Research Article

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Safety and effectiveness of riociguat for chronic thromboembolic pulmonary hypertension in real-world clinical practice: interim data from post-marketing surveillance in Japan

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Abstract

This multicenter, prospective, non-interventional study (ClinicalTrials.gov: NCT02117791) evaluated the safety and effectiveness of riociguat for chronic thromboembolic pulmonary hypertension in Japanese clinical practice, registering all patients with chronic thromboembolic pulmonary hypertension treated with riociguat following its launch in Japan in April 2014. Safety was assessed by analyzing the adverse drug reactions. Effectiveness measurements included the assessment of change in World Health Organization functional class, six-minute walk test, and hemodynamics. Overall, 1031 patients were included in the safety analysis with 811 (78.7%) patients in World Health Organization functional class II/III. The mean treatment duration was 591.4 days (median 441.0 days). Adverse drug reactions were reported in 19.5% of patients, the most common being hypotension (5.9%), headache (3.0%), dizziness (1.9%), and gastroesophageal reflux disease (1.5%). Serious adverse drug reactions were reported in 2.1% of patients. Estimated survival was 97.0% at one year, 95.8% at two years, and 94.4% at three years. The effectiveness analysis ($n = 1027$) showed significant increases from baseline in six-minute walking distance, and significant reductions from baseline in mean pulmonary arterial pressure and pulmonary vascular resistance. These interim results of riociguat in Japanese patients with chronic thromboembolic pulmonary hypertension demonstrated a safety profile that was generally consistent with those of pivotal clinical studies. The study is ongoing, and will continue to provide insights into the safety and effectiveness of riociguat in real-world practice.

Keywords

riociguat, chronic thromboembolic pulmonary hypertension, soluble guanylate cyclase, product surveillance, post-marketing

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by obstruction of the pulmonary vasculature by organized thromboembolic material, as a consequence of major vessel thromboembolism, leading to increased pulmonary vascular resistance (PVR), progressive pulmonary hypertension (PH), and, potentially, death due to right heart failure.[1–3] In addition to mechanical obstruction of proximal arteries, some patients with CTEPH develop pulmonary small-vessel disease (microvasculopathy), similar to that observed in idiopathic pulmonary

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arterial hypertension (PAH).[3] CTEPH is a rare disease that had a very poor prognosis before the development of effective treatments. In 1982, survival rates at five years were reported to be 30% in patients with mean pulmonary arterial pressure (mPAP) >40 mmHg and 10% in patients with mPAP >50 mmHg.[4] However, a number of treatment options are now available and the management of this disease has advanced substantially in recent years.

Pulmonary endarterectomy (PEA), also referred to as pulmonary thromboendarterectomy, is the recommended treatment for CTEPH, as it is potentially curative.[5,6] However, up to 40% of patients with CTEPH are ineligible for PEA, and up to 51% develop persistent/recurrent PH after PEA.[6–13] Another treatment option for CTEPH is balloon pulmonary angioplasty (BPA), in which balloon dilatation is used to restore blood flow across stenotic or occluded pulmonary vascular lesions.[14] CTEPH in Japan differs from that described in international studies in having less frequent use of PEA and more frequent use of BPA (which was developed largely in Japan).[15,16]

Riociguat was approved in January 2014 in Japan as the first and only drug for the treatment of inoperable or persistent/recurrent CTEPH after PEA. The approval of riociguat for CTEPH followed the CHEST-1 trial,[17] in which riociguat demonstrated clinical effectiveness in improving six-minute walking distance (6MWD), hemodynamic endpoints, and various secondary endpoints both in patients with inoperable CTEPH and in those with persistent/recurrent PH after PEA.[18] The improvements in 6MWD, World Health Organization functional class (WHO FC), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) seen in CHEST-1 were maintained in the long-term extension study, CHEST-2.[19] However, the numbers of Japanese subjects were limited in these clinical trials, and they did not include BPA, which is now widely used in Japan. Therefore, a post-marketing surveillance (PMS) study investigated patients with CTEPH who were prescribed riociguat in order to evaluate the safety and effectiveness of riociguat in real-world clinical practice in Japan.

