Report on the Deliberation Results

December 10, 2013

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau Ministry of Health, Labour and Welfare

[Brand name]	Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg
[Non-proprietary name]	Riociguat (JAN*)
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	May 17, 2013

[Results of deliberation]

In the meeting held on November 29, 2013, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the product is 10 years. Both the drug substance and the drug product are classified as powerful drugs, and the drug product is not classified as a biological product or a specified biological product.

[Conditions for approval]

The applicant is required to conduct a drug use-results survey involving all treated patients after the market launch until data from a certain number of patients have been accumulated in order to grasp the characteristics of patients treated with this product, since the product has been studied only in a limited number of patients in Japan; and at the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.

*Japanese Accepted Name (modified INN)

Review Report

November 19, 2013 Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name] [Non-proprietary name] [Applicant] [Date of application] [Dosage form/Strength] [Application classification] [Chemical structure] Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg Riociguat Bayer Yakuhin, Ltd. May 17, 2013 A film-coated tablet containing 0.5, 1.0, or 2.5 mg of Riociguat Prescription drug (1) Drug with a new active ingredient



Molecular formula: Molecular weight: Chemical name: C₂₀H₁₉FN₈O₂ 422.42 Methyl *N*-(4,6-diamino-2-{1-[(2-fluorophenyl)methyl]-1*H*pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)-*N*-methylcarbamate

[Items warranting special mention]

Orphan drug (Notification No. 0908-6 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 8, 2011) Office of New Drug II

[Reviewing office]

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Results

[Brand name] [Non-proprietary name] [Applicant] [Date of application] Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg Riociguat Bayer Yakuhin, Ltd. May 17, 2013

[Results of review]

Based on the submitted data, it is concluded that the efficacy of the product in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or those with postoperative persistent or recurrent CTEPH has been demonstrated and its safety is acceptable in view of its observed benefits. The safety in patients with systolic blood pressure of <95 mmHg, in patients with renal impairment, and in patients with hepatic impairment should be investigated via post-marketing surveillance etc.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

[Indication]	Inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or postoperative persistent or recurrent CTEPH
[Dosage and administration]	Containing on possiplitative periods of recallent of the first of the first of period. Dose titration period The usual initial dosage for adults is 1.0 mg of Riociguat administered orally 3 times daily. If the systolic blood pressure remains at \geq 95 mmHg for 2 weeks and the patient shows no signs or symptoms of hypotension, the dose should be increased by 0.5 mg at 2-week intervals up to the maximum daily dose of 2.5 mg 3 times daily. If the systolic blood pressure is <95 mmHg but the patient shows no signs or symptoms of hypotension, the current dose should be maintained. If the patient shows any signs or symptoms of hypotension, the dose should be reduced by 0.5 mg 3 times daily.
	Dose maintenance period The dose determined during the dose titration period should be maintained. The maximum daily dose is 2.5 mg 3 times daily during the dose maintenance period as well. If not tolerated (e.g., occurrence of signs or symptoms of hypotension), the dose should be reduced by 0.5 mg 3 times daily.
[Conditions for approval]	The applicant is required to conduct a drug use-results survey involving all treated patients after the market launch until data from a certain number of patients have been accumulated in order to grasp the characteristics of patients treated with this product, since the product has been studied only in a limited number of patients in Japan; and at the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.

Review Report (1)

I. Product Submitted for Registration

[Brand name]	Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg
[Non-proprietary name]	Riociguat
[Name of applicant]	Bayer Yakuhin, Ltd.
[Date of application]	May 17, 2013
[Dosage form/Strength]	A film-coated tablet containing 0.5, 1.0, or 2.5 mg of Riociguat
[Proposed indication]	Inoperable or postoperative persistent or recurrent chronic thromboembolic pulmonary hypertension

[Proposed dosage and administration]

Dose titration period

The usual initial dosage in adults is 1.0 mg of Riociguat administered orally 3 times daily (with a dosing interval of approximately 6-8 hours) for 2 consecutive weeks. If the systolic blood pressure remains at \geq 95 mmHg and the patient shows no signs or symptoms of hypotension, the dose should be increased by 0.5 mg at 2-week intervals up to the maximum daily dose of 2.5 mg 3 times daily. If the systolic blood pressure is <95 mmHg but the patient shows no signs or symptoms of hypotension, the current dosage should be maintained. If the patient shows any signs or symptoms of hypotension, the dose should be reduced by 0.5 mg 3 times daily.

Dose maintenance period

The dose determined during the dose titration period should be maintained. The maximum daily dose is 2.5 mg 3 times daily during the dose maintenance period as well. If the dose is not tolerated (e.g., occurrence of signs or symptoms of hypotension), the dose should be reduced. In the case that a dose is missed, the patient should continue with the next dose as scheduled.

After dose interruption

If the treatment is interrupted for 3 days or longer, the oral dose of riociguat should be resumed at 1.0 mg 3 times daily and the dose level should be continued for 2 weeks. Thereafter, the dose should be adjusted according to the procedure as described above.

II. Summary of the Submitted Data and Outline of Review by Pharmaceuticals and Medical Devices Agency

The data submitted in this application and the outline of review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by chronic stenosis/obstruction of the pulmonary arterial lumen due to the organized thrombus and resultant increase in pulmonary vascular resistance, presenting with clinical symptoms such as exertional breathlessness. It is reported that, in CTEPH, the nitric oxide (NO)-soluble guanylate cyclase

(sGC)-cyclic guanosine monophosphate (cGMP) signal transduction pathway is blocked by chronic pulmonary vascular disorder, resulting in a decreased cGMP concentration.

sGC is activated by NO, resulting in an increase in cGMP concentration within vascular smooth muscle cells and platelets. Riociguat increases cGMP concentration by directly stimulating and activating sGC, and is therefore expected to be effective in CTEPH.

Development of riociguat as a therapeutic agent for CTEPH and for pulmonary arterial hypertension (PAH), a disease with clinical characteristics similar to those of CTEPH, was initiated by Bayer HealthCare (Germany) in 1997, and the application was submitted for approval in February 2013 in Europe and the US with the proposed indications for inoperable or post-operative persistent or recurrent CTEPH and PAH. As of September 2013, riociguat is approved in Canada with the indication for CTEPH.

In Japan, development of riociguat tablets (the drug product) was initiated by Bayer Yakuhin, Ltd. in 2006. Based on the results from global clinical studies in which Japanese patients also participated, a marketing application of riociguat with the proposed indication of "inoperable or postoperative persistent or recurrent chronic thromboembolic pulmonary hypertension" has now been filed. An application for the indication of PAH is scheduled to be submitted.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to yellowish crystalline powder. The determined general properties include description, specific rotation, pH, dissociation constant (pKa), partition coefficient, hygroscopicity, density, solubility, melting point, particle size, and crystalline polymorphism. Riociguat exists in 2 crystalline forms, Form I and Form II, in 3 different solvated forms, and in amorphous form.

The chemical structure of riociguat has been elucidated by elemental analysis, mass spectrometry, ultraviolet-visual spectrophotometry (UV), infrared spectrophotometry (IR), Raman spectroscopy, and nuclear magnetic resonance spectroscopy (¹H-NMR, ¹³C-NMR).

2.A.(1).2) Manufacturing process

The following studies were performed using the quality-by-design (QbD) approach.

- •
- Identification of critical processes and critical process parameters (CPPs) affecting critical quality attributes (CQAs).
- Identification of the proven acceptable range (PAR) of CPP based on the design of experiments and one variable at a time (OVAT)

2.A.(1).3) Control of drug substance



2.A.(1).4) Stability of drug substance

Table 1 shows the main stability studies for the drug substance. Results of the photostability testing showed the drug substance is photostable.

Table 1. Main stability studies for drug substance							
Study	Reference batch	Temperature	Humidity	Container	Storage period		
Long-term testing	3 commercial	25°C	60% RH	Polypropylene or	24 months		
Accelerated batches testing	40°C	75% RH	polyethylene bag	months			

A retest period of 36 months has been proposed for the drug substance when stored in a polypropylene or polyethylene bag at room temperature, based on the "Evaluation for Stability Data," (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing will be continued up to 36 months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product

The drug product is a film-coated tablet containing 0.5, 1.0, or 2.5 mg of the drug substance. The drug product contains, as excipients, mycrocrystalline cellulose, crospovidone, hypromellose, lactose hydrate, magnesium stearate, sodium lauryl sulfate, hydroxypropylcellulose, propylene glycol, titanium oxide, and yellow ferric oxide (1.0 and 2.5 mg tablets) or redferric oxide (2.5 mg tablets).

2.A.(2).2) Manufacturing process

The drug product is manufactured by a process mainly comprising granulation, blending, tableting, coating, and packaging. The following studies were performed using the QbD approach.

- •
- Identification of critical processes and process parameters affecting CQAs, based on the quality risk assessment and the design of experiments

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include content, description (appearance), identification (near-infrared spectrometry [NIR], HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity test [HPLC]), microbial limits (microbial limit test), dissolution (paddle method [HPLC]), and assay (HPLC).

2.A.(2).4) Stability of drug product

Table 2 shows the main stability studies for the drug product. Results of the photostability testing showed the drug product is photostable.

Study	Reference batch ^a	Temperature	Humidity	Container	Storage period
Long-term testing	- 3 pilot scale batches	25°C	60% RH	- PTP packaging ^b	36 months
Accelerated testing		40°C	75% RH		6 months

Table 2. Main stability studies for drug product

a: Drug product manufactured using the drug substance that did not meet the proposed specifications for related substance (Related Substance B)

b: Packaging consisting of polypropylene film and aluminum foil

The shelf life of the drug product was determined to be 36 months when stored at room temperature packaged in PTP sheets.

2.B Outline of the review by PMDA

Based on the review of the submitted data and the responses to inquiries, PMDA concluded that the quality of the drug product is controlled appropriately. The main issues in the review were as shown below.

2.B.(1) Stability tests of drug product

The drug product used in stability studies (long-term testing, accelerated testing) were manufactured from the batches of the drug substance that contained greater amounts of related substances than the final drug substance, with amount of Related Substance B exceeding the acceptance criteria proposed for this application. Therefore, PMDA asked the applicant to explain the difference in the impurity profile between the to-be-marketed formulation and the formulation used in stability studies, taking account of the manufacturing processes of the drug substance and the drug product, and to explain whether or not it is appropriate to evaluate the stability of the to-be-marketed formulation, based on the results of the stability studies shown in Table 2.

The applicant responded as follows:

The manufacturing processes were different, but, except for the difference in the amount of Related Substance B which was produced as a by-product in the manufacturing process of the drug substance, there was no difference in the impurity profile between the drug substance used in manufacturing the formulation for stability studies (batches and the final drug substance when the amount and type of impurities were compared. Neither have been detected any new impurities. The amount of the Related Substance B did not increase in the long-term testing or the accelerated testing of the drug substance, or in the -week longterm testing of the formulation manufactured during the development, suggesting that the Related Substance B was not a degradation product from the drug substance or the drug product. There were differences in the manufacturing process between the to-be-marketed formulation and the formulation used in the stability studies shown in Table 2, due to the differences in the specifications of the equipment for the manufacturing. However, the physical properties and the results of quality tests were comparable between the two formulations, suggesting that the differences in the manufacturing process did not affect the quality of the formulation. Stability studies (storage conditions: 25°C/60% RH, 40°C/75% RH) are now being conducted using the to-be-marketed formulation that was manufactured in a commercial scale using the final drug substance. Results so far obtained after -month storage has shown that there is no difference in

the stability between the to-be-marketed formulation and the formulation used in the main stability studies.

Based on the above, the applicant considered that it was appropriate to evaluate the stability of the to-be-marketed formulation based on the results of the stability studies shown in Table 2.

PMDA considers as follows:

Although the amount of the Related Substance B in the drug substance did not meet the proposed specifications, it is unlikely to affect the evaluation of the stability of the drug product, taking account of the applicant's explanation that, except for the amount of the Related Substance B, there was no difference in the impurity profile between the final drug substance used for manufacturing the to-be-marketed formulation and the drug substance used for manufacturing the formulation for the stability studies, and that the amount of the Related Substance B in the drug product is unlikely to increase over time. Furthermore, there was no difference in the stability between the to-be-marketed formulation and the formulation used for the stability studies, as determined by the 6-month results of the accelerated testing. Therefore, it is acceptable to evaluate the stability of the drug product based on the results of the stability studies shown in Table 2.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) In vitro studies

(a) Soluble guanylate cyclase stimulation

i) Soluble guanylate cyclase (Attached document 4.2.1.1.1 [Reference data], 4.2.1.1.2) Riociguat (0.01-100 μ M) was added to a mixture of recombinant rat soluble guanylate cyclase (sGC) and [³²P]-labeled guanosine triphosphate (GTP), and the mixture was incubated in the presence or absence of nitric oxide (NO) donor diethylamine/NO complex (DEA/NO) (0.001-0.1 μ M), and the concentration of [³²P]-labeled cyclic guanosine monophosphate (cGMP) generated was measured (n = 4-8). The specific activity of sGC, expressed in the ratio of [³²P]-labeled cGMP formed in the absence of riociguat to that in the presence of riociguat, was used as the index of the sGC-stimulating effect. Also, both riociguat and a sGC inhibitor ODQ¹ (100 μ M) were added to a mixture of sGC and [³²P]-labeled GTP, and the specific activity of sGC was calculated in a similar manner.

In the absence of DEA/NO, riociguat stimulated sGC in a concentration-dependent manner over the range from 0.1 to 100 μ M, increasing sGC activity 2- to 73-fold compared with that in the absence of riociguat. Combined addition of riociguat and DEA/NO further increased sGC activity to a level exceeding the activity observed in the presence of either of the drugs, over the concentration range of the drugs examined. In the presence of the maximum concentrations of both drugs (100 μ M of riociguat, 0.1 μ M of DEA/NO), sGC activity increased 112-fold compared with the activity without the drugs. The sGC-stimulating activity of riociguat was almost completely inhibited by ODQ. Also, riociguat did not stimulate sGC from which heme group had been removed by treatment with 0.5% Tween-20. Riociguat did not change the UV absorption spectrum of sGC either in the presence or in the absence of NO, showing that riociguat did not affect the heme group of sGC.

ii) Vascular endothelial cells (Attached document 4.2.1.1.5)

Riociguat (0.001-1 μ M) was added to vascular endothelial cells prepared from pig arterial vessels, and the mixture was incubated in the presence or absence of DEA/NO (0.01-1 μ M) (n = 5-8). The

¹⁾ 1H -[1,2,4] Oxadiazolo[4,3-a]quinoxalin-1-one

concentration of cGMP (mol/well) generated was measured by immunoradiometric assay using [¹²⁵I]-labeled anti-cGMP antibody. The sGC-stimulating effect was expressed in the ratio of cGMP concentration in the drug-treated group to that in the untreated group. In a separate experiment, vascular endothelial cells were incubated in the presence of riociguat (0.001-1 μ M) together with ODQ (10 μ M) (n = 5) or in the presence of riociguat (0.03-3 μ M) together with an NO-releasing factor bradykinin (30 nM) (n = 5-11), and cGMP concentration was measured in a similar manner.

Riociguat (0.01-1 μ M) increased cGMP concentration in vascular endothelial cells in a concentration-dependent manner, with cGMP in the 1 μ M group being 6.7 times that in the untreated group. cGMP concentration in the presence of 0.1 μ M of DEA/NO was 3.2 times that in the untreated group. cGMP concentration in the presence of the maximum concentrations of both riociguat and DEA/NO (1 μ M of riociguat, 0.1 μ M of DEA/NO) was 37.7 times that in the untreated group. The sGC-stimulating effect of riociguat was inhibited by the simultaneous addition of ODQ. Upon treatment with bradykinin to enhance NO release from vascular endothelial cells, intracellular cGMP concentration increased from 0.98 pmol/well to 1.65 pmol/well, and combined addition of both riociguat and bradykinin further increased cGMP concentration to a level between 11.96 and 49.60 pmol/well.

