


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

Kazuya Hosokawa ,¹ Kohtaro Abe,¹ Junji Kishimoto,² Yuko Kobayakawa,² Koji Todaka,² Yuichi Tamura,³ Koichiro Tatsumi,⁴ Takumi Inami,⁵ Nobutaka Ikeda,⁶ Yu Taniguchi,⁷ Shun Minatsuki,⁸ Toyoaki Murohara,⁹ Satoshi Yasuda,¹⁰ Keiichi Fukuda,¹¹ Hiroyuki Tsutsui¹

To cite: Hosokawa K, Abe K, Kishimoto J, *et al*. Efficacy and safety of edoxaban in patients with chronic thromboembolic pulmonary hypertension: protocol for a multicentre, randomised, warfarin-controlled, parallel group trial - KABUKI trial. *BMJ Open* 2022;**12**:e061225. doi:10.1136/bmjopen-2022-061225

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-061225>).

KH and KA contributed equally.

Received 20 January 2022
Accepted 04 July 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Kazuya Hosokawa;
hosokawa.kazuya.712@m.yushu-u.ac.jp

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 lability 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. This trial is designed to prove the non-inferiority of edoxaban to warfarin in terms of efficacy and safety in patients with chronic thromboembolic pulmonary hypertension (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.^{5–9} 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 anti-thrombotic 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 trial¹⁴ and HOKUSAI-VTE trial.²¹ 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

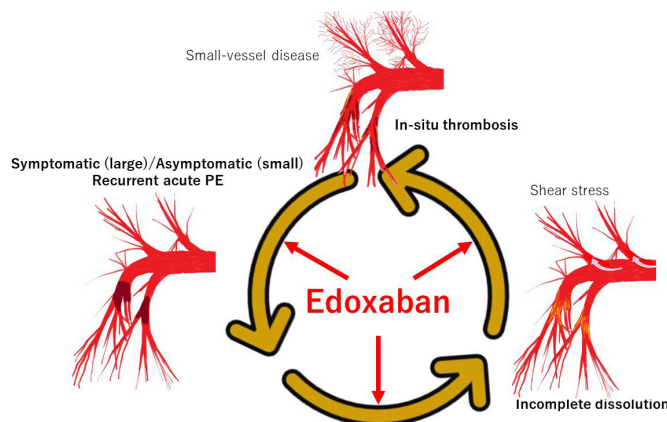


Figure 1 Pathogenesis of CTEPH and potential targets of action of edoxaban. Large pulmonary thromboembolism and/or small recurrent asymptomatic pulmonary thromboembolism may cause the development of CTEPH. Incomplete clot dissolution causes persistent pulmonary circulation impairment and consequently 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.

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

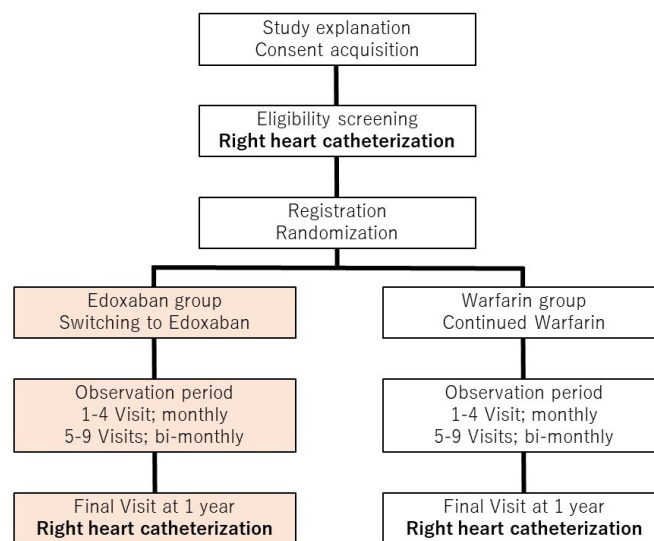


Figure 2 Study flow diagram. After obtaining consent, the subjects undergo eligibility screening and right heart catheterisation including pulmonary vascular resistance measurement. Subjects will be randomly assigned to the edoxaban group or the warfarin group at 1:1 ratio. The investigators will carry 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.^{24 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 pulmonology 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 a central system. Subjects in the two groups are matched 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