Methods

Study design and patient enrollment

This study was a non-interventional PMS study (ClinicalTrials.gov: NCT02117791). As a condition for approval of riociguat in Japan, all-case surveillance was conducted, with every hospital in Japan that prescribed riociguat obliged to participate, enrolling all patients with CTEPH receiving riociguat from the start of marketing in April 2014. The study was approved by the health authority (Pharmaceutical and Medical Devices Agency) and conducted in compliance with the Ministerial Ordinance on Good Post-marketing Study Practice for Drugs in Japan.

Treatment

Treatment with riociguat was based on the product label in Japan at the discretion of the investigator. The label recommends a starting dose of 1.0 mg three times daily (tid) orally for two weeks, increased in two-week intervals by 0.5-mg increments to a maximum of 2.5 mg tid, and adjusted according to systolic blood pressure, and the presence or absence of signs or symptoms of hypotension. The maximum total daily dose of riociguat is 7.5 mg. Medication other than riociguat, including other PAH-targeted therapies, could be taken at the discretion of the investigator.

Patient registration and data collection

In this analysis, patients were registered from 20 April 2014 to 19 September 2019. During this period, 1074 case report forms were collected and the data were fixed on 19 September 2019. The PMS data were captured in electronic patient case report forms. The standard observation period was 12 months from the first treatment with riociguat. In addition, extension observations will be carried out annually for a further seven years, giving a maximum duration of riociguat therapy of eight years. The following data were collected at baseline, 4 months, 12 months, and annual extension observations, if obtained by the investigator in routine practice: status of riociguat treatment, concomitant treatment, 6MWD, right heart catheterization measurements, vital signs, echocardiography, blood gas analysis, brain natriuretic peptide (BNP), NT-proBNP, WHO FC, time to clinical worsening, laboratory findings, and adverse events (AEs).

Data analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). For the safety analysis, data for all AEs (diseases, symptoms, etc.) that occurred after the beginning of treatment with riociguat were collected, regardless of whether they were considered treatment-related. For each AE, the investigator assessed and documented the seriousness, duration, relationship to riociguat treatment, action taken, and outcome of the event. Adverse drug reactions (ADRs) were defined as AEs for which a causal relationship to riociguat could not be ruled out. ADRs were summarized using the Medical Dictionary for Regulatory Activities coding system. ADRs were considered serious ADRs if they resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, were congenital anomalies or birth defects, or were another medically important serious event.

Effectiveness measurements included the assessment of the change in WHO FC, 6MWD, and hemodynamics. Time to clinical worsening was calculated in terms of the first occurrence of all-cause death, heart/lung

transplantation, rescue PEA, rescue BPA, hospitalization due to persistent worsening of PH, or start of new PAH-targeted treatment due to persistent worsening of PH, or persistent decrease in 6MWD, or persistent worsening of WHO FC due to worsening PH. Overall survival and clinical worsening-free survival were estimated by the Kaplan–Meier method.[20]

Statistical considerations

Statistical analyses were descriptive and were performed using basic summary statistics. Continuous data were described by median, mean, standard deviation, minimum, maximum, and 25th and 75th percentiles. Categorical data were presented in frequency tables, showing patients with missing data as a separate category. Safety analysis included all patients who received at least one dose of riociguat and had at least one reported observation.

Results

Patient disposition

From 20 April 2014 through 19 September 2019, 1298 patients were registered and 1074 case report forms were collected. A total of 1031 patients were analyzed for safety following exclusion of 42 patients because they changed hospital, and 1 patient because riociguat was not administered. Four non-CTEPH patients were excluded from the effectiveness analyses, which therefore included 1027 patients (Fig. 1).