(b) Isolated blood vessels and tissues (Attached document 4.2.1.1.7)

Ring specimens were prepared from the aorta and saphenous artery of male and female NZW rabbits and from the femoral vein of male and female FBI dogs. Also, slices of corpus cavernosum were prepared from the penis of male NZW rabbits. To each specimen thus prepared was added riociguat (final concentration of 1 ng/mL to 0.01 mg/mL, n = 5-9) before or after the addition of phenylephrine. Similarly, riociguat (final concentration of 0.1 ng/mL to 0.01 mg/mL, n = 8) was added to coronary artery ring specimens prepared from pigs, after the addition of U46619, a thromboxane A₂ analog.

Riociguat inhibited the phenylephrine-induced contraction of the ring specimens of the aorta and saphenous artery of rabbits, femoral vein of dogs, and the slices of corpus cavernosum of the penis of rabbits in a concentration-dependent manner, with the 50% inhibitory concentration (IC_{50}) being 95, 200, 340, and 110 nM, respectively. Riociguat also inhibited U46619-induced contraction of coronary artery ring specimens of pigs in a concentration-dependent manner with IC_{50} of 380 nM.

3.(i).**A.**(1).**2**). *In vivo* studies

(a) Effect on hemodynamics

i) Dogs (Attached document 4.2.1.1.13)

Riociguat (0.3, 1, 3, 10, 30, 100 μ g/kg) was bolus-administered intravenously under anesthesia to male and female dogs (20-30 kg), which caused a dose-dependent decrease in the mean arterial pressure and increases in coronary blood flow, heart rate, and oxygen saturation in the coronary sinus (n = 2-6). The mean rate of change from baseline in the riociguat 30 μ g/kg group was a 24% decrease in mean arterial pressure, a 29% increase in coronary blood flow, a 9% increase in heart rate, and a 35% increase in oxygen saturation in the coronary sinus. Riociguat did not affect the left ventricular contractile force (maximum rate of change in left ventricular pressure).

(b) Effect in pulmonary hypertension model animals

i) Monocrotaline-induced pulmonary hypertension rat model (Attached document 4.2.1.1.1 [Reference data])

After severe pulmonary hypertension was induced in rats by subcutaneous administration of monocrotaline (MCT, 60 mg/kg), repeated doses of riociguat (10 mg/kg) or vehicle were given orally to the rats once daily from Day 21 to Day 35 of MCT administration (n = 8). The control group received saline subcutaneously instead of MCT. As a result, the right ventricular systolic

pressure was 25.8 ± 1.9 mmHg in the control group, 51.7 ± 5.4 mmHg in the vehicle group (Day 21 of MCT administration), 84.1 \pm 0.6 mmHg in the vehicle group (Day 35 of MCT administration), and 55.4 ± 2.5 mmHg in the riociguat group (Day 35 of MCT administration), showing a significant decrease in the riociguat group compared with the vehicle group on Day 35. The total pulmonary vascular resistance and the myocardial mass ratio of the right ventricle also showed a similar relationship among treatment groups as observed with the right ventricular systolic pressure. No change was observed in the systemic arterial pressure in any of the groups. Assay results of muscularized in the control group, whereas in the vehicle group, the percentage of non-muscularized pulmonary arteries decreased and, at the same time, the percentage of fully muscularized pulmonary arteries increased both on Day 21 and on Day 35. In the riociguat group, the percentage of non-muscularized pulmonary arteries increased both on Day 21 and on Day 35. In the riociguat group, the percentage of non-muscularized pulmonary arteries increased significantly, and the percentage of non-muscularized pulmonary arteries increased significantly, compared with the vehicle group on Day 35.

ii) SU5416 and hypoxia-induced pulmonary hypertension rat model (Attached document 4.2.1.1.15 [Reference data])

After subcutaneous administration of SU5416 (20 mg/kg), a vascular endothelial growth factor receptor inhibitor, to male SD rats (200-250 g), pulmonary hypertension was induced in the animals by exposure to hypoxia (10% oxygen) for 21 or 35 days. Then, riociguat (10 mg/kg) or vehicle was repeatedly administered orally to the animals once daily from Day 21 to Day 35 of the SU5416 (n = 7-9). The riociguat group showed a significantly lower myocardial mass ratio of the right ventricle, a significantly greater cardiac output, and a significantly lower total pulmonary vascular resistance compared with the vehicle group. Echocardiography showed improvements in the right ventricular function and the morphology in the riociguat group compared with the vehicle group. Also, the riociguat group showed a significantly lower collagen content in the right ventricle, a significantly lower percentage of occluded arteries, and a significantly lower neointima to media ratio compared with the vehicle group. The pulmonary homogenate prepared from rats treated with riociguat showed a significantly higher cGMP concentration, compared with the homogenate prepared from rats treated with the homogenate prepared from rats treated with the vehicle.

3.(i).A.(1).3) Pharmacological effect of metabolite M-1

M-1, which is the main metabolite of riociguat in humans, is an active metabolite. Results of the studies on direct comparison of the pharmacological effect between riociguat and M-1 are described below.

(a) Isolated blood vessels (Attached document 4.2.1.1.22)

The effect of M-1 and riociguat on the isolated blood vessels was evaluated using the same *in vitro* test system as described in 1).(b) above. As a result, IC_{50} values of M-1 against phenylephrine-induced contraction of the ring specimens of male NZW rabbit aorta and saphenous artery were 6862 and 5470 nM, respectively, and IC_{50} values of riociguat were 640 and 554 nM, respectively (n = 7 or 8). IC_{50} values of M-1 and riociguat against U46619-induced contraction of the ring specimen of pig coronary artery were 5220 and 601 nM, respectively (n = 7).

(b) Dogs (Attached document 4.2.1.1.28)

M-1 (100 μ g/kg), riociguat (30 μ g/kg), or vehicle was continuously administered intravenously for 60 minutes to male and female anesthetized dogs (20-30 kg) with autonomic nervous system blockade. The mean artery pressure at 15, 30, 45, and 60 minutes post-dose was decreased by 7.6%, 13.4%, 18.3%, and 20.9%, respectively, following M-1 treatment, and by 7.0%, 15.3%, 22.5%, and 28.0%, respectively, following riociguat treatment (n = 3 or 4), compared with baseline. In both M-1 and riociguat groups, the blood pressure at 60 minutes post-dose was maintained during the 3-hour observation period.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) In vitro studies

(a) Specificity (Attached document 4.2.1.2.1 to 4.2.1.2.5)

Radioligand-binding study or enzymatic analysis was performed using approximately 70 types of receptors and enzymes. Riociguat up to $10 \,\mu\text{M}$ did not bind to any of the receptors tested by $\geq 50\%$ or did not inhibit any of the enzymes tested by $\geq 50\%$ (n = 2).

By enzymatic analysis using radioligands, the effect of riociguat on recombinant human phosphodiesterase (PDE)-11A, 9A, 8A, 7B, 4B, 3B, and 2A, human platelet PDE-5, and bovine PDE-6 and PDE-1 was investigated. IC₅₀ against PDE-7B was 2.9 μ M while IC₅₀ values against other PDEs were all higher than 10 μ M (n = 3).

Using CHO reporter cell²⁾ line overexpressing membrane-bound rat guanylate cyclase A (GC-A, ANP/BNP receptor) and rat guanylate cyclase B (GC-B, CNP receptor), stimulating effect of riociguat on each guanylate cyclase was investigated by cGMP reporter assay. As a result, riociguat up to 30 μ M stimulated neither GC-A nor GC-B (n = 3).

(b) Platelet aggregation (Attached document 4.2.1.2.7, 4.2.1.2.8)

Using platelet-rich plasma collected from healthy adult subjects, the effect of riociguat (2-237 μ M) on drug-induced platelet aggregation was investigated. As a result, riociguat inhibited collagen-, adenosine diphosphate (ADP)-, and thrombin receptor activating peptide-6 (TRAP-6)-induced platelet aggregation in a concentration-dependent manner (n = 5 or 6).

Vasodilator-stimulated phosphoprotein (VASP), a substrate of cGMP-dependent protein kinase (PKG) and cAMP-dependent protein kinase (PKA), is phosphorylated by these enzymes and involved in the inhibition of platelet aggregation. In washed platelets collected from humans and rats, riociguat (0.03-10 μ M) increased phosphorylation of VASP at Ser²³⁹ and Ser¹⁵⁷ in a concentration-dependent manner (n = 4-8), which suggested the possibility that riociguat activates the cGMP-PKG-VASP signal transduction pathway.

3.(i).A.(2).2) In vivo studies

(a) Erectile response (Attached document 4.2.1.2.13)

Riociguat (0.03, 0.1, 0.3, 1, 3 mg/kg) or vehicle was administered orally in a single dose to male chinchilla rabbits (2.8-4.1 kg). As a result, mild erectile response was observed only in the riociguat 3 mg/kg group (n = 6 or 12). When NO donor sodium nitroprusside (0.2 mg/kg) was administered intravenously at 90 minutes after riociguat administration, dose-dependent increases in the penile length and in the erectile duration were observed.

3.(i).**A.**(2).**3**) Secondary pharmacodynamics of metabolite M-1 (Attached document 4.2.1.2.14 to 4.2.1.2.20)

Secondary pharmacokinetics of metabolite M-1 was investigated regarding the specificity, platelet aggregation, etc., and the results showed similar effects as observed with riociguat.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on the central nervous system (Attached document 4.2.1.3.7, 4.2.1.3.8)

Riociguat (0.3, 1, 3 mg/kg) or vehicle was administered orally in a single dose to male Wistar rats (181-220 g), and evaluated for effects on general symptoms, body temperature, and locomotor activity in the open field (n = 6), and on the threshold of pentylenetetrazole-induced convulsive

²⁾ CHO cells co-expressing calcium-sensitive luminescent protein aequorin and cGMP gate-type cation channel (CNG2) (cGMP production was measured as the amount of luminescence generated by aequorin.)

seizures, nociceptive response to heat stimulation, and hexobarbital-induced sleep duration (n = 7-8). As a result, riociguat did not affect general symptoms, body temperature, locomotor activity, threshold of pentylenetetrazole-induced convulsive seizures, or hexobarbital-induced sleeping time, while the drug caused a dose-dependent increase in the duration of nociceptive response to heat stimulation, which showed a significant difference between the riociguat 3 mg/kg group and the vehicle group.

3.(i).A.(3).2) Effects on cardiovascular system and respiratory system

(a) In vitro studies (Attached document 4.2.1.3.1 [Reference data], 4.2.1.3.2 [Reference data])

Riociguat (0.1, 1, 10 μ M) was added to CHO cells expressing human ether-a-go-go-related gene (hERG) channels. Riociguat did not affect hERG current at any concentrations tested.

Purkinje fibers isolated from the heart of female chinchilla rabbits (2-5 kg) were perfused with riociguat solution (0.1, 1, 10 μ M). As a result, riociguat had no effect on the resting membrane potential, action potential amplitude, maximum upstroke velocity, plateau potential, or action potential duration at 20% or 50% repolarization (APD₂₀, APD₅₀) (n = 4). Riociguat at 0.1 or 1 μ M did not affect action potential duration at 90% repolarization (APD₉₀) but, at 10 μ M, significantly prolonged APD₉₀ (14% prolonged from the value before riociguat perfusion).

(b) In vivo studies

i) Conscious telemetered dogs (Attached document 4.2.1.3.5)

A single dose of riociguat (0.05, 0.1, 0.3 mg/kg) or vehicle was administered orally to telemetered male and female beagle dogs (13.1-19.0 kg). As a result, riociguat at 0.05 and 0.1 mg/kg caused a slight decrease in the arterial pressure and, at 0.3 mg/kg, induced a marked and lasting decrease in the arterial pressureand a marked increase in heart rate. These effects disappeared almost completely at the end of the 15-hour observation period (n = 5).

An electrocardiogram (ECG) did not show any effects on QRS intervals. With the riociguatinduced increase in heart rate, PQ intervals and QT intervals decreased. QT intervals were corrected for heart rate using Bazett and Fridericia formulae and QTcB intervals and QTcF intervals obtained by the correction were shown to be prolonged. Riociguat had no effect on QTcV intervals which were obtained by heart rate correction using van de Water formula. The applicant determined that riociguat did not prolong QT/QTc intervals, based on the following findings: (i) it is reported that, in beagle dogs, since QT intervals are overcorrected by Bazett and Fridericia formulae if the heart rate is high, it is more appropriate to use van de Water formula for correction (Hanson LA et al., *J Pharmacol Toxicol Methods*. 2006;54:116-129, Hanton G et al., *Toxicology Methods*. 2001;11:21-40, Miyazaki H et al., *Exp Anim*. 2002;51:465-475, Tattersall ML et al., *J Pharmacol Toxicol Methods*. 2006;53:11-19), and (ii) in the present study, heart rate increased by 10% to 64%, which suggested that the observed prolongation of QT/QTc interval values was due to overcorrections at high heart rate using Bazett and Fridericia formulae.

3.(i).A.(3).3) Effects on the respiratory system (Attached document 4.2.1.3.4)

Riociguat (0.01, 0.03, 0.1, 0.3 mg/kg) or vehicle was administered in a single intraduodenal dose to male and female beagle dogs (10.6-15.7 kg) under anesthesia. Riociguat at any doses did not have any clinically significant effects on the maximum inspiratory pressure, maximum expiratory pressure, respiratory volume, compliance and resistance, oxygen and carbon dioxide concentration in the expired and inspired air, arterial blood gases (oxygen partial pressure, carbon dioxide partial pressure), acid-base equilibrium, or plasma potassium and sodium concentrations (n = 3).

3.(i).A.(3).4) Effects on other organs and functions

(a) Bleeding time (Attached document 4.2.1.3.12 [Reference data])

Riociguat (0.3, 1, 3 mg/kg) or vehicle was administered orally in a single dose to male Wistar rats (198-240 g) and, after approximately 45 minutes, animals were anesthetized by intraperitoneal administration of pentobarbital sodium (60 mg/kg). Another 15 minutes later, the tail of each rat was cut off at 2 mm from the tip (n = 11 or 12), and time to hemostasis was measured. As a result, bleeding time tended to increase in the riociguat 3 mg/kg group but was not significantly different from that in the vehicle group.

3.(i).A.(3).5) Safety pharmacology of metabolite M-1

(a) Effects on the central nervous system (Attached document 4.2.1.3.19, 4.2.1.3.20)

M-1 at 1 or 3 mg/kg did not have any clinically significant effects on the central nervous system in male Wistar rats (166-233 g) but, at 10 mg/kg, caused irregular respiration, decreased motor activity, decreased muscle tone, eyelid ptosis, piloerection, and a slight decrease in body temperature (n = 5-8).

(b) Effects on cardiovascular system (Attached document 4.2.1.3.13 [Reference data], 4.2.1.3.14 [Reference data], 4.2.1.3.17)

In HEK293 cells expressing hERG channel, 20% inhibitory concentration of M-1 against hERG potassium current was 11 μ M.

When Purkinje fibers isolated from the heart of female NZW rabbits were perfused with 10 μ M of M-1 solution, a significant increase in APD₉₀ was observed (6.4% increase compared with the value observed before M-1 perfusion) (n = 5).

A single dose of M-1 (0.15, 0.5, 1.5 mg/kg) or vehicle was administered orally to telemetered male and female beagle dogs (11.7-17.7 kg). As a result, M-1 at 0.5 mg/kg caused a decrease in arterial pressure and, at 1.5 mg/kg, induced a lasting decrease in arterial pressure over an extended period. These effects almost disappeared at the end of study. M-1 at 0.5 and 1.5 mg/kg caused an increase in heart rate (n = 5).