Table 1 Inclusion and exclusion criteria in KABUKI trial

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Male and female patients ≥ 20 and ≤ 85 years of age. ▶ 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. ▶ WHO functional class I–III ▶ Patient with 6-minute walking distance ≥ 150 m. ▶ Treatment with vitamin K antagonists for at least 3 months prior to study enrolment. ▶ Patient who meets (A) and (B) at 90 days before eligibility screening. <p>No addition, reduction or change of endothelin antagonists, soluble guanylate cyclase stimulants, phosphodiesterase-5 inhibitors, prostacyclin and its derivatives, or calcium antagonists.</p> <p>No BPA or PEA has been done.</p>	<ul style="list-style-type: none"> ▶ Prior PEA < 180 days or BPA < 90 days or start/dose change of pulmonary vasodilators < 90 days before eligibility screening. ▶ 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). ▶ Comorbidities requiring vitamin K antagonist. ▶ Contraindicated for edoxaban. ▶ Female of reproductive age not using an acceptable form of contraception. ▶ Pregnant or breast feeding. ▶ 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 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

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 the

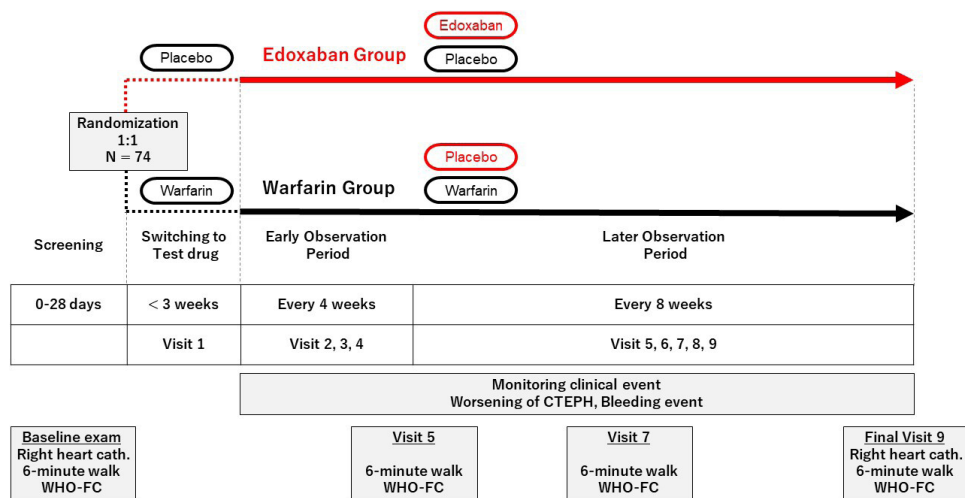


Figure 3 Study time course. After screening for eligibility, warfarin used at baseline is switched to warfarin placebo (dummy, edoxaban group) or unlabeled warfarin (warfarin group) in the period of switching to test drug. At the commencement of intervention, the edoxaban group starts edoxaban while 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 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 visit 9
Eligibility	X				
Height, weight	X				X
BP, PR, SpO ₂	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
6-minute walk test	X			X (visits 5, 7)	X
ECG	X			X (visits 5, 7)	X
Right heart catheterisation	X				X
Medical interview (clinical worsening of CTEPH, bleeding events)			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.

following P-glycoprotein inhibitors: ciclosporin, dronedarone, 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. $\geq 15\%$ 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, retroperitoneal, 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.