Baseline demographic and disease characteristics including hemodynamics are shown in Table 1. Mean age of the patients was 66 years, 74.2% were female, and approximately 90.4% had disease deemed to be inoperable, most commonly because of technical difficulty or patient condition. Within 90 days before commencement of riociguat, 502 patients (48.7%) had received PAH medication: endothelin receptor antagonists in 263 patients (25.5%), phosphodiesterase type 5 inhibitors (PDE5i) in 199 patients (19.3%), and prostacyclin analogs in 262 patients (25.4%). Mean 6MWD was 352.6 m, and 78.7% of patients were in WHO FC II or III.

The mean daily dose of riociguat during the study was 5.2 mg. At data cut-off, treatment had been withdrawn from 415 patients (40.3%) because of AEs (8.7%), hospital non-attendance (8.1%), BPA (4.9%), PEA (3.6%), death (3.0%), patient withdrawal (1.6%), insufficient effectiveness (0.9%), and other reasons (12.7%), mainly improved clinical condition (10.8%).

During the study, 287 patients (27.9%) received concomitant endothelin receptor antagonists, 241 (23.4%) received concomitant prostacyclin analogs, and 17 (1.7%) received concomitant PDE5i. Adjunctive therapies are shown in Table 2. In total, 401 patients (38.9%) underwent BPA and 47 (4.6%) underwent PEA. If the patient had more than one concomitant medication/adjunctive therapy, each concomitant medication/adjunctive therapy was counted.

Safety

The mean treatment duration was 591.4 days (median 441.0 days). ADRs and serious ADRs were reported in 201 patients (19.5%) and 22 patients (2.1%), respectively. The ADRs reported in ≥0.5% of patients were hypotension (5.9%), headache (3.0%), dizziness (1.9%), gastroesophageal reflux disease (1.5%), diarrhea (1.3%), nausea (1.0%), abdominal discomfort (0.9%), peripheral edema (0.8%),

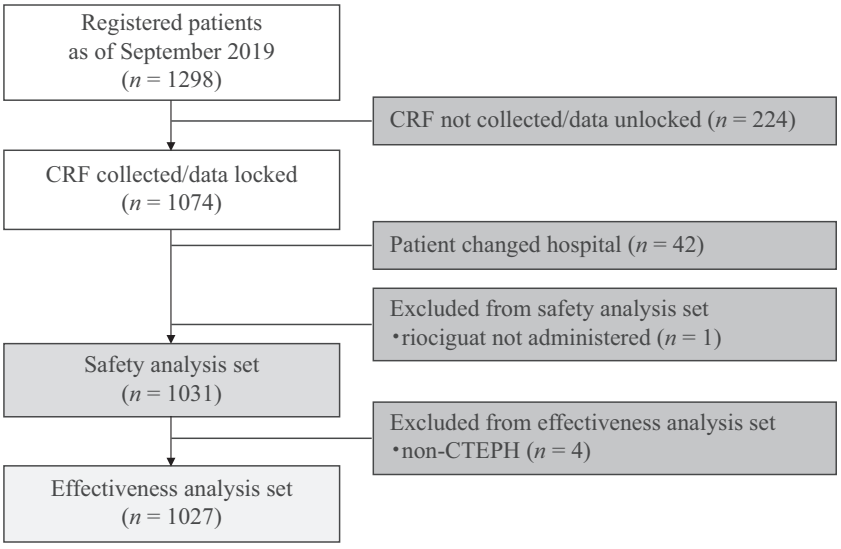

Fig. 1. Patient disposition.
CRF: case report form; CTEPH: chronic thromboembolic pulmonary hypertension.

Table 1. Baseline demographic and disease characteristics for safety analysis set ($n = 1031$).