(c) Effects on respiratory system (Attached document 4.2.1.3.16)

M-1 (0.3-1.0 mg/kg) or vehicle was administered in a single intraduodenal dose to male and female beagle dogs (10.0-15.1 kg) under anesthesia. M-1 did not have any clinically significant effects on respiration, pulmonary function, or blood gases (n = 3).

3.(i).A.(4) Pharmacodynamic interactions

3.(i).A.(4).1) Effects on hemodynamics

(a) Concomitant use with PDE-5 inhibitors

i) Concomitant use with vardenafil in rats (Attached document 4.2.1.4.1)

Riociguat (0.1, 0.3, 1, 3 μ g/kg/min), vardenafil (1, 10 μ g/kg/min), or vehicle was continuously administered intravenously, or concomitant use of riociguat (1, 3 μ g/kg/min) and vardenafil (10 μ g/kg/min) was continuously administered intravenously, to male Wistar rats (270-320 g). The concomitant use of riociguat with vardenafil enhanced the decrease in the mean arterial pressure and the increase in the heart rate compared with either drug used alone (n = 9-12).

ii) Concomitant use with sildenafil in dogs (Attached document 4.2.1.4.3)

Sildenafil (30, 100, 300 μ g/kg/h) or vehicle (0.25 mL/kg/h) was continuously administered intravenously to anesthetized male and female dogs (20-30 kg, with autonomic nervous system blockade) and, after 60 minutes, riociguat or vehicle was bolus-administered intravenously at 30-minute intervals (in the order of vehicle, riociguat 3, 10, 30, 100 μ g/kg). Riociguat caused a further dose-dependent decrease in the mean arterial pressure during concomitant use with sildenafil (n = 3-5).

(b) Concomitant use with nitrate in dogs (Attached document 4.2.1.4.4)

Glycerol trinitrate (GTN, 0.5, 1, 3 µg/kg) was bolus-administered intravenously to anesthetized male and female dogs (20-30 kg, with autonomic nervous system blockade) at intervals of 30 to 50 minutes (all doses were administered sequentially to each animal after all cardiovascular parameter values returned close to baseline levels at each time; Cycle 1). As a result, a dosedependent decrease in the mean arterial pressure was observed for a short time (n = 3). Then, at 60 to 120 minutes after initiation of continuous intravenous administration of vehicle, the same doses of GTN as above were again bolus-administered intravenously to the same animals (Cycle 2). Results showed the dogs did not develop tolerance to nitrate. The blood pressure-decreasing effect of intravenous dose of GTN 3 µg/kg was similar to that observed with intravenous dose of riociguat at 60 µg/kg/h. In this test system, each dose of GTN was bolus-administered intravenously (Cycle 2) during continuous intravenous administration of riociguat at 60 µg/kg/h (60-120 minutes) after Cycle 1. As a result, blood pressure further decreased from the level observed during the riociguat administration, and the decrease was GTN dose-dependent (n = 5). In Cycle 2, noradrenaline was continuously administered intravenously for a short period to induce vasoconstriction, simultaneously with continuous intravenous administration of riociguat, and GTN was bolus-administered intravenously under the vasoconstriction condition. As a result, the concomitant use with GTN decreased blood pressure in a dose-dependent manner, and the extent of GTN-induced blood pressure decrease was greater than that observed when GTN alone was given.

3.(i).**A.**(4).2) Effects of concomitant use with rivaroxaban, iloprost, clopidogrel, or aspirin on hemostasis in rats (Attached document 4.2.1.4.5)

Riociguat (0.5, 3 mg/kg at 60 minutes before bleeding time measurement) and rivaroxaban (3 mg/kg at 60 minutes before bleeding time measurement), iloprost (2 mg/kg at 30 minutes before bleeding time measurement), or aspirin (45 mg/kg at 60 minutes before bleeding time measurement) was administered to male Wistar rats (186-241 g), and the effect on hemostasis was investigated (n = 10 or 14). A slight increase in bleeding time was observed in the riociguat alone group (0.5, 3 mg/kg) compared with the vehicle group. When administered alone, rivaroxaban, clopidogrel, and iloprost showed increased bleeding time compared with vehicle, but did not show any further increases in the bleeding time when concomitantly administered with riociguat. Aspirin alone increased the bleeding time compared with vehicle, and showed a further increase in the bleeding time when concomitantly administered (3 mg/kg).

3.(i).**A.**(4).**3**) Pharmacodynamic interactions of metabolite M-1 (Attached document 4.2.1.4.6 to 4.2.1.4.10)

The effect on hemodynamics after concomitant use of M-1 with PDE-5 inhibitors or nitrate was investigated. Results showed that M-1 had similar effects as riociguat did.

3.(i).B Outline of the review by PMDA

The applicant explained the mechanism of action of riociguat to improve pulmonary hypertension as follows:

In *in vitro* systems, riociguat stimulated sGC in a concentration-dependent manner and, in the presence of NO, synergistically enhanced the sGC-stimulating effect, which suggests that riociguat enhances cGMP generation by activating the NO-sGC-cGMP signal transduction pathway by 2 mechanisms: directly stimulating sGC in a NO-independent manner; and stabilizing the binding of NO with sGC thereby enhancing the sensitivity of sGC to NO. Also, in various pulmonary hypertension animal models, riociguat exhibited anti-pulmonary hypertensive effects (e.g., decreases of right ventricular systolic pressure, right ventricular hypertrophy, total pulmonary vascular resistance) and suppression of pulmonary vascular remodeling (fibrosis). Based on the above, the applicant considers that riociguat induces vasodilation and suppresses

pulmonary vessel remodeling by enhancing cGMP generation in the impaired NO-sGC-cGMP signal transduction pathway in patients with pulmonary hypertension, thereby improving the disease.

PMDA considers as follows:

Results of *in vitro* and *in vivo* studies have demonstrated that riociguat enhanced cGMP production and exhibited an anti-pulmonary hypertensive effect in multiple animal models of pulmonary hypertension. Therefore, riociguat is expected to improve pulmonary hypertension in humans. However, since there is a concern that riociguat, by its pharmacological effect, may decrease not only pulmonary arterial pressure but also systemic blood pressure, resulting in hypotension, an appropriate caution statement for the proper use of riociguat should be considered based on the results of clinical studies [see "4.(iii).B.(4) Safety"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Pharmacokinetics of riociguat was investigated in mice, rats, and dogs. Plasma concentrations of riociguat and *N*-demethylated form of riociguat (M-1) were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limit of quantification of plasma concentration of riociguat and M-1 was 1 μ g/L in mice and 0.5 μ g/L in other animal species. Radioactivity concentration in test samples was measured in a liquid scintillation counter. In studies to investigate the metabolite profiles in plasma, urine, and feces, test samples were first applied to high performance liquid chromatography (HPLC) and eluted solutions were then subjected to radioactivity measuring in a liquid scintillation counter. Pharmacokinetic parameter values are expressed in geometric means unless otherwise specified.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration (Attached document 4.2.2.2.1 to 4.2.2.2.3)

Riociguat (0.3, 1 mg/kg) or ¹⁴C-labeled riociguat (3 mg/kg) was administered orally in a single dose to male rats (n = 3/group). Time for riociguat to reach the maximum plasma concentration (t_{max}) was 1.00 hour in the riociguat 0.3 mg/kg group, 0.500 hour in the riociguat 1 mg/kg group, and 1.50 hours in the ¹⁴C-labeled riociguat 3 mg/kg group; the maximum plasma concentration (C_{max}) was 26.7, 146, and 420 µg/L, respectively; the area under plasma concentration-time curve from the study drug dosing to infinity (AUC_∞) was 79.6, 363, and 1524 µg·h/L, respectively; and elimination half-life ($t_{1/2}$) was 1.42, 1.17, and 1.15 hours, respectively. Following a single intravenous dose of riociguat (0.3 mg/kg) or ¹⁴C-labeled riociguat (1 mg/kg) to male rats (n = 3/group), AUC_∞ of riociguat was 228 µg·h/L in the riociguat 0.3 mg/kg group and 820 µg·h/L in the ¹⁴C-labeled riociguat 1 mg/kg group; $t_{1/2}$ was 0.748 and 0.992 hour, respectively; total body clearance (CL) was 1.32 and 1.22 L/h/kg, respectively; and distribution volume at steady state (V_{ss}) was 1.16 and 1.23 L/kg, respectively. The absolute bioavailability (BA) following oral dose of riociguat 0.3 mg/kg relative to intravenous dose of 0.3 mg/kg was 34.9%, and the absolute BA following single oral dose of riociguat at 1 and 3 mg/kg relative to intravenous dose of 1 mg/kg was 44.2% and 62.0%, respectively.

Following a single intravenous dose of ¹⁴C-labeled riociguat (1 mg/kg) to male rats (n = 3), AUC_∞ of radioactivity was 1291 μ g eq·h/L and t_{1/2} of that was 8.63 hours. Following a single oral dose of ¹⁴C-labeled riociguat (3 mg/kg) to male rats (n = 3), t_{max} of radioactivity was 1.50 hours; C_{max} of that was 736 μ g eq/L; AUC_∞ of that was 2572 μ g eq·h/L; and t_{1/2} of that was 17.1 hours.

Following a single oral dose of riociguat (0.03, 0.3 mg/kg) to female dogs (n = 3/group), t_{max} of riociguat was 1 and 1.44 hours, respectively; C_{max} was 16.1 and 211 µg/L, respectively; AUC_∞ was 55.9 and 876 µg·h/L, respectively; and $t_{1/2}$ was 1.50 and 1.88 hours, respectively. Following an intravenous dose of riociguat (0.03 mg/kg) for 1 hour to female dogs (n = 3), AUC_∞ of riociguat was 95.0 µg·h/L; $t_{1/2}$ was 1.66 hours; CL was 0.316 L/h/kg; and V_{ss} was 0.610 L/kg.

Following a single oral dose of ¹⁴C-labeled riociguat (0.6 mg/kg) to female dogs (n = 3), t_{max} of radioactivity was 2.88 hours; C_{max} was 358 μ g eq/L; AUC_∞ was 5120 μ g eq·h/L; t_{1/2} was 85.7 hours; t_{max} of riociguat and M-1 was 0.909 and 3.30 hours, respectively; C_{max} was 205 and 151 μ g/L, respectively; AUC_∞ was 1163 and 1574 μ g·h/L, respectively; and t_{1/2} was 3.04 and 4.82 hours, respectively. Following an intravenous dose of ¹⁴C-labeled riociguat (0.3 mg/kg) for 1 hour to female dogs (n = 3), AUC_∞ of radioactivity was 3293 μ g eq·h/L; t_{1/2} was 91.2 hours; AUC_∞ of riociguat and M-1 was 1203 and 926 μ g·h/L, respectively; and t_{1/2} was 2.42 and 4.90 hours, respectively.

The absolute BA following oral dose of riociguat at 0.03 and 0.3 mg/kg relative to intravenous dose of 0.03 mg/kg was 58.0% and 79.1%, respectively, and the absolute BA following oral dose of 0.6 mg/kg relative to intravenous dose of riociguat 0.3 mg/kg was 48.3%.

3.(ii).A.(1).2) Repeat-dose administration (Attached document 4.2.3.2.6, 4.2.3.2.10)

Riociguat (3, 10, 30 mg/kg) were administered once daily in repeated oral doses to male and female rats (n = 3/sex/group) for 13 weeks. As a result, C_{max} of riociguat and the area under plasma concentration-time curve up to 24 hours post-dose (AUC₂₄) on Day 91 increased in a dose-proportional manner in each dose group, showing no clear sex differences. On Day 91, C_{max} of riociguat in the 3, 10, and 30 mg/kg groups was 1.44, 3.17, and 3.84 times, respectively, that on Day 1 and AUC₂₄ was 0.946, 1.82, and 1.60 times respectively, that on Day 1, showing an increase in the daily exposure level by repeated administration in the 10 and 30 mg/kg groups. The ratio of AUC₂₄ of M-1 to that of riociguat on Day 91 was 0.103 in the 10 mg/kg group and 0.112 in the 30 mg/kg group.

Riociguat (0.3, 1, 3 mg/kg) were administered once daily in repeated oral doses to male and female dogs (4 females/group, 3 males/group) for 13 weeks. As a result, C_{max} and AUC_{24} of riociguat after 12 weeks of treatment did not show clear sex differences and increased in a dose-proportional manner in the 0.3 and 1 mg/kg groups, while their values in the 3 mg/kg group increased less than dose-proportionally. The ratio of AUC_{24} of M-1 to that of riociguat after 12 weeks of treatment was 1.08, 0.808, and 0.708 times in the 0.3, 1, and 3 mg/kg groups, respectively, decreasing with increase in dose. C_{max} and AUC_{24} of riociguat after 12 weeks of treatment were 0.873 to 1.20 times and 0.761 to 1.05 times, respectively, those observed on Day 1.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution (Attached document 4.2.2.3.3, 4.2.2.3.4, 4.2.2.3.6)

¹⁴C-labeled riociguat was administered orally (3 mg/kg) or intravenously (1 mg/kg) in a single dose to male albino rats (n = 1/time point), and administered orally (3 mg/kg) in a single dose to female albino rats (n = 1/time point), and tissue distribution of radioactivity was evaluated in a qualitative manner by whole-body autoradiography. Radioactivity was distributed roughly uniformly in almost all organs and tissues except the brain and spinal cord, and disappeared almost completely at 7 days post-dose, but residual radioactivity was detected in the large intestinal content, skin, and liver. No irreversible binding of radioactivity was observed. No difference was observed in the qualitative distribution pattern between oral and intravenous administrations or between males and females. Following a single oral dose of ¹⁴C-labeled riociguat (3 mg/kg) to pigmented male rats (n = 1/time point), particularly high radioactivity was detected in melanin-containing tissues.

¹⁴C-labeled riociguat (3 mg/kg) was administered orally in a single dose to male albino rats (n = 3/time point), and tissue distribution of radioactivity at 0.5, 1.5, 4, 8, 24, 72, and 168 hours post-dose was evaluated in a quantitative manner by whole-body autoradiography. Tissue radioactivity concentration peaked at 4 hours post-dose in the seminal vesicle and testis and at 0.5 and 1.5

hours post-dose in other tissues. The maximum radioactivity concentration in the tissue was 2849 μ g eq/L in the liver, followed by, in descending order, 2688 μ g eq/L in the renal outer medulla, 2429 μ g eq/L in adrenal cortex, 1584 μ g eq/L in renal cortex, and 1187 μ g eq/L in the renal inner medulla, whereas the concentration was low in white adipose tissue (210 μ g eq/L), testis (78.7 μ g eq/L), eyes (41.6 μ g eq/L), and brain (7.86 μ g eq/L). In most organs and tissues, radioactivity decreased below the lower limit of quantification (approximately 5 μ g eq/L) at 72 hours post-dose, with t_{1/2} of radioactivity in terminal phase being 30 to 50 hours in most organs and tissues.

¹⁴C-labeled riociguat (3 mg/kg) was administered orally in a single dose to male pigmented rats (n = 1/time point), and tissue radioactivity distribution at 24, 72, 168, and 336 hours post-dose was evaluated in a quantitative manner by whole-body autoradiography. Radioactivity concentration decreased with time, while $t_{1/2}$ in the eye wall and pigmented skin was 114 and 120 hours, respectively, showing a delayed elimination in pigmented tissues.

¹⁴C-labeled riociguat (3 mg/kg) was administered orally once daily for 14 days to male albino rats (n = 3/time point), and tissue radioactivity distribution at the end of the repeated administration was evaluated in a quantitative manner by whole-body autoradiography. The pattern of tissue radioactivity distribution was similar to that observed after single dose administration. The maximum radioactivity concentration in each tissue after repeated administration was less than twice that observed after single dose administration.