Statistical consideration

Sample size

Non-inferiority margin and sample size are determined according to the FDA Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry. The 1 year/baseline PVR ratio for a hypothetical placebo group (ie, CTEPH subjects without anticoagulation) is estimated to be 1.54 based on exhaustive literature review and expert opinions. The PVR ratio in the warfarin group is 1.09 (SD 1.22) based on our clinical database.²⁷

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 (M_1) is 1.41. The non-inferiority margin (M_2), which is 50% of M_1 , 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 $\alpha=0.025$, the sample size required to ensure adequate statistical power $\beta=0.9$ 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.¹³ 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.^{32 33} 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).

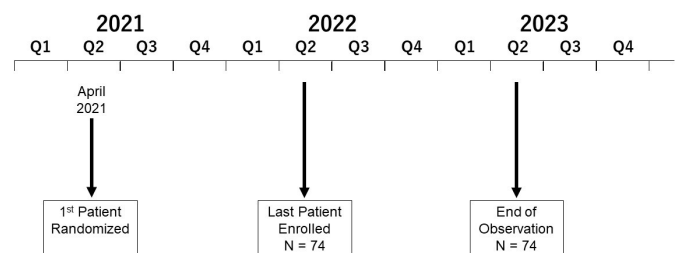


Figure 4 Projected study timeline. Approximate KABUKI trial timeline is shown from enrolment of the first patient. Key study benchmarks are shown. The study ends when 74 subjects complete the evaluation or drop out from the trial. The estimated recruitment period is 1 year, and the observation period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

Author affiliations

¹Department of Cardiovascular Medicine, Faculty of Medical Sciences, Fukuoka, Japan

²Center for Clinical and Translational Research, Kyushu University Hospital, Fukuoka, Japan

³Department of Cardiology, International University of Health and Welfare Mita Hospital, Tokyo, Japan

⁴Department of Respiriology, Graduate School of Medicine, Chiba University, Chiba, Japan

⁵Department of Cardiovascular Medicine, Kyorin University School of Medicine, Tokyo, Japan

⁶Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan

⁷Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

⁸Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

⁹Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

¹⁰Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

¹¹Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

Twitter Kazuya Hosokawa @KazuyaHosokawa2

Contributors KH and KA contributed to the conception and design of the study, drafted the protocol and supervised the revision. JK supervised the statistical design. TI, NI, YTan, SM, TM, SY, YTam, KTO, KF, YK and KTa provided intellectual input to improve the study design and revise the protocol. HT contributed to and supervised the conception and design of the study. All authors read and approved the final manuscript.

Funding This study is funded by Daiichi Sankyo Co., Ltd. (Grant Number: N/A), and Japan Agency for Medical Research and Development (Grant Number: JP18ek0109371, JP19lk0201102, JP22lk0201125) based on a contract.

Competing interests HT received honoraria for scientific lectures from Daiichi Sankyo Co., Ltd.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The de-identified participant data collected in this study will be shared with manufacturers of investigational drugs, Ministry of Health, Labor and Welfare and regulatory authorities related to pharmaceutical affairs. Data are attributed to Kyushu University and Daiichi Sankyo Co., Ltd. Protocols, informed consent form and statistical analysis plans will be shared upon reasonable request. Contact: abe.kotaro.232@m.kyushu-u.ac.jp.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Kazuya Hosokawa <http://orcid.org/0000-0003-1517-3660>