Age (years)	66.1 ± 12.7
Female	765 (74.2)
Weight (kg)	56.4 ± 13.0
BMI (kg/m^2)	22.9 ± 4.1
Operability	
Inoperable	932 (90.4)
Technically difficult	460 (44.6)
Patient condition	220 (21.3)
Patient refusal	96 (9.3)
Awaiting PEA	79 (7.7)
Mild disease	77 (7.5)
Persistent/recurrent	95 (9.2)
Prior antithrombotic agent	976 (94.7)
WHO FC	
I	39 (3.8)
II	380 (36.9)
III	431 (41.8)
IV	60 (5.8)
Not reported	121 (11.7)
SBP (mmHg)	117.7 ± 18.1 ($n = 965$)
DBP (mmHg)	68.9 ± 12.3 ($n = 965$)
HR (bpm)	76.9 ± 13.8 ($n = 930$)
CO (L/minute)	4.03 ± 1.31 ($n = 778$)
mPAP (mmHg)	36.8 ± 11.4 ($n = 801$)
PVR (dyn·s·cm^{-5})	637.9 ± 418.1 ($n = 663$)
PAWP (mmHg)	9.2 ± 4.4 ($n = 769$)
RAP (mmHg)	6.1 ± 4.0 ($n = 772$)
SvO_2 (%)	63.6 ± 11.0 ($n = 530$)
6MWD (m)	352.6 ± 116.5 ($n = 614$)
BNP (pg/mL)	214.0 ± 352.3 ($n = 888$)
NT-proBNP (pg/mL)	1581.8 ± 2912.7 ($n = 96$)

Note: Values are expressed as mean ± SD or *n* (%) unless otherwise stated.
6MWD: six-minute walking distance; BMI: body mass index; BNP: brain natriuretic peptide; CO: cardiac output; DBP: diastolic blood pressure; HR: heart rate; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PAWP: pulmonary arterial wedge pressure; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SBP: systolic blood pressure; SvO_2: systemic venous oxygen saturation; WHO FC: World Health Organization functional class.

dyspepsia (0.6%), hemoptysis (0.6%), vomiting (0.6%), and fatigue (0.5%). Incidence rates for ADRs per observation period are shown in Table 3. The serious ADRs reported in >0.1% of patients were hypotension in 0.4% (4/1031), dizziness in 0.2% (2/1031), and hypoxia in 0.2% (2/1031).

A total of 17 patients (1.7%) received a PDE5i concomitantly with riociguat at some time during the study, of whom 3 (0.3% of the total safety population) experienced an AE.

Estimated survival by Kaplan–Meier analysis (which involves censoring of data) was 97.0% at one year, 95.8% at two years, and 94.4% at three years (Fig. 2).

Table 2. Concomitant/adjunctive therapy at any time during treatment with riociguat in the safety analysis set ($n = 1031$).

Concomitant medication[a]	
Any	1026 (99.5)
Antithrombotic medication	1002 (97.2)
PAH-targeted therapy	
ERA[b]	287 (27.9)
PCA[c]	241 (23.4)
PDE5i[d]	17 (1.7)
Diuretics/cardiac therapy	562 (54.5)
Other	735 (71.3)
Adjunctive therapy[a]	
Any	837 (81.2)
Supplemental oxygen	732 (71.0)
PEA	47 (4.6)
BPA	401 (38.9)
Inferior vena cava filter	8 (0.8)
Others	7 (0.7)

Note: Values are *n* (%).
[a]Counted duplicate: if the patient had more than one concomitant medication/adjunctive therapy, each concomitant medication/adjunctive therapy was counted.
[b]Ambrisentan, bosentan, and macitentan.
[c]Beraprost, epoprostenol, and selexipag.
[d]Sildenafil and tadalafil.
BPA: balloon pulmonary angioplasty; ERA: endothelin receptor antagonist; PAH: pulmonary arterial hypertension; PCA: prostacyclin analog; PDE5i: phosphodiesterase type 5 inhibitor; PEA: pulmonary endarterectomy.