3.(ii).A.(2).2) Plasma protein binding (Attached document 4.2.2.3.1)

¹⁴C-labeled riociguat (final concentration of 0.0476-2.36 mg/L) was added to mouse, rat, dog, and rabbit plasma samples, and plasma protein binding of riociguat was investigated. The plasma unbound fraction was not dependent on the concentration of riociguat added, with the arithmetic mean value being 20.1%, 15.7%, 17.1%, and 4.17%, respectively.

3.(ii).A.(2).3) Distribution in blood cells (Attached document 4.2.2.3.1)

When ¹⁴C-labeled riociguat (final concentration of 0.0489-2.39 mg/L) was added to rat and dog blood samples, the plasma/blood concentration ratio of ¹⁴C-labeled riociguat was 1.10 and 1.15, respectively.

3.(ii).A.(2).4) Placental transfer (Attached document 4.2.2.3.5)

¹⁴C-labeled riociguat (3 mg/kg) was administered orally in a single dose to rats on Gestation day 19 (n = 1/time point), and tissue radioactivity distribution in maternal animals and in fetuses was evaluated in a quantitative manner by whole-body autoradiography. Radioactivity was uniformly distributed in fetal tissues, with the mean exposure in fetal tissue to radioactivity being approximately 56% of the exposure in the blood of maternal animals. The exposure in fetal brain to radioactivity was approximately 46% of the exposure in fetal blood and 4.6 times higher than that in the brain of maternal animals.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) In vitro metabolism (Attached document 4.2.2.4.1)

 14 C-labeled riociguat (1 μ M, final concentration) was added to mouse, male and female rat, dog, rabbit, and monkey liver microsomes and the mixture was incubated for 60 minutes. As a result, 81.8% to 95.9% of the added radioactivity remained unchanged in mouse, male and female rat, dog, and rabbit liver microsomes, and M-1 was the main metabolite observed. In cynomolgus monkey liver microsomes, 53.6% of added radioactivity was recovered as the unchanged riociguat and 30.7% as M-1.

¹⁴C-labeled riociguat (1 μ M) was added to rat hepatocytes (n = 2) and the mixture was incubated for 4 hours. As a result, 13.8% and 28.7% of the added radioactivity were detected as the unchanged riociguat, 13.8% and 20.5% as M-1, 20.6% and 11.8% as glutathione conjugate of

riociguat (M-15), and 9.6% and 8.8% as *N*-debenzylated form of riociguat (M-3). In dog hepatocytes, 70.6% of the added radioactivity was detected as the unchanged riociguat and 24.6% as M-1.

3.(ii).A.(3).2) In vivo studies (4.2.2.4.7 to 4.2.2.4.10)

Following a single oral dose of ¹⁴C-labeled riociguat (3 mg/kg) to male mice (n = 3), riociguat and M-1 accounted for 0.748 and 0.166, respectively, of the AUC₂₄ of plasma radioactivity.

Following a single oral dose of ¹⁴C-labeled riociguat (3 mg/kg) to male rats (n = 3), riociguat and M-1 accounted for 0.750 and 0.095, respectively, of the AUC₂₄ of plasma radioactivity. Following a single oral dose of ¹⁴C-labeled riociguat (3 mg/kg) to male and female rats (5 males, 3 females), 10.7% and 15.2%, respectively, of the administered radioactivity were excreted in urine, and 83.8% and 79.1%, respectively, were excreted in feces by 48 hours post-dose. The unchanged riociguat excreted in urine accounted for 1.66% and 2.09%, respectively, of the administered radioactivity. The unchanged riociguat excreted in feces accounted for 36.6% and 40.5%, respectively, of the administered radioactivity, M-1 in feces accounted for 4.07% and 3.93%, and the fluorobenzyl-hydroxylated form (M-9) accounted for 20.1% and 19.1%.

Following a single oral dose of ¹⁴C-labeled riociguat (0.6 mg/kg) to female dogs (n = 3), riociguat and M-1 accounted for 0.383 and 0.563, respectively, of the AUC₂₄ of plasma radioactivity. The unchanged riociguat and M-1 excreted in urine by 72 hours post-dose accounted for 1.37% and 6.33%, respectively, of the administered radioactivity, and the unchanged riociguat and M-1 excreted in feces during the same period accounted for 7.50% and 35.4%, respectively, of the administered radioactivity.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Excretion in urine and feces (Attached document 4.2.2.5.1, 4.2.2.5.2)

Following a single intravenous dose of ¹⁴C-labeled riociguat (1 mg/kg) to male rats (n = 5), 17.0% (arithmetic mean) and 81.9% of the administered radioactivity were excreted in urine and feces, respectively, by 7 days post-dose. Following a single oral dose of ¹⁴C-labeled riociguat (0.6 mg/kg) to male rats (n = 5), 14.5% and 82.2% of the administered radioactivity were excreted in urine and feces, respectively, by 7 days post-dose.

Following a single intravenous dose of ¹⁴C-labeled riociguat (0.3 mg/kg) to female dogs (n = 3), 15.6% and 76.3% of the administered radioactivity were excreted in urine and feces, respectively, by 7 days post-dose. Following a single oral dose of ¹⁴C-labeled riociguat (0.6 mg/kg) to female dogs (n = 3), 12.9% and 81.6% of the administered radioactivity were excreted in urine and feces, respectively, by 7 days post-dose.

3.(ii).A.(4).2) Excretion in bile (Attached document 4.2.2.5.1)

Following a single intravenous dose of ¹⁴C-labeled riociguat (1 mg/kg) to bile duct-cannulated male rats (n = 3), 19.3% (arithmetic mean), 24.4%, and 51.3% of the administered radioactivity were excreted in urine, feces, and bile, respectively, by 24 hours post-dose.

3.(ii).A.(4).3) Excretion in milk (Attached document 4.2.2.5.3)

Following a single oral dose of ¹⁴C-labeled riociguat (3 mg/kg) to lactating rats (n = 3) on Lactation day 8 to Lactation day 10, radioactivity concentration in milk at 1, 2, 4, 8, 24, and 32 hours post-dose was 2.41 to 5.47 times the plasma radioactivity concentration at each time point, and 2.2% of the administered radioactivity was excreted in milk by 32 hours post-dose.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Absolute BA of riociguat

PMDA asked the applicant to explain the reason why the absolute BA increased with dose in the single-dose study in rats.

The applicant responded as follows:

In the toxicokinetics study in which riociguat was administered to rats using the vehicle containing neither ethanol nor PEG 400, the AUC normalized by the dose (AUC_{norm}) at steady state (Day 91) was generally constant within the dose range of 3 to 30 mg/kg. In contrast, in the single-dose study in which riociguat was administered orally to rats using the vehicle containing ethanol and PEG 400, AUC_{norm} increased with dose within the dose range of 0.3 to 3 mg/kg. This dose-dependent increase is considered to be due to the riociguat-solubilizing effect of ethanol and PEG400, leading to the increased absorption of riociguat from the intestinal tract, which resulted in the saturation of the first-pass effect. Thus, the dose-dependent increase in the absolute BA in rats appears to be due to the addition of ethanol and PEG 400, solvents with riociguat-solubilizing activities, in the vehicle used in the study.

PMDA considered that, in the single oral dose study in rats, addition of components with riociguat-solubilizing activities in the vehicle was likely to have increased the dissolution rate of riociguat, thereby affecting the amount of riociguat absorbed, and accepted the explanation of the applicant.

3.(ii).B.(2) Distribution of riociguat and metabolites in pigmented tissues

In the study on the tissue distribution of ¹⁴C-labeled riociguat in pigmented rats, a marked accumulation of radioactivity and delay in its elimination were observed in pigmented tissues such as the eye wall and pigmented skin. Therefore, PMDA asked the applicant to explain the possibility that the accumulation of components derived from riociguat in pigmented tissues such as the iris could be toxic in humans.

The applicant responded as follows:

The marked accumulation of radioactivity and delay in its elimination in pigmented tissues such as the eye wall (which consists of sclera, uvea, and retina) and pigmented skin in pigmented rats appear to be due to the binding of riociguat-derived components with melanin. It is reported that, for many drugs with no similarity either in chemical structure or pharmacological activity, melanin-binding activity is not correlated with ocular toxicity (Leblanc B et al., *Regul Tox Pharmacol.* 1998;28:124-132, Gokulgandhi MR et al., *Expert Opin Drug Metab Toxicol.* 2012;8:1277-1291, Brock WJ et al., *Int J Toxicol.* 2013;32:171-181.). Ocular toxicity of riociguat was evaluated in the repeat-dose toxicity study in albino rats, a white rodent species, and in the repeat-dose toxicity study in dogs, a pigmented non-rodent species. As a result, no morphological changes were observed in the eyes of either animal species, from which the applicant considered that riociguat-derived components accumulated in pigmented tissues such as iris were unlikely to cause any toxicity.

In phase III comparative studies in patients with pulmonary hypertension (Study 11348, Study 12934), the incidence of adverse events classified as eye disorders (system organ class) in Study 11348 was 7.5% in the riociguat group, which was higher than 3.4% in the placebo group, but each of the adverse events occurred with a low incidence (0.6%-1.2%). In Study 12934, the incidence of eye disorders was similar between the riociguat dose adjustment group (6.3%) and the placebo group (6.3%). In both studies, most eye disorders observed were rated mild in severity, with no severe cases being observed. Adverse events classified as eye disorders were not observed in the Japanese population in either of the studies. Based on the above, the applicant considered that there were no findings clearly suggesting riociguat-induced eye disorders in clinical studies.

PMDA accepted the explanation of the applicant.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

The following toxicology studies were conducted on riociguat: single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other toxicities (study on the mechanism of toxicity, toxicity of metabolites, toxicity in juvenile animals, phototoxicity, toxicity of impurities).

3.(iii).A.(1) Single-dose toxicity (Attached document 4.2.3.1.1, 4.2.3.2.9)

As single-dose toxicity studies in rodents, oral dose studies in NMRI mice and Wistar rats and an intravenous dose study in NMRI mice were conducted. The approximate lethal dose was determined to be >300 mg/kg and <2000 mg/kg in oral administration in mice and rats, and 30 mg/kg in intravenous administration in mice. Findings observed after oral administration in mice and rats included decreased locomotor activity, labored respiration, diarrhoea, and gait instability, and findings observed after intravenous administration in mice included decreased locomotor activity, labored respiration, diarrhoea, site instability, and findings observed after intravenous administration in mice included decreased locomotor activity, labored respiration, shivering, and convulsions.

As for non-rodents, a single-dose toxicity was evaluated from general symptoms after the first dose in the 4-week repeated oral dose study in beagle dogs. The approximate lethal dose was determined to be >6 mg/kg/day in dogs. Findings observed after oral dose in dogs were convulsions, salivation, vomiting, rectal tenesmus, and gait instability.

3.(iii).A.(2) Repeat-dose toxicity

As repeat-dose toxicity studies, oral dose studies were conducted in mice (13 weeks), rats (4, 13, 26 weeks), and dogs (4, 13, 26, 52 weeks). Riociguat affected the cardiovascular system (rats, dogs), gastrointestinal system (mice, rats), adrenals (rats, dogs), liver (mice, rats), kidney (rats), and bone (rats), among others. The applicants considered that the increased hematopoiesis observed in the bone marrow and spleen of mice and rats was a phenomenon to compensate for hemodilution secondary to riociguat-induced vasodilation and for decreased peripheral blood parameter values due to mild diarrhoea, intestinal inflammation, and oedema. The applicants also considered that increased adrenal weight and hypertrophy of zona glomerulosa observed in rats and dogs were due to the renin-angiotensin system-mediated compensatory action against the decreased blood pressure due to the hemodynamic or vasodilating action of riociguat. Therefore, the applicant considered neither of the observations as toxic findings. The ratios of the exposures (AUC) to riociguat at the no observed adverse effect level (NOAEL) in rats (26 weeks) and dogs (52 weeks) (2.5 mg/kg in male rats, 10 mg/kg in female rats; 0.3 mg/kg in male and female dogs) to that at the maximum recommended clinical dose (7.5 mg/day) were <1 in rats (<0.4 in males, 0.8 in females) and <1 in dogs (0.2 in both males and females).

3.(iii).**A.**(2).1) Thirteen-week repeated dietary administration study in mice (Attached document 4.2.3.2.2, 4.2.3.2.3)

Riociguat was administered in the diet for 13 weeks to male CD-1 mice (n = 10/group) at 0, 2.6, 15.8, 42.0, and 85.8 mg/kg/day and to female CD-1 mice (n = 10/group) at 0, 5.8, 23.6, 67.2, and 124.1 mg/kg/day. As a result, 7 males in the 85.8 mg/kg group and 6 females in the 124.1 mg/kg group died, accompanied by aggravation of the systemic conditions such as pallor, increased abdominal girth, and abdominal distension. The applicant discussed that the death was caused by the excessive hemodynamic effect of riociguat. Findings observed in surviving animals were increased relative weight of liver, hypertrophy of hepatocytes, and prominent Paneth cells in the small intestine in the \geq 23.6 mg/kg groups; increased reticulocyte, splenic hypertrophy, and increased relative weight of spleen in the 42.0 mg/kg group and the \geq 67.2 mg/kg groups; and decreased water intake, decreased red blood cell count, decreased hemoglobin, decreased hematocrit, increased white blood cell count, increased neutrophil count, increased atypical

lymphocyte count, increased platelet count, decreased lymphocyte count, increased hematopoiesis in the bone marrow, extramedullary hematopoiesis in the spleen and liver, cecal inflammation, and dilatation, elongation, and change in the content of the intestine in the 85.8 and 124.1 mg/kg groups. The applicant discussed that the effect on the gastrointestinal tract was due to dysbiosis caused by the decreased mobility of the gastrointestinal tract induced by the smooth muscle-relaxing effect of riociguat and to the chronic inflammation accompanied by the degeneration and regeneration of the mucosal membrane. The applicant also considered that the findings observed in the 23.6 mg/kg group were due to the pharmacological effect of riociguat or to the adaptable changes, from which the NOAEL was determined to be 15.8 mg/kg/day in males and 23.6 mg/kg/day in females.

3.(iii).A.(2).2) Four-week repeated oral dose study in rats (Attached document 4.2.3.2.5) Riociguat (0, 1.5, 5, 15, 30 mg/kg/day) was administered orally for 4 weeks to male and female Wistar rats (n = 10/sex/group). Findings observed were increased hemoglobin, increased hematocrit, and increased reticulocyte count in the \geq 1.5 mg/kg groups; increased blood urea, cytoplasmic changes in centrilobular hepatocytes, and increased relative weight of liver in the \geq 5 mg/kg groups; increased histiocytes in the mesenteric lymph nodes, thickening of femoral growth plate, and decreased relative weight of thymus in the \geq 15 mg/kg groups; and penile erection, reduced body weight gain, decreased blood potassium, and increased relative weight of spleen and adrenal glandin the 30 mg/kg group. Findings observed in the \leq 5 mg/kg groups were all mild and well tolerated, from which the NOAEL was determined to be 5 mg/kg/day.

