPH, chronic thromboembolic pulmonary hypertension; NT-proBNP, N-terminal pro-brain natriuretic peptide; PR, pulse rate; PT-INR, international normalised ratio of prothrombin time; SpO₂, oxygen saturation on pulse oximeter; WHO, World Health Organisation.
Although the experience and available haemodynamic data for patients with CTEPH taking edoxaban are limited, data for all DOACs including edoxaban in our database shows that the change in PVR is comparable to that of warfarin. Hence, in this sample size calculation, the point estimate and SD of the PVR ratio for the edoxaban group was assumed to be same as that of warfarin.27 The ratio of placebo PVR ratio/warfarin PVR ratio (M₁) is 1.41. The non-inferiority margin (M₂), which is 50% of M₁, is calculated to be 1.19. A 20% increase in the PVR ratio is acceptable as a margin of measurement error. For a non-inferiority test with one-tailed significance level α=0.025, the sample size required to ensure adequate statistical power β=0.9 would be 30 cases per group (60 cases in two groups). Taking into account a 20% dropout rate, the sample size for this study is set at 74 patients (37 in the edoxaban group and 37 in the warfarin group).

Analysis population
The primary analyses for the primary, secondary and safety endpoints follow the per-protocol set principle. The sensitivity analyses follow the full analysis set principle. The full analysis set includes all subjects who were randomised and received at least one dose of study drug. The per-protocol set includes all subjects who are in the full analysis set, have no major protocol deviations and have taken more than 70% of the planned study drug.

Missing data
Subjects who prematurely withdraw from study treatment will be followed for further data collection. As long as the subject does not withdraw consent for any further data collection, every effort will be made to collect at least the data on the components of the primary endpoint up to the next visit. If a subject does not attend the regular study visits, the investigator will contact the subject via telephone to collect at least data for the primary endpoint. Missing data are imputed by the worst case possible value in case of CTEPH worsening, or by the last observation carried forward method in case of no worsening.

Data collection
An electronic, clinical-test data collection system (Research Electronic Data Capture) is used for collecting data as an electronic case report form (eCRF). When the system is unavailable, a manual case report form—an alternative data collection form—is used, and the data are later entered into the electronic data capture system. The data are anonymised at each site and transmitted over the internet. The data are protected by encryption. Linkable anonymisation by central registration number is used to identify the subjects for monitoring, curation and other purposes. The investigators who enter information into the electronic data capture system are responsible for ensuring accuracy and completeness of information. Data will be stored for 10 years in anonymised format.

Data management and monitoring
Data management and monitoring are carried out by independent clinical research entities to avoid bias. Data management is conducted by Department of Data Center, Center for Clinical and Translational Research of Kyushu University Hospital. Data monitoring is conducted by EP-CRSU, Japan. The investigator/investigational site will permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of the clinical study. The monitor is responsible for visiting site(s) at regular intervals (as detailed in the monitoring plan) throughout the study to verify adherence to the protocol; completeness, accuracy and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. The monitor will communicate deviations from the protocol, standard operating procedures, GCP and applicable regulations to the investigators and will ensure that appropriate action designed to prevent recurrence of the detected deviations are taken and documented. The investigators agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are documented and addressed. In accordance with ICH GCP, this study is reviewed for audit by representatives from the independent clinical research organisation. Inspection of site facilities (including pharmacy, drug storage areas and laboratories) and review of study-related records will be conducted in order to evaluate the study conduct and compliance with the protocol, ICH GCP and applicable regulatory requirements.

Independent, blinded endpoint adjudication
PVR is calculated from mean pulmonary artery pressure, pulmonary arterial wedge pressure and cardiac output obtained by right heart catheterisation. Cardiac output is measured by the thermo-dilution method at least five times. An independent core laboratory judges the outliers of reported cardiac output and determines PVR in a blinded manner (endpoint blind). The independent Clinical Events Committee (CEC) judges clinical worsening of CTEPH and all the reported bleeding events on whether they satisfy the criteria of major bleeding or CRNMB. Clinical worsening of CTEPH and bleeding events are first identified by the principal investigators and then judged by the CEC on whether they meet the definitions. All personnel involved in the judging process remain blind to the randomisation. The clinical events adjudicated by the CEC are used in the final safety and efficacy analyses. An independent Data Safety Monitoring Board (DSMB) will meet at the request of the coordinating investigator or the principal investigators to
make recommendations for continuation of the current protocol, modification of the current protocol or discontinuation of the study.