Effectiveness

Effectiveness data were calculated from paired observations from the subgroup of patients who had at least one baseline and one on-treatment measurement. Changes from baseline to the last observation in CTEPH-related parameters with riociguat were assessed. There were significant increases in 6MWD and cardiac output, and significant reductions in mPAP, PVR, BNP, and NT-proBNP compared with baseline (Table 4). After four months of treatment, the proportion of patients in WHO FC I or II increased from 46.0% to 71.8%, with a corresponding decrease in the proportion in class III or IV from 54.0% to 28.2% (Fig. 3). No patients with available WHO FC data showed a deterioration of at least two classes at two years, and approximately 26–38% improved by at least one class at four months, one year, two years, and at last observation (Supplementary Table 1). A further analysis assessed changes in CTEPH-related parameters from baseline to the last observation in patients who underwent BPA after starting riociguat and those who did not undergo BPA during the study. Patients who underwent PEA during the study were excluded from this analysis. There were significant increases in 6MWD and cardiac output, and significant reductions in mPAP, PVR, BNP, and NT-proBNP compared with baseline in both groups. 6MWD and hemodynamics improved to greater

Table 3. Time course of ADRs in the safety analysis set ($n = 1031$).

	All periods	1 month (administration–30 days)	2–3 months (31–91 days)	4–6 months (92–182 days)	7–9 months (183–273 days)	10–12 months (274–365 days)	13–24 months (366–730 days)
Number of patients analyzed	1031	1031	1031	965	754	707	482
Number of patients experiencing overall ADRs	201	110	27	30	16	13	22
MedDRA PT[a], *n* (%)							
Hypotension	61 (5.9)	33 (3.2)	4 (0.4)	6 (0.6)	5 (0.7)	7 (1.0)	6 (1.2)
Headache	31 (3.0)	25 (2.4)	5 (0.5)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.4)
Dizziness	20 (1.9)	8 (0.8)	4 (0.4)	3 (0.3)	3 (0.4)	0 (0.0)	2 (0.4)
GERD	15 (1.5)	7 (0.7)	4 (0.4)	3 (0.3)	0 (0.0)	0 (0.0)	2 (0.4)
Diarrhea	13 (1.3)	9 (0.9)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	10 (1.0)	7 (0.7)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Abdominal discomfort	9 (0.9)	6 (0.6)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)
Peripheral edema	8 (0.8)	2 (0.2)	5 (0.5)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	6 (0.6)	2 (0.2)	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)
Hemoptysis	6 (0.6)	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.3)	0 (0.0)
Vomiting	6 (0.6)	6 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	5 (0.5)	2 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)

[a]ADRs observed in $\geq 0.5\%$ of patients over the course of the study.
ADR: adverse drug reaction; GERD: gastroesophageal reflux disease; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term.

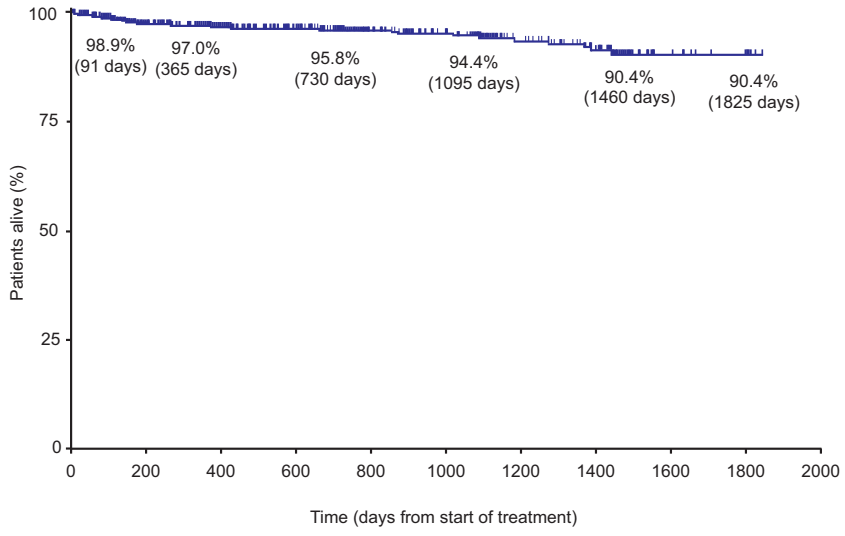

Fig. 2. Kaplan–Meier plot of overall survival.

extents in patients who underwent BPA than in those who did not (Supplementary Table 2).