3.(iii).A.(2).3) Thirteen-week repeated oral dose study in rats (Attached document 4.2.3.2.6)

Riociguat (0, 3, 10, 30 mg/kg/day) was administered orally for 13 weeks to male and female Wistar rats (n = 10/sex/group). Findings observed were increased red blood cell count, increased hematocrit, increased hemoglobin, decreased plasma total protein, increased hematopoiesis in the bone marrow, and hypertrophy of the adrenal zona glomerulosa in the ≥ 3 mg/kg groups; ear redness, increased water intake, increased blood inorganic phosphate, increased urine output, decreased urine specific gravity, decreased urea in urine, decreased urinary creatinine, decreased urinary protein, increased phase I drug-metabolizing enzymes (7-ethoxyresorufin Odeethylase [EROD], 7-ethoxycoumarin O-deethylase [ECOD], aldolase [ALD], carnitine acetyltransferase [CA-T], epoxide hydrolase [EH]), increased phase II drug-metabolizing enzymes (glutathione-S-transferase [GS-T], UDP-glucuronate transferase [GLU-T]), cytoplasmic concentration of hepatocytes, increased relative weight of liver, increased adrenal weight, dilated space between mesenteric veins, and vacuolation of Paneth cells in the small intestine in the ≥ 10 mg/kg groups; and penile erection, decreased body temperature, decreased activity, reduced body weight gain, emaciation, increased monocyte count, increased atypical white blood cell count, increased alanine aminotransferase (ALT), decreased blood triglycerides, increased blood calcium, and decreased prostate, vesicular gland, and epididymis weights in the 30 mg/kg group. The applicant considered the findings observed in the $\leq 3 \text{ mg/kg}$ groups to be due to the pharmacological effect of riociguat or adaptive changes and the NOAEL was determined to be 10 mg/kg/day using the reduced body weight gain as the index.

3.(iii).**A.**(2).4) Thirteen-week repeated dietary administration study in rats (Attached document 4.2.3.2.7)

Riociguat (0, 4, 20, 100 mg/kg/day) was administered in the diet for 13 weeks to male and female Wistar rats (n = 10/sex/group). Findings observed were increased reticulocyte count, increased intestinal length, hypertrophy of the adrenal zona glomerulosa, and hypertrophy of Paneth cells in the \geq 4 mg/kg groups; reduced body weight gain, increased food and water intake, increased red blood cell parameter values, increased urine output, decreased urine specific gravity, decreased urea in urine, decreased urinary creatinine concentration, decreased blood triglycerides, increased relative weight of heart and liver, decreased relative weight of prostate, increased phase

I and II drug-metabolizing enzymes, increased hematopoiesis in the bone marrow, cytoplasmic concentration of hepatocytes, decreased periportal lipid accumulation, pigmentation of renal tubules, and enhanced femoral and sternal remodeling in the \geq 20 mg/kg groups; and changes in general symptoms (e.g., abdominal distention, diarrhoea, penile erection, emaciation, piloerection), decreased blood total protein and calcium, increased relative weight of brain, adrenals, testis, and spleen, decreased relative weight of thymus and vesicular gland, distended cecum, thickening of the tunica media of coronary artery, reticular changes of mesenteric veins, decreased frequency of chronic advanced nephropathy, increased hematopoiesis in the spleen, periportal inflammation, hypertrophy of parathyroid gland, and hyperplasia of the bile duct in the 100 mg/kg group. The applicant considered that the hypertrophy of Paneth cells observed in the \geq 4 mg/kg groups reflected the enhanced protective factor secretion induced by the enhanced cGMP production caused by riociguat, because cGMP is involved in the secretion of the factors in these cells, and therefore that it was not a toxic finding. The applicant also considered that all other findings were changes secondary to the pharmacological action of riociguat and the NOAEL was determined to be 4 mg/kg/day.

3.(iii).**A.**(2).**5**) Twenty-six-week repeated oral dose study in rats (Attached document 4.2.3.2.8)

Riociguat (0, 2.5, 10, 40 mg/kg/day) was given orally for 26 weeks to male and female Wistar rats (n = 20/sex/group). One female in the 40 mg/kg group died, but the death was caused by an error in blood sampling and was not related to riociguat treatment. Findings observed in surviving animals were skin redness in males and females, hepatic hypertrophy and decreased blood potassium in males, and pigmentation in renal tubules in females in the ≥ 2.5 mg/kg groups; increased water intake, increased blood urea, extended intestinal tract, hypertrophy of the adrenal zona glomerulosa, and increased adrenal weight in males and females, penile erection, enhanced femoral remodeling and hyperostosis in males, and decreased blood T3, increased hepatic weight, decreased periportal lipid accumulation in females in the ≥ 10 mg/kg groups; and decreased blood total protein and triglycerides, increased urine output, decreased urine specific gravity, reticular changes of mesenteric veins in males and females, decreased weight of prostate, seminal vesicle, and epididymis, decreased periportal lipid accumulation, and pigmentation of renal tubules in males, and increased abdominal girth, increased white blood cell count, increased lymphocyte count, increased atypical lymphocyte count, distended cecum, increased weight of spleen and kidney, hepatic hypertrophy, hepatocyte hypertrophy and cytoplasmic changes, enhanced femoral remodeling and hyperostosis, and prominent Paneth cells in females in the 40 mg/kg group. Pigmentation of renal tubules could be due to increased urine output caused by the pharmacological action of riociguat, but it is a well-known age-related spontaneous change and is of little toxicological significance. Also, decreased blood T3 did not correlate with the dose, nor was it accompanied by related histological changes. Therefore, the applicant did not consider these changes as toxic effects of riociguat. Based on the above, the NOAEL was determined to be 2.5 mg/kg/day in males and 10 mg/kg/day in females, using the histological changes of bone as the index.

3.(iii).A.(2).6) Four-week repeated oral dose study in dogs (Attached document 4.2.3.2.9)

Riociguat (0, 0.6, 2, 6 mg/kg/day) was administered orally for 4 weeks to male and female beagle dogs (n = 3/sex/group). In the 6 mg/kg group, riociguat administration was interrupted by the end of Week 2 because of aggravation of general symptoms, decreased food intake, and decreased body weight, and the oral administration was resumed at the dose of 4 mg/kg/day in Week 3 and decreased to 2 mg/kg/day in Week 4. Findings observed include decreased blood pressure and increased heart rate in the \geq 0.6 mg/kg groups; and aggravation of general symptoms (e.g., muscle tremor, salivation, vomiting, and rectal tenesmus), decreased food intake, decreased body weight, abnormal urinalysis values (increased protein, bilirubin, urobilinogen, triphosphates, pH), increased basophilic renal tubules, and clear hepatocytes in the 6 mg/kg group. The applicant

considered that the decreased blood pressure was caused by the pharmacological action of riociguat and the NOAEL was determined to be 2 mg/kg/day.

3.(iii).A.(2).7) Thirteen-week repeated oral dose study in dogs (Attached document 4.2.3.2.10)

Riociguat (0, 0.3, 1, 3 mg/kg/day) was administered orally for 13 weeks to male and female beagle dogs (n = 4/sex/group). Findings observed were decreased blood pressure, endocarditis, and periarterial oedema in the cardiac muscle in the ≥ 0.3 mg/kg groups; vomiting, salivation, increased heart rate, and thickening of myocardial arterial walls in the ≥ 1 mg/kg groups; and mushy stool, liquid stool, red colored stools, hypertrophy of the adrenal zona glomerulosa, and increased adrenal weight in the 3 mg/kg group. The NOAEL was not determined in this study.

3.(iii).A.(2).8) Twenty-six-week repeated oral dose study in dogs (Attached document 4.2.3.2.11)

Riociguat (0, 0.3, 1, 3 mg/kg/day) was administered orally for 26 weeks to male and female beagle dogs (n = 4/sex/group). One female in the 3 mg/kg group died, accompanied by aggravation of general symptoms, but the cause of death was not able to be identified. Findings observed in surviving animals were hypertrophy of the adrenal zona glomerulosa in \geq 0.3 mg/kg groups; mushy and liquid stools, decreased blood pressure, increased heart rate, increased QTc interval, and increased adrenal weight in \geq 1 mg/kg groups; and vomiting and salivation in the 3 mg/kg group. Based on the above, the NOAEL was determined to be 0.3 mg/kg/day.

3.(iii).A.(2).9) Fifty-two-week repeated oral dose study in dogs (Attached document 4.2.3.2.12)

Riociguat (0, 0.3, 1, $3\rightarrow 2$ mg/kg/day) was administered orally for 52 weeks to male and female beagle dogs (n = 4/sex/group). In the $3\rightarrow 2$ mg/kg group, decreased food intake, decreased body weight, and muscle tremor were observed after 3 mg/kg administration. Therefore, the dose was decreased to 2 mg/kg/day from Day 31. Subsequently, 1 male in the $3\rightarrow 2$ mg/kg group showed aggravation of systemic conditions, such as diarrhoea and decreased body weight, and died probably due to riociguat administration. Findings observed in surviving animals were decreased blood pressure, increased heart rate, increased adrenal weight, and thickening of the tunica media of myocardial artery in the ≥ 0.3 mg/kg groups; salivation, vomiting, diarrhoea, and emaciation in the ≥ 1 mg/kg groups; and changes in general symptoms (e.g., indifference, decreased motility, tremor), dehydration, decreased food intake, and deceased blood T3 in the $3\rightarrow 2$ mg/kg/day group. The applicant considered that the decreased blood pressure, increased heart rate, increased adrenal weight, and thickening of the tunica media of myocardial artery observed in the ≥ 0.3 mg/kg groups were changes secondary to the vasodilating action of riociguat. No clear sex difference was observed in toxic findings, and the NOAEL was determined to be 0.3 mg/kg/day.

3.(iii).A.(3) Genotoxicity studies (Attached document 4.2.3.3.1.1, 4.2.3.3.1.2, 4.2.3.3.2.1 to 4.2.3.3.2.3)

The following genotoxicity studies were conducted: a bacterial reverse mutation assay, a chromosomal aberration assay in Chinese hamster V79 cells, a micronucleus assay in mice, and a chromosomal aberration assay in mouse bone marrow cells. Riociguat did not show genotoxicity in any of these studies.

3.(iii).A.(4) Carcinogenicity

Two-year oral dose studies were conducted in mice and rats to evaluate carcinogenicity. Tumors in the cecum and colon were observed in mice, whereas no carcinogenicity was observed in rats. The ratio of the exposure (AUC) to riociguat at the non-carcinogenic dose in mice to that at the maximum recommended clinical dose was 0.4 (the ratio of the exposure to unbound riociguat was 1.5). The applicant considered that the tumors were induced by a mechanism unique to mice and were therefore unlikely to be relevant to humans.

3.(iii).A.(4).1) Carcinogenicity study in mice (Attached document 4.2.3.4.1.1)

Riociguat was administered orally for 2 years to male CD-1 mice at the doses of 0, 6.2, 12.4, or 24.9 mg/kg/day and to female CD-1 mice at the doses of 0, 7.6, 15.7, or 32.5 mg/kg/day. Neoplastic lesions observed were adenocarcinoma of cecum in 2 of 50 females in 15.7 mg/kg group (0 of 50 females [control group], 0 of 50 females [7.6 mg/kg group], 0 of 50 females [32.5 mg/kg group]); and adenocarcinoma of colon in 1 of 50 males in 24.9 mg/kg group (0 of 50 males [control group], 0 of 50 males [6.2 mg/kg group], 0 of 50 males [12.4 mg/kg group]), and adenoma of colon in 1 of 50 males [6.2 mg/kg group], 0 of 50 males, 0 of 50 males, 0 of 50 males, respectively). Proliferative lesions observed were mucosal membrane hyperplasia of cecum, colon, and rectum, lymphoid tissue hyperplasia of cecum, and cellularity and hyperplasia of mesenteric lymph nodes. The applicant discussed that these neoplastic and proliferative changes in cecum, colon, etc., were caused by chronic inflammation unique to mice.

Riociguat-related non-neoplastic changes observed included cecum dilatation, thickening of intestinal wall, increased hepatic nodes, gallbladder dilatation, fluid retention in body cavity, chronic inflammation, erosion, ulcer and diverticulum formation in cecum, activation of hepatic Kupffer cells, hyperemia and erythrophagocytosis in mesenteric lymph nodes, and extramedullary hematopoiesis in the spleen.

3.(iii).A.(4).2) Carcinogenicity study in rats (Attached document 4.2.3.4.1.2)

Riociguat (0, 5, 10, 20 mg/kg/day) was administered orally for 2 years to male and female Wistar rats. Increased incidences of death were observed during the study in males of the \geq 10 mg/kg groups (19 of 50 males [control group], 22 of 50 males [5 mg/kg group], 31 of 50 males [10 mg/kg group], 31 of 50 males [20 mg/kg group]). The applicant discussed, for the deaths observed in males of \geq 10 mg/kg groups, that there were no findings suggestive of any specific causes, that there were no sex differences in the findings observed, that the deaths did not occur dose-dependently, and that no clear relationship was observed between riociguat administration and the total number of deaths in males and females combined, including those in satellite groups. No riociguat dose-dependent increase in neoplastic lesions was observed. As proliferative lesions, diffuse C-cell hyperplasia of the thyroid gland and diffuse hyperplasia of the parathyroid gland were observed in males. These changes were mild in severity and no related neoplastic lesions were observed. Also, the changes are known to occur spontaneously in aged rats. Based on the above, the applicant considered that the changes were of little toxicological significance and therefore that riociguat is not carcinogenic in rats.

Riociguat-related non-neoplastic lesions observed included hypertrophy of the heart, adrenals, and kidneys, hardness change and dilatation of the intestinal tract, reticular changes of mesenteric veins, mineral deposition in the lung, biliary cyst of the liver, and erythrophagocytosis in mesenteric lymph nodes.

3.(iii).A.(5) Reproductive and developmental toxicity

The following reproductive and developmental toxicity studies were conducted: a study of fertility and early embryonic development in rats, studies for effects on embryo-fetal development in rats and rabbits, and a study for effects on pre- and postnatal development in rats. Riociguat caused total resorption of embryos in rats, and abortion and total resorption of embryos in rabbits. Effects on fetuses observed were ventricular septal defect and delayed ossification in rats. The ratio of the exposure (AUC) to riociguat at the NOAEL for embryo-fetal development to that at the maximum recommended clinical dose was 0.5 in rats and 4.5 in rabbits. In rats, riociguat was shown to cross the placenta and to be excreted in milk [see "3.(ii).A.(2) Distribution" and "3.(ii).A.(4) Excretion"].

3.(iii).**A.**(5).1) Study of fertility and early embryonic development in rats (Attached document 4.2.3.5.1.1)

Riociguat (0, 3, 10, 30 mg/kg/day) was administered orally to male and female Wistar rats (n = 24/sex/group) from 4 weeks before mating until necropsy (males) or from 2 weeks before mating until Gestation day 7 (females). One male in the 30 mg/kg group died because of an erroneous administration, while there was no death caused by riociguat. Findings observed were ear redness in males and females in the \geq 3 mg/kg groups; piloerection, salivation, increased water intake, and increased urine output in males and females, and reduced body weight gain in males in the \geq 10 mg/kg groups; and decreased food intake and decreased body weight in males and females, and increased time to insemination and decreased testicular weight in males in the 30 mg/kg group. The applicant discussed that the increased time to insemination observed in the 30 mg/kg group was secondary to the aggravation of the systemic conditions and not the direct effect on the male fertility. Based on the above, the NOAEL was determined to be 3 mg/kg/day in males and 10 mg/kg/day in females for general toxicity in parental animals, 10 mg/kg/day for male fertility, and 30 mg/kg/day for female fertility and early embryonic development.