Protocol amendments
If protocol amendments are considered necessary by the investigators, a trial coordinating committee including investigators modifies the protocol appropriately. Any amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a summary of changes document. These protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety.

Trial organisation
The list of investigators and trial committees is shown in online supplemental appendix. The KABUKI trial is funded by Daiichi Sankyo Co., Ltd., (Tokyo, Japan) and Japan Agency for Medical Research and Development (Tokyo, Japan) based on a contract. The KABUKI trial is conducted in collaboration with the Department of Cardiovascular Medicine and Academic Research Organisation, Kyushu University Hospital (Fukuoka, Japan). An executive committee consisting of national academic opinion leaders and supported by the coordinating investigator, principal investigators from participating institutions, DSMB and CEC will oversee all aspects of the KABUKI trial. Statistician(s) at the independent DSMB and external DSMB will have access to all the data and randomisation codes throughout the trial. The executive committee will have equal access to and possession of the data once they are unblinded. The executive committee will be primarily responsible for the preparation, review and submission of publications and presentations related to the major aspects of the study. The executive committee will encourage and support other manuscripts for publication and presentation of similar materials by the principal investigators and/or investigators as deemed appropriate.

DISCUSSIONS
Promising therapies for CTEPH, such as PEA, BPA and riociguat, have contributed to improve the prognosis of CTEPH. On the other hand, the major CTEPH guidelines recommend lifelong therapy with the conventional anticoagulant, warfarin, due to the lack of evidence for DOACs. While DOACs are increasingly being used by patients with CTEPH in real-world clinical practice, the efficacy and safety of DOACs in patients with CTEPH have not been evaluated. Past randomised controlled studies demonstrated that DOACs are not an alternative to warfarin in all diseases. The RE-ALIGN trial that evaluated the efficacy and safety of dabigatran in patients after cardiac mechanical valve replacement showed higher incidence of stroke or systemic embolism and bleeding in the dabigatran group compared with warfarin. The KABUKI trial seeks to answer whether edoxaban is non-inferior to warfarin in terms of efficacy and safety in patients with CTEPH.

Since CTEPH is a rare disease, a large-scale clinical trial on CTEPH using clinical outcome as the primary endpoint is not feasible. Thus, the KABUKI trial evaluates the change in PVR as a surrogate primary endpoint. PVR is an important clinical index reflecting the severity and prognosis of CTEPH. Several recent clinical studies of CTEPH also used PVR as the primary endpoint. PVR reflects the status of pulmonary circulation and vascular bed, consequently providing an outcome measure for the effect of anticoagulants on thrombotic progression in CTEPH.

Study limitations
Since the KABUKI trial is a single-blind trial, evaluation bias may be unavoidable among clinicians cooperating in this study depending on their experience with edoxaban and warfarin. Blinded, independent endpoint adjudication is expected to eliminate the bias. PVR, which is not a clinical outcome, is used as the primary endpoint, because the sample size calculated statistically based on clinical outcome would be impossible to achieve. Clinical data from the Japanese national CTEPH registry (UMIN000033784) is expected to complement the KABUKI trial.

SUMMARY
The KABUKI trial is a new industry-academia-government collaborative phase III trial aiming to validate non-inferiority of edoxaban to warfarin in patients with CTEPH (WHO functional class I–III). The goal of the study is to make lifelong anticoagulation safer and more convenient for patients with CTEPH. A substantial nationwide effort is now underway to recruit appropriate patients. The first patient was randomised on 1 April 2021. Study enrolment is expected to be completed before the end of March 2022 (figure 4).

Figure 4 Projected study timeline. Approximate KABUKI trial timeline is shown from enrolment of the first patient. Key study benchmarks are shown. The study ends when 74 subjects complete the evaluation or drop out from the trial. The estimated recruitment period is 1 year, and the observation period is 1 year.
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