In addition, we assessed changes in CTEPH-related parameters from baseline to the last observation in patients who did not undergo BPA or receive PAH-targeted therapy other than riociguat during the study. Patients who underwent PEA were excluded from this analysis. There were significant increases in 6MWD and cardiac output, and significant reductions in mPAP, PVR, BNP, and NT-proBNP compared with baseline in this group (Supplementary Table 3).

Discussion

PMS studies are valuable in providing information for a patient population from a wide variety of real-world clinical settings as opposed to clinical trials where a narrow and generally homogeneous population of patients is selected based on inclusion/exclusion criteria. This PMS study assessed the safety and effectiveness of riociguat in patients with persistent/recurrent or inoperable CTEPH in real-world clinical practice in Japan. This study is the first and largest study to include patients treated by BPA and to

Table 4. Key effectiveness parameters for riociguat in patients with at least one baseline and on-treatment value from effectiveness analysis set ($n = 1027$).

	n	Baseline	Last observation	Change from baseline to last observation
mPAP, mmHg	532	37.3 (11.5)	26.9 (9.0)	–10.4 (11.5)[a]
PVR, dyn·s·cm^{-5}	401	643.8 (409.7)	363.3 (327.9)	–280.4 (455.2)[a]
PAWP, mmHg	504	8.9 (4.1)	9.0 (4.0)	0.1 (4.9)
RAP, mmHg	494	6.1 (4.0)	4.6 (3.1)	–1.4 (4.4)[a]
CO, L/minute	505	4.1 (1.4)	4.7 (2.0)	0.7 (2.0)[a]
SvO_2, %	295	63.5 (10.5)	68.4 (9.4)	4.9 (11.7)[a]
6MWD, m	417	351.1 (116.1)	391.0 (116.5)	39.9 (88.1)[a]
Borg CR 10 Score	252	4.5 (2.7)	3.7 (2.4)	–0.8 (2.6)[a]
BNP, pg/mL	810	219.7 (362.1)	92.9 (188.9)	–126.9 (350.0)[a]
NT-proBNP, pg/mL	70	1719.8 (3180.6)	517.1 (888.4)	–1202.6 (2855.3)[a]
TRPG, mmHg	720	61.0 (24.0)	45.3 (20.8)	–15.8 (23.1)[a]

[a]$P < 0.001$ (paired t-test).

Note: Data are mean (SD) for patients with data at baseline and at last observation.

6MWD: six-minute walking distance; BNP: brain natriuretic peptide; CO: cardiac output; CR: category ratio; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SvO_2: systemic venous oxygen saturation; TRPG: tricuspid regurgitation peak gradient.

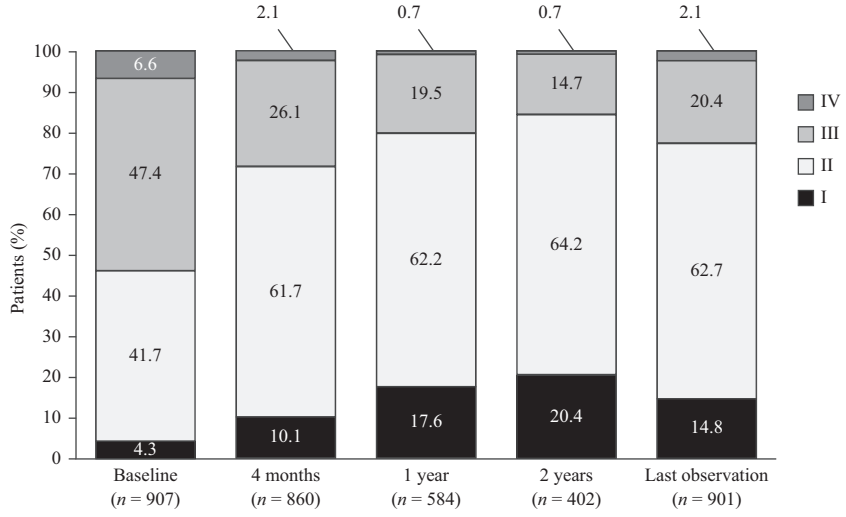

Fig. 3. Changes in distribution of WHO FC during the study.