REFERENCES

- Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, *et al.* Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J* 2017;49:1601792.
- Delcroix M, Kerr K, Fedullo P. Chronic thromboembolic pulmonary hypertension. epidemiology and risk factors. *Ann Am Thorac Soc* 2016;13 Suppl 3:S201–6.
- Simonneau G, Torbicki A, Dorfmueller P, *et al.* The pathophysiology of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2017;26:160112.
- Gall H, Hoeper MM, Richter MJ, *et al.* An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. *Eur Respir Rev* 2017;26:160121.
- Delcroix M, Lang I, Pepke-Zaba J, *et al.* Long-Term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation* 2016;133:859–71.
- Ogawa A, Satoh T, Fukuda T, *et al.* Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: results of a multicenter registry. *Circ Cardiovasc Qual Outcomes* 2017;10:e004029.
- Simonneau G, D'Armini AM, Ghofrani H-A, *et al.* Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). *Eur Respir J* 2015;45:1293–302.
- Aoki T, Sugimura K, Tatebe S, *et al.* Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thrombo-embolic pulmonary hypertension: long-term effects and procedure-related complications. *Eur Heart J* 2017;38:3152–9.
- Tanabe N, Ogo T, Hatano M, *et al.* Safety and effectiveness of riociguat for chronic thromboembolic pulmonary hypertension in real-world clinical practice: interim data from post-marketing surveillance in Japan. *Pulm Circ* 2020;10:1–9.
- Galiè N, Humbert M, Vachiery J-L, *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint Task force for the diagnosis and treatment of pulmonary hypertension of the European Society of cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), International Society for heart and lung transplantation (ISHLT). *Eur Heart J* 2016;37:67–119.
- Fukuda K, Date H, Doi S, *et al.* Guidelines for the treatment of pulmonary hypertension (JCS 2017/JPCPHS 2017). *Circ J* 2019;83:842–945.
- Connolly SJ, Ezekowitz MD, Yusuf S, *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
- Schulman S, Kearon C, Kakkar AK, *et al.* Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342–52.
- Giugliano RP, Ruff CT, Braunwald E, *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
- Patel MR, Mahaffey KW, Garg J, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.
- EINSTEIN Investigators, Bauersachs R, Berkowitz SD, *et al.* Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499–510.
- Granger CB, Alexander JH, McMurray JJV, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
- EINSTEIN-PE Investigators, Büller HR, Prins MH, *et al.* Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.
- Agnelli G, Buller HR, Cohen A, *et al.* Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799–808.
- Agnelli G, Buller HR, Cohen A, *et al.* Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;368:699–708.
- Hokusai-VTE Investigators, Büller HR, Décousus H, *et al.* Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406–15.
- Weitz JI, Lensing AWA, Prins MH, *et al.* Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med* 2017;376:1211–22.
- Raskob G, Ageno W, Cohen AT, *et al.* Extended duration of anticoagulation with edoxaban in patients with venous thromboembolism: a post-hoc analysis of the Hokusai-VTE study. *Lancet Haematol* 2016;3:e228–36.
- Sena S, Bulent M, Derya K, *et al.* Real-Life data of direct anticoagulant use, bleeding risk and venous thromboembolism

- recurrence in chronic thromboembolic pulmonary hypertension patients: an observational retrospective study. *Pulm Circ* 2020;10:1–10.
- 25 Bunclark K, Newnham M, Chiu Y-D, *et al.* A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension. *J Thromb Haemost* 2020;18:114–22.
- 26 Multi-Center registry of chronic thromboembolic pulmonary hypertension in Japan. UMIN000033784 2020.
- 27 Hosokawa K, Abe K, Tsutsui H. Use of direct oral anticoagulants prevents increase in pulmonary vascular resistance and incidence of clinical worsening in patients with chronic thromboembolic pulmonary hypertension. *Thromb Res* 2019;180:43–6.
- 28 Ikeda N, Amemiya K, Sato S, *et al.* Evolution of patients with chronic thromboembolic pulmonary hypertension treated by balloon pulmonary angioplasty, according to their anticoagulant regimens. *Heart Vessels* 2021;36:910–5.
- 29 Rosendaal FR, Cannegieter SC, van der Meer FJM, *et al.* A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;69:236–9.
- 30 Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692–4.
- 31 Kaatz S, Ahmad D, Spyropoulos AC, *et al.* Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost* 2015;13:2119–26.
- 32 Ghofrani H-A, Simonneau G, D'Armini AM, *et al.* Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir Med* 2017;5:785–94.
- 33 investigators S. A study to find out if selexipag is effective and safe in patients with chronic thromboembolic pulmonary hypertension when the disease is inoperable or Persistent/Recurrent after surgery (select). NCT03689244 2020.