3.(iii).**A.**(5).2) Study for effects on embryo-fetal development in rats (Attached document 4.2.3.5.2.1)

Riociguat (0, 1, 5, 25 mg/kg/day) was administered orally to pregnant Wistar rats (n = 22/group) from Gestation day 6 to Gestation day 17. Findings observed in maternal animals were reduced body weight gain and decreased food intake in the \geq 5 mg/kg groups; and decreased body weight, piloerection, red vaginal discharge, increased water intake, increased urine output, and total resorption of embryos in the 25 mg/kg group. Findings observed in fetuses were decreased body weight, ventricular septal defect, and delayed ossification in the 25 mg/kg group. In the ≥ 1 mg/kg groups, there was a statistically significant increase in the incidence of delayed ossification (incomplete ossification of the arch of the fourth sacral vertebra) (2.5% in the control group, 11.0% in the 1 mg/kg group, 12.8% in the 5 mg/kg group, 18.9% in the 25 mg/kg group). The applicant discussed that the finding was of little toxicological significance for the following reasons: (i) the incidence rates in the riociguat groups were all within this laboratory's historical range (4.9%-29.9%) suggesting spontaneous occurrences, and (ii) the incidence rate in the control group happened to be lower than the laboratory's historical range, suggesting that this caused the apparent statistical significance. Based on the above, the NOAEL was determined to be 1 mg/kg/day for the general toxicity in parental animals and 5 mg/kg/day for embryo-fetal development.

3.(iii).A.(5).3) Study for effects on embryo-fetal development in rabbits (Attached document 4.2.3.5.2.2)

Riociguat (0, 0.5, 1.5, 5 mg/kg/day) was administered orally to pregnant Himalayan rabbits (n = 20/group) from Gestation day 6 to Gestation day 20. Findings observed in maternal animals included abortion and red vaginal discharge in the \geq 1.5 mg/kg groups; and discolored urine, decreased water intake, decreased urine output, total resorption of embryos, partial necrosis of placenta, and increased placental weight in the 5 mg/kg group. In fetuses, enhanced ossification of sternebrae was observed in the 5 mg/kg group. Based on the above, the NOAEL was determined to be 0.5 mg/kg/day for general toxicity in parental animals and 1.5 mg/kg for embryo-fetal development.

3.(iii).A.(5).4) Study for effects on pre- and postnatal development in rats (Attached document 4.2.3.5.3.1)

Riociguat (0, 1.5, 5, 15 mg/kg/day) was administered orally to pregnant Wistar rats (n = 24/group) from Gestation day 6 through Lactation day 21. In maternal animals, decreased food intake, reduced body weight gain, and prolongation of pregnancy period were observed in the 15 mg/kg group, whereas riociguat had no effect on pups. Based on the above, the NOAEL was determined

to be 5 mg/kg/day for general toxicity and fertility in parental animals and 15 mg/kg/day for preand postnatal development.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Study in juvenile animals (Attached document 4.2.3.5.4.2)

Riociguat (0, 0.3, 1, 3 mg/kg/day) was administered orally to 6-day-old male and female Wistar rats for 4, 13, or 14 weeks. Findings observed after 4-week administration were increased splenic weight in the \geq 0.3 mg/kg groups and increased blood calcium concentration in the 3 mg/kg group. Findings observed after 13-week administration were increased blood potassium and calcium concentrations in the \geq 0.3 mg/kg groups, decreased blood magnesium concentration in the \geq 1 mg/kg groups, and increased reticular changes of mesenteric veins in the 3 mg/kg group. In the preliminary study in 6-day-old male and female Wistar rats, morphological abnormalities in epiphyses and marrow cavity of the femur and tibia, decreased bone marrow cells, and hyperostosis and enhanced remodeling of metaphyses and diaphysis were observed in the \geq 10 mg/kg groups after 2-week repeated oral administration (Attached document 4.2.3.5.4.1). No new toxic findings or new organs showing toxicity were observed compared with the results in the repeat-dose toxicity study in 7-week-old rats.

3.(iii).**A.**(6).2) Study on the mechanism of toxicity causing osseous changes (Attached document 4.2.3.7.3.1)

Repeated oral dose of riociguat induces morphological changes of bones in juvenile and adolescent rats. Therefore, in order to investigate the mechanism of osseous changes in individuals after the completion of growth, a study on bone density and morphology was conducted in adult rats. Riociguat was administered orally to male Wistar rats for 6 months at the doses of 0, 10, and $50\rightarrow 25$ mg/kg/day (50 mg/kg/day until Day 8, 25 mg/kg/day from Day 9 onward). Animals were investigated for bone morphology, bone length and density, as well as blood concentrations of type I collagen cross-linked C-telopeptide, type I collagen cross-linked N-telopeptide, parathyroid hormone, osteocalcin, and calcitonin. As a result, a slight decrease in the bone density in the femoral diaphysis was observed in the $50\rightarrow 25$ mg/kg/day group. The applicant discussed that the observed decrease reflected the aggravation of general conditions during the early stage of treatment and that there were no osseous changes clearly related to riociguat.

3.(iii).A.(6).3) Toxicity studies on metabolite

The toxicity of M-1, the main metabolite of riociguat in humans, was evaluated in repeat-dose toxicity studies, a genotoxicity study, a reproductive and developmental toxicity study, and other studies. Toxic findings observed in these studies were similar to those observed with riociguat, except for the effect on the kidney. The ratio of the exposure (AUC) to M-1 at the NOAEL to that at the maximum recommended clinical dose was approximately 4.5 in rats and approximately 1 in dogs in repeat-dose toxicity studies, and 1.0 in rats and 11.9 in rabbits for embryo-fetal development. The outlines of the main studies are described below.

(a) Fourteen-week dietary administration study in mice (Attached document 4.2.3.7.5.3)

M-1 was administered in the diet for 14 weeks to male and female CD-1 mice (n = 10/sex/group) at the doses of 0, 16.7, 50.1 or 165.6 mg/kg/day (males) and 27.7, 84.2, or 225.6 mg/kg/day (females). As a result, decreased food intake, decreased red blood cell count, decreased hematocrit, and decreased hemoglobin were observed in the 225.6 mg/kg group.

(b) Four-week repeated oral dose study in rats (Attached document 4.2.3.7.5.5)

M-1 (0, 4, 20, 100 mg/kg/day) was administered orally for 4 weeks to male and female Wistar rats (n = 10/sex/group). Findings observed in the \geq 20 mg/kg groups were reduced body weight gain and increased relative weight of adrenal gland, and findings observed in the 100 mg/kg group included increased water intake, decreased blood glucose and triglycerides, increased urine output,

decreased urinary protein excretion, increased relative weight of kidney, decreased relative weights of thymus, prostate gland, seminal vesicle, and uterus, decreased hardness of gastrointestinal tract, prominent and vacuolized adrenal zona glomerulosa, thickening of femoral growth plate, thickening of distal tubular epithelium, and hyperplasia of the epithelium of collecting tubules. Based on the above, the NOAEL was determined to be 4 mg/kg/day.

(c) Thirteen-week repeated oral dose study in rats (Attached document 4.2.3.7.5.6)

M-1 was administered orally to male and female Wistar rats (n = 10/sex/group) for 13 weeks at the doses of 0, 5, 15, or 50 mg/kg/day (males) and 0, 10, 30, or 100 mg/kg/day (females). Findings observed were reduced body weight gain in males in the \geq 15 mg/kg groups; thickening and hyperplasia of distal tubular epithelium, dilatation of collecting tubules, and hyperplasia of the epidermis of collecting tubules in renal papillae in the 50 mg/kg group; and increased kidney weight, thickening and hyperplasia of distal tubular epithelium, dilatation of collecting tubules, hyperplasia and degeneration of the epidermis of collecting tubules in renal papillae, thickening of femoral and tibial growth plate, trabecular abnormality, diaphyseal hyperostosis, etc., in the 100 mg/kg group. Based on the above, the NOAEL was determined to be 5 mg/kg/day in males and 30 mg/kg/day in females.

(d) Twenty-eight-week repeated oral dose study in rats (Attached document 4.2.3.7.5.9)

M-1 (0, 3, 10, 30 mg/kg/day) was administered orally for 28 weeks to male and female Wistar rats (n = 20/sex/group). Increased urinary excretion of *N*-acetyl- β -glucosaminidase (NAG) was observed in the \geq 10 mg/kg groups, and decreased platelet count, thickening of the tunica media of blood vessels in the heart and pancreas, reticular changes of mesenteric veins, hyperplasia of the epidermis of collecting tubules in renal papillae, etc., were observed in the 30 mg/kg/day group. Based on the above, the NOAEL was determined to be 10 mg/kg/day.

(e) Four-week repeated oral dose study in dogs (Attached document 4.2.3.7.5.11)

M-1 (0, 0.5, 1.5, 5 mg/kg/day) was administered orally for 4 weeks to male and female beagle dogs (n = 3/sex/group). One male in the 5 mg/kg group died. The animal showed acute myocardial degeneration of papillary muscle. Findings observed in surviving animals were decreased blood pressure, increased heart rate, fibrogenesis of left ventricular papillary muscles, myocarditis, perivascular and vascular oedema, and endocarditis in the \geq 1.5 mg/kg groups; and salivation, vomiting, diarrhoea, inflammation and myenteric plexus hypertrophy of rectum, and myenteric ganglionitis of cecum in the 5 mg/kg group. Based on the above, the NOAEL was determined to be 0.5 mg/kg/day.

(f) Thirteen-week repeated oral dose study in dogs (Attached document 4.2.3.7.5.12)

M-1 (0, 0.3, 1, 3 mg/kg/day) was administered orally for 13 weeks to male and female beagle dogs (n = 4/sex/group). Increased blood creatinine concentration and thickening of the tunica media of cardiac arterioles were observed in the \geq 1 mg/kg groups, and diarrhoea, decreased blood pressure, and increased heart rate were observed in the 3 mg/kg group. The applicant discussed that the thickening of the tunica media of cardiac arterioles was a change compensatory to the hemodynamic effect of M-1 and was therefore not the direct toxic effect of riociguat. Based on the above, the NOAEL was determined to be 1 mg/kg/day using gastrointestinal symptom as the index.

(g) Thirty-nine-week repeated oral dose study in dogs (Attached document 4.2.3.7.5.13) M-1 (0, 0.3, 1, 3 mg/kg/day) was administered orally for 39 weeks to male and female beagle dogs (n = 4/sex/group). Decreased blood pressure was observed in the \geq 0.3 mg/kg groups, thickening of the tunica media of cardiac arterioles was observed in the \geq 1 mg/kg groups, and increased heart rate, vomiting, and diarrhoea were observed in the 3 mg/kg group. Based on the above, the NOAEL was determined to be 1 mg/kg/day using the gastrointestinal symptoms as indices.

(h) Genotoxicity studies (Attached document 4.2.3.7.5.15-17)

As genotoxicity studies on M-1, a bacterial reverse mutation assay, a chromosomal aberration assay using Chinese hamster V79 cells, and a mouse micronucleus assay were conducted. M-1 did not show genotoxicity in any of the assays.

(i) Embryo-fetal developmental toxicity study in rats (Attached document 4.2.3.7.5.20)

M-1 (0, 2, 10, 50 mg/kg/day) was administered orally to pregnant Wistar rats (n = 22/group) from Gestation day 6 to Gestation day 17. Findings observed in maternal animals were decreased food intake in the \geq 10 mg/kg groups; and death (1 animal), aggravation of general conditions such as reduced body weight gain, piloerection, and abnormal feces in the 50 mg/kg group. Findings observed in fetuses were smaller thyroid gland in the \geq 10 mg/kg groups; and decreased fetal weight, delayed ossification, skeletal anomaly (wavy ribs), elongation of thymus toward cranial side, and missing thyroid gland in the 50 mg/kg group. Based on the above, the NOAEL was determined to be 2 mg/kg/day for general toxicity in parental animals and for embryo-fetal development.

(j) Embryo-fetal developmental toxicity study in rabbits (Attached document 4.2.3.7.5.21)

M-1 (0, 0.5, 1.5, 5 mg/kg/day) was administered orally to pregnant Himalayan rabbits (n = 20/group) from Gestation day 6 to Gestation day 20. Findings observed in maternal animals were decreased food and water intake, decreased body weight, abortion, and placental hypoperfusion in the 5 mg/kg group. No toxic findings were observed in fetuses. Based on the above, the NOAEL was determined to be 1.5 mg/kg/day for general toxicity in parental animals and 5 mg/kg/day for embryo-fetal development.

(k) Study on the mechanism of nephrotoxicity (Attached document 4.2.3.7.5.23, 4.2.3.7.5.24)

M-1 (0, 100 mg/kg/day) was administered for 13 weeks to female rats, and changes in renal lesions were analyzed over time. Throughout the treatment period, animals showed increased water intake, increased urinary creatinine, increased urinary NAG excretion, decreased urinary γ -glutamyltransferase (GGT) excretion, increased urinary lactate dehydrogenase (LDH) excretion, increased urinary glucose, increased urinary amino acids, and increased urinary 3-hydroxybutyric acid excretion. Histopathological examination showed degeneration of the tubular epithelium and dilatation of the renal tubules from Day 3 onward, and hypertrophy and hyperplasia of the distal renal tubules from Day 15 onward. Regeneration and hyperplasia of the tubular epithelium secondary to the degeneration of the renal tubular were also observed.

3.(iii).A.(6).4) Evaluation of the toxicity of impurities (Attached document 4.2.3.7.6.1)

For Related Substances A and B, impurities for which acceptance criteria in the drug substance were defined in excess of the qualification threshold,³⁾ *in vitro* and *in vivo* genotoxicity studies and repeat-dose toxicity studies in rats and dogs, using the batches containing these impurities in excess of the amount in the maximum clinical dose, were performed. Based on the results of these studies, the applicant considered that the safety of these impurities was demonstrated.

3.(iii).A.(6).5) Phototoxicity studies

As phototoxicity studies, a study using mouse-derived 3T3 fibroblasts and a local lymph node assay/integrated model for the differentiation of the skin reactions (LLNA/IMDS) using mice were conducted. As a result, the applicant concluded that riociguat had no clinically significant

³⁾ At the application for registration, the acceptance criterion for Related Substance A had been defined at a level exceeding the qualification threshold. During the review process, the value was changed to the level below the qualification threshold.

phototoxicity.

(a) **3T3 NRU phototoxicity study (Attached document 4.2.3.7.7.1)**

Riociguat (10-300 μ g/mL) was added to mouse-derived 3T3 fibroblasts, and the mixture was irradiated with UVA (5 J/cm²). In non-UVA-irradiated cells, riociguat concentration allowing 50% viability (EC₅₀) exceeded 300 μ mol/mL, whereas in UVA-treated cells, EC₅₀ was 120 μ mol/mL, showing an effect on cell viability upon photoirradiation.

(b) Local lymph node assay/integrated model for the differentiation of the skin reactions (LLNA/IMDS) (Attached document 4.2.3.7.7.2)

Riociguat (0, 3, 10, 30 mg/kg/day) was administered orally for 3 days to female NMRI mice. The animals were irradiated with UVA (20 J/cm²) for 30 minutes once daily after oral administration, and were monitored for light-induced skin sensitization and irritation. No UVA-irradiation-related changes were observed in any of the test parameters including the thickness or weight of the ear, local lymph node weight, and cell count in the lymph node, indicating that riociguat had no phototoxicity.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Toxicities of riociguat administration

3.(iii).B.(1).1) Effect on cardiovascular system and on adrenals

PMDA asked the applicant to discuss the mechanism of riociguat effects on the heart, blood vessels, and adrenals, which were observed as main findings in the repeat-dose toxicity studies on riociguat, and to discuss the clinical risk.