Note: Patients with missing data are excluded.

WHO FC: World Health Organization functional class.

assess the safety of riociguat in such patients, and to provide data regarding pulmonary hemodynamics and exercise capacity in patients with and without concomitant BPA. The study population was similar to that reported in a Japanese CTEPH registry[15] in terms of mean age, preponderance of female patients, WHO FC, and PVR. The use of BPA in approximately one-third of patients reflects the widespread adoption of this technique in Japan in recent years. Approximately 90% of patients were deemed inoperable with the reasons for inoperability including technical difficulty (44.6%), patient condition (21.3%), patient refusal (9.3%), awaiting PEA (7.7%), and mild disease (7.5%). Outside Japan, operability is considered to be determined by the surgical accessibility of lesions, but Japanese physicians might tend to comprehensively judge operability not only on the surgical accessibility of lesions but also on the condition of the patient.

Although riociguat and PDE5i influence intracellular cyclic guanosine monophosphate levels through different modes of action, both act as vasodilators and an additive effect can be anticipated. Concomitant administration of riociguat with PDE5i is contraindicated based on the

open-label extension of the PATENT PLUS study in patients with PAH, which revealed potentially unfavorable safety signals, including discontinuation due to systemic hypotension over the long term, and no evidence of a positive benefit:risk ratio.[21–23] In the present study, despite this contraindication, 17 patients (1.7%) received this combination, of whom 3 (0.3% of the overall population) experienced an AE.

The most common ADRs (Table 3) and the overall safety profile were similar to that seen in CHEST-1 and -2.[17–19] ADRs mostly occurred relatively early after administration (mainly within one month after the initiation of riociguat) and their incidence decreased over time; there was no ADR with an incidence that increased over time. In summary, the ADRs were generally consistent with the known safety profile of riociguat and no new safety risks were identified in this surveillance study. The prognosis of CTEPH in this study population was favorable, with an estimated overall survival of 94.4% at three years. An overall survival of 87.3% at five years has been reported elsewhere in medically treated Japanese patients with CTEPH.[16]

In the CHEST-1 trial, riociguat significantly improved 6MWD as well as secondary outcomes including WHO FC, NT-proBNP, and hemodynamic parameters compared with placebo at 16 weeks.[19] In CHEST-2, the improvements in 6MWD, WHO FC, and NT-proBNP were maintained at two years.[21] In this PMS, 6MWD, WHO FC, and hemodynamic parameters were examined to evaluate riociguat in the real-world clinical setting, and trends to improvement were seen, comparable with the pivotal trials. However, in the current study, the parameters were obtained from a limited number of patients for whom it was possible to measure data at this point in time. Final analysis with more data is expected to have more conclusive results.

Combining treatment options for CTEPH, which target different pathogenic manifestations in different parts of the pulmonary vascular bed, is expected to become a viable option. While PEA is used to remove thromboembolic lesions primarily in the proximal main artery, and lobar and segmental arteries, BPA mainly targets distal lesions in the segmental and subsegmental vasculature, down to small pulmonary arteries of 2–5 mm in diameter, and riociguat targets microvasculopathy, including intimal thickening and fibromuscular proliferation, in vessels of 0.1–0.5 mm in diameter. The combination of riociguat and PEA/BPA may provide better treatment options for some patients with CTEPH.[24] In this PMS study, almost 40% of patients underwent BPA, reflecting the widespread adoption of this technique in Japan in recent years. Effectiveness appeared to be greater in patients who underwent BPA after starting riociguat administration than in those who did not undergo BPA (Supplementary Table 2). However, this was not a randomized comparison, this study was not designed to assess this subgroup, and the results may be biased. The potential role of medical therapy as combination therapy with BPA warrants additional study.

This study has several limitations. First, this was a single-arm, uncontrolled, non-interventional, observational study conducted in the real-world setting, involving a single cohort where patients were not randomized by age or treatment group. Second, the doses/treatment periods of riociguat, concomitant therapies, patient selection, and assessment of clinical parameters were determined by the investigators' clinical judgment. In addition, this all-case surveillance study is a regulatory obligation based strictly on voluntary reporting, and follow-up may, therefore, become difficult when a patient relocates and, thus, changes their hospital.

Perspectives

In Japan, new PH-targeted therapies are approved and marketed at almost the same time as in other countries and are, therefore, free of the delays that can occur in the approval of new drugs (so-called "drug-lag"). This means that experience of use in other countries and information on post-marketing ADRs are very limited at the time of approval in Japan.

Clinical experience on appropriate use of riociguat in Japanese patients and patient selection criteria should be accumulated and shared as a priority. In the future, the long-term implications of riociguat treatment will emerge in follow-up data potentially up to eight years. These data will highlight a substantial gap for patients treated with riociguat between evidence-based patient management and its practical application. The findings obtained in the present study should, therefore, be applied to the clinical setting as soon as possible.

In conclusion, these interim results in Japanese patients with CTEPH treated in the real-world clinical setting demonstrate a safety profile for riociguat that is generally consistent with the known safety profile of riociguat from pivotal clinical studies, with no new safety risks identified. This study will formulate one of the largest cohorts of real-life evidence of CTEPH in Japan, and will continue to provide insights into the long-term safety and effectiveness of riociguat in real-world clinical practice.

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Contributorship

N.T., T.O., and M.H. are the PMS committee members of this study under contract with Bayer Yakuhin, Ltd, and contributed to the study design and interpretation of the data. A.K., S.S., and T.S. contributed to the study design, analysis, and interpretation of the data. All authors contributed to drafting and revising the manuscript, and provided final approval of the publication version.

Conflict of interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Tanabe reports grants and personal fees from Bayer Yakuhin, Ltd during the conduct of the study; personal fees from Actelion Pharmaceuticals Japan, grants and personal fees from Nippon Shinyaku, personal fees from Pfizer Japan, and personal fees from Daiichi Sankyo, outside the submitted work. Dr Ogo reports personal fees from Bayer Yakuhin, Ltd during the conduct of the study; grants and personal fees from Actelion Pharmaceuticals Japan, personal fees from GlaxoSmithKline, personal fees from Nippon Shinyaku, grants and personal fees from Pfizer Japan, and grants from Mochida pharmaceutical, outside the submitted work. Dr Hatano reports personal fees from Bayer Yakuhin, Ltd during the conduct of the study; personal fees from Actelion Pharmaceuticals Japan, grants and personal fees from Nippon Shinyaku, and personal fees from Pfizer Japan, outside the submitted work. Ayaka Kigawa, Toshiyuki Sunaya, and Shoichiro Sato are employees of Bayer Yakuhin, Ltd, Osaka, Japan.

Ethical approval

This investigation was conducted in accordance with the Japanese "Good Post-Marketing Study Practice," which was authorized by the Ministry of Health, Labour and Welfare (No. 171 in 2004, No. 87 in 2014, and No. 116 in 2017). Informed consent was not required from all individual participants included in this survey according to this Good Post-Marketing Study Practice. The agreement for publication on this survey was obtained from all the participating institutions. Institutional review board/ethics committee approval was obtained according to the rules of each institution as required for a PMS study. The rules of personal data confidentiality were fully respected.

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Guarantor

Shoichiro Sato is the guarantor of the data presented in this paper.

Supplemental material

Supplemental material for this article is available online.

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