The applicant responded as follows:

Riociguat showed the following effects on the cardiovascular system: thickening of the tunica media of coronary artery in rats, and endocarditis, myocardial fibrosis, angioedema, thickening, and hypertrophy of myocardial blood vessels in dogs. In all of the repeat-dose toxicity studies that showed these lesions, severe decreases in blood pressure and/or tachycardia were observed. Pathological findings were restricted to the coronary arteries, left ventricular papillary muscles, myocardial arteries, and subendocardial lesions, and were not accompanied by hemorrhage or necrosis. Similar cardiac findings were observed in toxicity studies in dogs using vasodilators such as adenosine agonists, hydrazine, minoxidil, theobromine, adrenergic cardiotonic agents, endothelin receptor blockers, PDE inhibitors, and calcium channel blockers (Clemo FAS et al., Toxicol Pathol. 2003;31:Suppl 25-31, Greaves P et al., Exp Toxic Pathol. 1998;50:283-293) and in toxicity studies in rats and dogs conducted by the applicant for application of vardenafil, a PDE-5 inhibitor. The mechanism of vasodilator-induced cardiac lesions is similar among these agents. Thus, under the conditions inducing decreased blood pressure and tachycardia, imbalance occurs between the demand and supply of oxygen in the cardiac muscles. It is reported that, particularly in dogs under such conditions, cardiac papillary muscles and the subendocardial region, where the amount of blood supply is small, are prone to be damaged (Detweiler DK. Toxicol Pathol. 1989;17:94-108), and that there is no correlation between vasodilator-induced cardiac lesions in dogs and cardiac toxicity in humans (Dogterom P et al., Crit Rev Toxicol. 1992;22:203-241.). These findings suggest that dogs are particularly sensitive to the vasodilating action.

Regarding the effects of riociguat on adrenals, hypertrophy or hyperplasia of the zona glomerulosa of adrenal cortex was observed in rats and dogs. Similar changes were observed in toxicity studies on PDE inhibitors, calcium channel blockers, etc. which cause the vasodilating action or hypotensive effect (Ito et al., *CLINICAL REPORT*. 1987;21:477-518, Iijima et al., *Pharmacometrics*. 1991;42:177-187.). These changes are renin-angiotensin system-mediated responses to compensate for decreased blood pressure directly caused by the hypotensive effect of riociguat or mediated by the vasodilating action of riociguat. In the carcinogenicity study in

rats and in the 52-week repeat-dose toxicity study in dogs, no effect on the adrenal zona glomerulosa was observed, neither was aggravation of findings observed after long-term treatment. Regarding the effect on hormone production in the zona glomerulosa of the adrenal cortex, a possibility of aldosterone secretion was considered. However, riociguat did not show any sodium concentration-related effects either in males or females although a slight decrease was observed in blood potassium concentration in male rats. These results suggest that the aldosterone level does not change in association with the hypertrophy of the zona glomerulosa of adrenal cortex.

Based on the above, the applicant considered that the effects of riociguat on the cardiovascular system and on the adrenal were changes to compensate for the blood pressure fluctuation and tachycardia caused by the hypotensive effect of riociguat, a mechanism similar to that expected for various vasodilator agents. Since riociguat is to be administered carefully while monitoring for hypotensive symptoms in clinical settings, riociguat is unlikely to cause chronic or excessive hypotension as observed in toxicity studies of riociguat. Therefore, the applicant considers that the effects on the cardiovascular systems and adrenals as observed in animal studies do not pose any safety problems in humans.

PMDA considers as follows:

The ratio of the exposure to riociguat at the maximum level not causing cardiovascular or adrenal findings in the repeat-dose toxicity studies to the exposure at the recommended clinical dose is <1, which indicates that there is no sufficient safety margin against these toxicities. However, PMDA accepts the explanation of the applicant that similar findings are also observed in toxicity studies of various vasodilator agents, and the changes are caused by the hypotensive effect of riociguat and unlikely to be unique to riociguat. PMDA also accepts the explanation of the applicant that since, in clinical settings, riociguat is administered carefully to avoid excessive blood pressure decrease according to the procedure stipulated in the package insert (draft), the effects on the cardiovascular systems and adrenals caused by the hypotensive effect of riociguat as observed in toxicity studies are unlikely to pose any safety problems in humans.

3.(iii).B.(1).2) Effects on bones

PMDA asked the applicant to discuss the mechanism of effects on bones observed in the repeatdose toxicity studies of riociguat and to discuss the clinical risks.

The applicant responded as follows:

In the repeat-dose toxicity studies in 7-week-old rats (at the ininitiation of the study) and juvenile rats, enhanced bone remodeling and hyperostosis were observed, whereas no such findings were observed in adult rats with completed bone growth or in dogs with almost completed growth. Riociguat acts on sGC and thereby enhances intracellular cGMP production. Therefore, riociguat stimulates osteoblasts via the natriuretic peptide (NP)-particulate GC (pGC)-cGMP signal transduction pathway or the NO-sGC-cGMP pathway (Wimalawansa SJ. Ann N Y Acad Sc. 2010;1192:391-403), thereby inhibiting the growth and differentiation of osteoclasts, leading to hypertrophy of trabecular bones at the metaphysis and remodeling of cortical bones. In the repeatdose toxicity study in 7-week-old rats, effects on bones were induced by repeated dose of riociguat at the exposure which was 1.7 times that at the maximum recommended dose in humans, whereas no clear effect on bones was observed in the study in adult rats 17 weeks old at the initiation of the study. Also, the ratio of the exposure to unbound riociguat at the maximum dose in the adult rat study (50 \rightarrow 25 mg/kg/day) to that at the maximum recommended dose in humans is as high as \geq 8. In addition, the clinical studies of riociguat did not show any clinically significant changes possibly affecting bone metabolism during treatment. Based on the above, the applicant considered that riociguat had little impact on bones in adult humans.

PMDA accepted the explanation of the applicant that riociguat would have no clinically significant effect on bones when used in adult humans.

3.(iii).B.(1).3) Effects on kidney

PMDA asked the applicant to discuss the mechanism of nephrotoxicity observed in the repeatdose toxicity study of M-1 in rats and to discuss clinical risks.

The applicant responded as follows:

The repeat-dose toxicity study of M-1 and the study on M-1-induced nephrotoxicity showed increased NAG excretion, degeneration, thickening, and hyperplasia of the proximal renal tubules, distal renal tubules, and epithelium of collecting tubules. It appears that these findings were caused by the direct effects of M-1 on renal tubular epithelia, but the mechanism is unknown. In the study on the mechanism of nephrotoxicity in rats, early stage degeneration occurred in the proximal and distal renal tubules, as well as in the collecting tubules. Hyperplasia of the distal renal tubules or the epithelium of collecting tubules occurred as changes following these early stage degenerations. Regarding these early stage changes, i.e., increased NAG secretion and degeneration of renal tubules, the ratio of the exposure to unbound M-1 at the maximum nontoxic dose to that at the maximum recommended dose in humans was 3.3 and 13.0, respectively. In dogs, administration of M-1 alone had no effect on the renal tubules, and the ratio of the exposure to unbound M-1 at the maximum recommended dose in humans was 6.0. Based on the above safety margin of exposure to unbound M-1, the applicant considered that the degeneration of renal tubules was unlikely to occur in humans and therefore that hyperplasia secondary to the renal tubules was unlikely to occur.

PMDA asked the applicant to explain whether or not there were laboratory changes indicating the degeneration of renal tubules or any other findings suggesting the degeneration in clinical studies.

The applicant responded as follows:

Phase III comparative studies of riociguat (Studies 11348 and 12934) did not show any adverse changes in renal function-related laboratory parameters including creatinine clearance, estimated glomerular filtration rate, and cystatin C in riociguat groups compared with the placebo group. In a clinical study using M-1,⁴⁾ safety was evaluated using indices for renal tubule impairment, including NAG, NAG/creatinine ratio, GGT, GGT/creatinine ratio, LDH, and LDH/creatinine ratio. As a result, no clinically significant changes were observed, nor were noted any adverse events suggestive of nephrotoxicity.

Taking account of the results of clinical studies on riociguat and M-1, PMDA accepted the response of the applicant that the renal changes observed in rats were unlikely to be relevant to humans, and concluded that the changes do not pose any problems in clinical use.

3.(iii).B.(2) Carcinogenicity

PMDA asked the applicant to explain the mechanism of the development of colon adenoma and adenocarcinoma observed in the carcinogenicity study in mice, and to explain their relevance to humans.

The applicant responded as follows:

Riociguat is considered to relax smooth muscles by increasing intracellular cGMP. Therefore, riociguat appears to decrease the motility of the intestinal tract, thereby inducing chronic dysbiosis. In the carcinogenicity study in mice, increased abdominal girth and abdominal dilatation occurred in a dose-dependent manner in riociguat groups both in males and females, resulting in a

⁴⁾ A clinical study of M-1 was conducted in healthy adult subjects and in patients with biventricular chronic heart failure and pulmonary hypertension.

decreased tolerance in the gastrointestinal tract. In the treatment groups in which colon adenoma and adenocarcinoma were observed, erosive/ulceric inflammation, degeneration, and regeneration of the mucous membrane were observed in the colon and rectum. It is reported that, in experimental mouse models, these chronic changes induced regenerative mucous membrane hyperplasia and a small number of epithelial colorectal tumors (Kanneganti M et al., *J Biomed Biotechnol.* 2011;2011:342637, Taketo MM et al., *Gastroenterology.* 2009;136:780-798.). These findings suggest that the chronic inflammation of the intestine following riociguat treatment is an important causative factor for tumor development.

Chronic inflammation of the intestinal tract may be induced also in other animal species such as rats and dogs by the mechanism caused by the smooth muscle-relaxing effect. However, in the carcinogenicity study in rats and the long-term repeat-dose toxicity study in dogs in which riociguat was administered at the exposure level similar to that in mouse studies, neither inflammatory changes nor neoplastic lesions were observed in the intestinal tract, suggesting that the occurrence of chronic inflammation in the large intestine is a specific effect of riociguat on the intestinal bacterial flora, an effect unique to mice. Based on the above, the applicant considered that colon adenoma and adenocarcinoma were caused by chronic inflammationmediated mechanism unique to mice, and therefore that they were unlikely to be relevant to humans.

PMDA accepted the explanation of the applicant that the severe intestinal inflammation and resultant colon adenocarcinoma observed in mice are unlikely to be relevant to humans in clinical use of riociguat.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods 4.(i).A Summary of the submitted data

Concentrations of riociguat and M-1, the N-demethylated metabolite of riociguat, in plasma and urine were measured simultaneously by the validated high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation for riociguat and M-1 in plasma varied depending on study, ranging from 0.1 to 2.0 μ g/L and from 0.2 to 2.0 μ g/L, respectively. The lower limit of quantitation for riociguat and M-1 in urine also varied depending on the study, ranging from 1.0 to 10 μ g/L for both analytes.

Riociguat 0.5, 1.0, 1.5, 2.0, and 2.5 mg tablets were used in phase III studies, and the 2.5 mg tablets in phase III clinical studies were used in the food effect study. The to-be-marketed formulation 0.5, 1.0, and 2.5 mg tablets were the same as the formulations in the phase III clinical studies regarding the component of the inner core but different in the ratio of coloring agents in the film layer. The bioequivalence (BE) between 0.5 and 1.0 mg tablets used in phase III clinical studies and the to-be-marketed formulation was confirmed by BE studies in humans (Studies 14769 and 14845), and BE between 2.5 mg tablets used in phase III clinical studies and the to-be-marketed formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 67 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012).

Pharmacokinetic parameter values are expressed in geometric means (geometric coefficient of variation [%]) unless otherwise indicated.

4.(i).A.(1) Absolute bioavailability study (Study 11910, Attached document 5.3.1.1.1 [Reference data])

Absolute bioavailability (BA) was evaluated by a two-treatment, two-period, crossover study in which riociguat 1.0 mg tablet was administered orally in a single dose, and riociguat 1.0 mg was administered intravenously over 1 hour, both under fasting conditions, to 22 foreign healthy adult male subjects (with a wash-out period of 7days between the treatment periods). The absolute BA of riociguat was 94.33% [83.11-107.07] (least squares mean [95% confidence interval (CI)]). Following the intravenous administration of riociguat 1.0 mg over 1 hour, the total body clearance (CL) of riociguat and M-1 was 3.861 (78.3%) and 4.958 (34.1%) L/h, respectively, the distribution volume at steady state (V_{ss}) was 30.09 (14.7%) and 115.9 (62.5%) L, and renal clearance (CL_R) was 0.3434 (26.6%) and 0.6131 (61.1%) L/h.

4.(i).A.(2) Food effect study (Study 13010, Attached document 5.3.1.1.4)

The effect of food intake on the pharmacokinetics of riociguat was evaluated by a two-treatment, two-period, crossover study in which riociguat 2.5 mg tablet was administered orally in a single dose under fasting conditions or after intake of a high fat diet to 23 foreign healthy adult male subjects (with a wash-out period of approximately 1 week between the treatment periods). The median (minimum-maximum) time to the maximum plasma riociguat concentration (t_{max}) after fasted and fed administration was 1.000 [0.5000-4.000] and 4.000 [1.500-6.000] hours, respectively; the maximum plasma concentration (C_{max}) was 84.19 (37.5%) and 54.79 (28.7%) µg/L, respectively; the area under plasma concentration-time curve from the initiation of the study drug to infinity (AUC_{∞}) was 572.2 (80.6%) and 505.6 (74.5%) µg·h/L, respectively; and the elimination half-life $(t_{1/2})$ was 5.538 (72.1%) and 6.135 (66.1%) hours, respectively. The t_{max} (median [minimum-maximum]) of M-1 after fasted and fed administration was 8.000 [3.000-24.00] and 12.00 [4.000-24.00] hours, respectively; C_{max} was 19.35 (55.2%) and 15.50 (53.7%) μ g/L, respectively; AUC_{∞} was 526.8 (28.2%) and 498.6 (27.4%) μ g·h/L, respectively; and t_{1/2} was 24.25 (27.6%) and 28.70 (33.1%) hours, respectively. The ratios of the geometric mean [90% CI] of C_{max} and AUC_{∞} of riociguat after fed administration to those after fasted administration were 0.6471 [0.5779-0.7245] and 0.8832 [0.8215-0.9496], respectively, and the ratios of the geometric mean [90% CI] of C_{max} and AUC_{∞} of M-1 after fed administration to those after fasted administration were 0.7950 [0.7172-0.8812] and 0.9447 [0.8943-0.9979], respectively.

4.(i).A.(3) BE between drug products

4.(i).A.(3).1) BE between formulations for clinical studies and to-be-marketed formulations in humans

(a) **BE study on 0.5 mg tablets in humans (Study 14769, Attached document 5.3.1.2.2)** Riociguat 0.5 mg tablet for clinical studies and riociguat 0.5 mg tablet for the to-be-marketed formulation were administered orally in a single dose under fasting conditions to 22 Japanese healthy adult male subjects in a two-treatment, two-period, crossover design (with a wash-out period of \geq 7 days between the treatment periods), and plasma riociguat concentration was measured up to 72 hours after administration. As a result, the ratio of the geometric mean [90% CI] of C_{max} and the area under the plasma concentration-time curve up to the time of the last measurable concentration (AUC_t) of the to-be-marketed formulation to that of the formulation for clinical studies was 0.982 [0.909-1.061] and 1.002 [0.963-1.042], respectively.

(b) BE study on 1.0 mg tablets in humans (Study 14845, Attached document 5.3.1.2.3)

Riociguat 1.0 mg tablet for clinical studies and riociguat 1.0 mg tablet for the to-be-marketed formulation were administered orally in a single dose under fasting conditions to 24 Japanese healthy adult male subjects in a two-treatment, two-period, crossover design (with a wash-out period of \geq 7 days between the treatment periods), and plasma riociguat concentration was measured up to 72 hours after administration. As a result, the ratio of the geometric mean [90% CI] of C_{max} and AUC_t of the to-be-marketed formulation to that of the formulation for clinical studies was 1.063 [0.993-1.137] and 0.959 [0.876-1.049], respectively.

4.(i).A.(3).2) Dissolution tests of to-be-marketed formulations with different strengths Dissolution tests were performed on 0.5 and 1.0 mg tablets intended for marketing under the conditions specified in "Guidelines for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (Guideline for Different Strengths) (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012). Under all test conditions, the formulations met the acceptance criteria for the equivalence in dissolution behavior stipulated by the Guideline for Different Strengths.

Dissolution tests of the to-be-marketed formulation 1.0 and 2.5 mg tablets were performed under the conditions specified in the Guideline for Different Strengths. In the dissolution test at pH , the volume of the dissolution medium and the number of test tablets were set at mL and tablets, respectively, for 1 mg tablets, and at mL and tablets, respectively, for 2.5 mg tablets. Under all test conditions, the formulations met the acceptance criteria for the equivalence in dissolution behavior stipulated by the Guideline for Different Strengths.

4.(i).B Outline of the review by PMDA

4.(i).B.(1) BE between to-be-marketed formulations with different strengths

The applicant explained the BE among to-be-marketed formulation tablets of 0.5, 1.0, and 2.5 mg, as follows:

BE between the to-be-marketed formulation tablets of 0.5 and 1.0 mg was demonstrated by the dissolution tests performed according to the Guideline for Different Strengths. The to-bemarketed formulation tablets of 1.0 and 2.5 mg met the acceptance criteria for equivalence in dissolution behavior under all test conditions except at pH compound, the solubility of riociguat decreases in a high pH range, thereby possibly affecting the dissolution behavior of the drug product at pH . Therefore, after confirming that the number of the tablets and the volume of the dissolution medium in the vessel did not affect the dissolution , the dissolution test was repeated by adjusting riociguat concentration in the profile at pH vessel in the test for 1.0 mg tablets to that in the test for 2.5 mg tablets (tablets and mL. respectively, for 1.0 mg tablets, and tablets and mL, respectively, for 2.5 mg tablets). As a result of the dissolution test with adjusted riociguat concentration, the tablets met the acceptance criteria for equivalence in dissolution behavior at pH as well, from which the applicant determined that the equivalence in dissolution behavior between the to-be-marketed formulation tablets of 1.0 and 2.5 mg was demonstrated. Therefore, the applicant considered that all test results, taken together, demonstrated the BE among the to-be-marketed formulation tablets of 0.5, 1.0, and 2.5 mg.

PMDA considers as follows:

In the dissolution tests performed to demonstrate the BE between the to-be-marketed formulation tablets of 1.0 and 2.5 mg under test conditions (1 tablet, 900 mL of dissolution medium) specified in the Guideline for Different Strengths, the tablets failed to meet the acceptance criteria for equivalence in dissolution behavior at pH **m**. However, in the dissolution test under the same riociguat concentration, performed after confirming that either the number of tablets or the volume of the test dissolution medium in the vessel did not affect the dissolution behavior, the to-be-marketed formulation tablets of 1.0 and 2.5 mg met the acceptance criteria for equivalence in dissolution behavior. The result thus obtained was consistent with the explanation of the applicant that since riociguat is a basic compound and the solubility decreases at high pH, the difference in the concentration of riociguat in the dissolution medium affected the dissolution behavior of riociguat at pH **m**. Based on the above, PMDA accepted the explanation of the applicant that BE between the to-be-marketed formulation tablets of 1.0 and 2.5 mg has been demonstrated.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A. Summary of the submitted data

4.(ii).A.(1) *In vitro* studies using human biomaterials

4.(ii).A.(1).1) Plasma protein binding (Attached document 4.2.2.3.1, 4.2.2.3.2)

¹⁴C-labeled riociguat (0.0492-2.37 mg/L, final concentration) was added to human plasma samples, and plasma protein binding of riociguat was investigated. The plasma unbound fraction (f_u) of ¹⁴C-labeled riociguat was 4.97% regardless of the concentration of riociguat.

When ¹⁴C-labeled riociguat (0.0922, 0.504 mg/L) was added to human serum albumin solution (40 g/L), f_u of ¹⁴C-labeled riociguat was 19.8% and 21.4%, respectively. When ¹⁴C-labeled riociguat (0.0965, 0.511 mg/L) was added to a solution of α_1 -acid glycoprotein (0.7 g/L), f_u of ¹⁴C-labeled riociguat was 22.6% and 25.4%, respectively.

¹⁴C-labeled riociguat (approximately 0.1 mg/L [0.0945-0.105 mg/L]) was added to human plasma samples, and plasma protein binding of riociguat was investigated in the presence of nonesterified fatty acid, i.e., oleic acid, palmitic acid, or stearic acid (2 mM). In the absence of nonesterified fatty acid, f_u of ¹⁴C-labeled riociguat was 3.86%, whereas in the presence of oleic acid, palmitic acid, or stearic acid, f_u was 1.63%, 1.98%, and 1.88%, respectively.

When ¹⁴C-labeled riociguat (approximately 0.1 mg/L [0.0964-0.108 mg/L]) was added to human plasma samples, f_u of ¹⁴C-labeled riociguat at pH 7.13, 7.42, 7.59, and 7.79 was 4.20%, 3.94%, 3.56%, and 3.35%, respectively.

¹⁴C-labeled riociguat (approximately 0.1 mg/L [0.0961-0.105 mg/L]) was added to human plasma samples, and plasma protein binding of riociguat was investigated in the presence of ibuprofen, warfarin, nifedipine, digitoxin, salicylic acid, atorvastatin, furosemide, sildenafil, or bosentan at the clinical concentration or at 5 times the clinical concentration. In the presence of the low or high concentrations of salicylic acid, f_u of ¹⁴C-labeled riociguat increased to 1.5 and 2.7 times, respectively, that in the absence of salicylic acid. In the presence of the drugs other than salicylic acid, f_u was similar to that in the absence of the drugs.

4.(ii).A.(1).2) Distribution in blood cells (Attached document 4.2.2.3.1)

When ¹⁴C-labeled riociguat (0.0462-2.34 mg/L, final concentration) was added to human blood samples, the ratios of ¹⁴C-labeled riociguat concentration in plasma to that in blood were similar regardless of the concentration of ¹⁴C-labeled riociguat tested, with the arithmetic mean of the ratio at each concentration being 1.51.

4.(ii).A.(1).3) In vitro metabolism

(a) Metabolism of riociguat (Attached document 4.2.2.4.1, 4.2.2.4.2)

When ¹⁴C-labeled riociguat (1 μ M, final concentration) was added to human liver microsomes and the mixture was incubated for 60 minutes, 90.6% of the added radioactivity was detected as unchanged riociguat and 8.3% as M-1.

When ¹⁴C-labeled riociguat (1 μ M) was added to human hepatocytes (n = 2) and the mixture was incubated for 4 hours, 95.6% and 81.1% of the added radioactivity was detected as unchanged riociguat and 4.2% and 16.0%, respectively, as M-1.

Riociguat (1 μ M) was administered to human liver microsomes, and amount of M-1 formed was measured in the presence or absence of the inhibitor of each cytochrome P450 (CYP) isoform. The amount of M-1 formed in the presence of α -naphthoflavone, an inhibitor of CYP1A1 and 1A2, was 60.6% of the amount formed in the absence of the inhibitor, whereas the amount of M-1 formed in the presence of fluvoxamine, a CYP1A2 inhibitor, was little different from that formed in the absence of the inhibitor. The amount of M-1 formed in the presence of CYP3A4/5

inhibitor azamulin, CYP2C8 inhibitor montelukast, and CYP2J2 inhibitor HET0016 was 82.0%, 77.9%, and 83.1%, respectively, of the amount formed in the absence of each inhibitor. When riociguat (1 μ M) was added to human lung microsomes prepared from smokers, the amount of M-1 formed in the presence of α -naphthoflavone was 10.8% of the amount formed in the absence of the inhibitor.

When riociguat (1 μ M) was added to microsomes expressing one of the human CYP isoforms (CYP1A1, 1A2, 2A6, 1B1, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 3A7, 4A11, 4F2, 4F3A, 4F3B, 4F12) and the mixture was incubated for 45 minutes, 52.8% of added riociguat was converted to M-1 in CYP1A1-expressing microsomes, whereas 2.03%, 18.8%, 0.66%, and 3.64% was converted to M-1 in CYP2C8, 2J2, 3A4, and 3A5-expressing microsomes, respectively. Little M-1 was formed in microsomes expressing other CYP isoforms.

(b) Inhibitory effect of riociguat on CYP, UDP-glucuronyl transferase, and sulfotransferase (Attached document 4.2.2.4.3 to 4.2.2.4.5)

A substrate for each CYP isoform (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2J2, 3A4) was added to human liver microsomes, and the mixture was incubated for 10 to 60 minutes in the absence or presence of 1.0 to 50 μ M of riociguat. The IC₅₀ value of riociguat against 4'-hydroxylation of mephenytoin, a CYP2C19 substrate, was 44.4 μ M, whereas metabolism of other CYP substrates was little inhibited by 50 μ M of riociguat. Ethoxyresorufin (4.0 μ M) or phenacetin (30 μ M) was added to CYP1A1-expressing microsomes, and the mixture was incubated for 10 or 15 minutes in the presence of 0.25 to 20 μ M or 0.1 to 2.5 μ M of riociguat. As a result, IC₅₀ values of riociguat against *O*-deethylation of ethoxyresorufin and against *O*-deethylation of phenacetin were 14.7 and 0.84 μ M, respectively. Chlorzoxazone (52.8 μ M) was added to CYP2E1-expressing microsomes, and the mixture was incubated for 30 minutes in the absence or presence of riociguat (50 μ M). Chlorzoxazone 6'-hydroxylation was little inhibited by 50 μ M of riociguat.

Riociguat (1.6-50 μ M) was added to human liver microsomes and the mixture was incubated for 30 minutes in the presence of a reduced nicotinamide adenine dinucleotide phosphate (NADPH)-regenerating system, after which midazolam (10 μ M) or testosterone (50 μ M) was added and the mixture was further incubated for 15 or 20 minutes. Neither midazolam 1'-hydroxylation nor testosterone 6 β -hydroxylation was inhibited by riociguat.

A substrate of UDP-glucuronyl transferase (UGT) 1A1, 1A6, 1A9, or 2B7, i.e., estradiol (20 μ M), α -naphthol (50 μ M), propofol (100 μ M), or zidovudine (200 μ M), was added to human liver microsomes, and the mixture was incubated for 30, 5, 15, or 60 minutes in the presence of riociguat (50 μ M). Glucuronidation of these UGT substrates was not inhibited by riociguat. Trifluoperazine (60 μ M) was added to UGT1A4-expressing microsomes and the mixture was incubated for 40 minutes in the presence of 50 μ M of riociguat. Glucuronidation of trifluoperazine was not inhibited by riociguat.

A substrate of sulfotransferase (SULT), i.e., 17β -estradiol (100 nM) or 17α -ethinyl estradiol (100 nM), was added to a human liver cytosol preparation, and the mixture was incubated for 20 minutes in the presence of riociguat (50 μ M). Sulfation of neither 17β -estradiol nor 17α -ethinyl estradiol was inhibited by riociguat.

In each of the above studies on the inhibitory effect of riociguat against CYP, UGT, SULT, it was confirmed that activity of each enzyme was decreased in the presence of a known inhibitor of each enzyme.

(c) Stimulatory effect of riociguat on CYPs (Attached document 4.2.2.4.6)

Human hepatocytes (n = 3) were exposed to riociguat for 5 days, after which CYP-inducing activity of riociguat was investigated by measuring the metabolism of a substrate for each CYP
isoform (phenacetin for CYP1A2, S-mephenytoin for CYP2B6 and CYP2C19, testosterone for CYP3A4). The amount of nirvanol formed (CYP2B6 activity) was little different between before and after exposure of hepatocytes to 5 to 1111 ng/mL of riociguat (final concentration), whereas after exposure to 10,000 ng/mL, the amount increased 2.7 to 3.5 times the amount formed before exposure. The amount of nirvanol formed after exposure to rifampicin, a known inducer of CYP2B6, was 2.7 to 7.0 times the amount formed before exposure. When hepatocytes were exposed to 3333 ng/mL of riociguat, the amount of 6β-hydroxytestosterone formed (CYP3A4 activity) increased approximately 1.5 times the amount formed before exposure in 1 out of 3 batches of the cells, whereas in the remaining 2 batches, the amount of 6β-hydroxytestosterone formed after exposure to 5 to 10,000 ng/mL was not different from the amount formed before exposure. After exposure to rifampicin, an inducer of CYP3A4, the amount of 6βhydroxytestosterone formed (CYP3A4 activity) increased 2.2 to 3.9 times the amount formed before exposure. After exposure to omeprazole and rifampicin, known inducers of CYP1A2 and CYP2C19, respectively, the amount of acetaminophen formed (CYP1A2 activity) and the amount of 4'-hydroxy S-mephenytoin formed (CYP2C19 activity) increased 10.6 to 23.6 times and 5.3 to 12.8 times, respectively, the amount of each formed before exposure, whereas exposure to 5 to 10,000 ng/mL of riociguat caused little change in the amount of acetaminophen or 4'-hydroxy Smephenytoin formed compared with the amount formed before exposure.

(d) Inhibitory effect of various drugs on riociguat metabolism (Attached document 4.2.2.6.1)

Riociguat (1.0 μ M) was added to CYP1A1-expressing microsomes, and the mixture was incubated for 15 minutes in the presence of drugs such as anticancer agents, analgesic agents, antiviral agents, antibiotics, or azole antifungal agents, after which the amount of M-1 formed was measured to evaluate the inhibitory effect of various drugs (87 different drugs, each at 6 concentrations) on the metabolism of riociguat to M-1. Azole antifungal agents (ketoconazole, clotrimazole, miconazole), tyrosine kinase inhibitors (erlotinib, gefitinib, imatinib, sorafenib, sunitinib), and 3 other drugs (carvedilol, ebastine, quercetin) markedly inhibited M-1 formation, with IC₅₀ values being 0.3 to 0.6 μ M, 0.2 to 4.2 μ M, and 0.6 to 2.5 μ M, respectively. Amiodarone, ethinyl estradiol, fenofibrate, naringenin, rosiglitazone, simvastatin, and terfenadine also inhibited M-1 formation with IC₅₀ values of 4.9 to 15.7 μ M.

Various drugs (each at 6 concentrations) were added to CYP1A1-expressing microsomes and the mixture was preincubated for 30 minutes, after which riociguat (1.0 μ M) was added and the mixture was incubated for 15 minutes. The amount of M-1 formed was measured to evaluate the time-dependent inhibition of each drug against the metabolism of riociguat to M-1. IC₅₀ value of tyrosine kinase inhibitors (erlotinib, gefitinib, imatinib, sorafenib, sunitinib) decreased to 0.05 to 0.7 μ M after preincubation, demonstrating the time-dependent inhibitory effect of these drugs.

Riociguat (1.0 μ M) was added to human liver microsomes and the mixture was incubated for 45 minutes in the presence of various drugs, after which the amount of M-1 formed was measured to evaluate the inhibitory effect of various drugs on the metabolism of riociguat to M-1. HIV protease inhibitors (ritonavir, atazanavir, indinavir) and azole antifungal agents (ketoconazole, clotrimazole, miconazole) markedly inhibited M-1 formation by human liver microsomes, with IC₅₀ values being 5.3 to 11.7 μ M and 0.6 to 5.7 μ M, respectively. Carvedilol, ethinyl estradiol, quercetin, terfenadine, and tyrosine kinase inhibitors (erlotinib, gefitinib, imatinib, sorafenib) also inhibited M-1 formation with IC₅₀ value of 6.9 to 20.1 μ M.

Various drugs (each at 6 concentrations) were added to human liver microsomes and the mixture was preincubated for 30 minutes, after which riociguat $(1.0 \ \mu\text{M})$ was added and the mixture was incubated for 45 minutes. The amount of M-1 formed was measured to evaluate the time-dependent inhibition of each drug against the metabolism of riociguat to M-1. For all drugs tested, IC₅₀ was similar to that observed without preincubation.

4.(ii).A.(1).4) Studies on transporters

(a) Caco-2 cell permeability (Attached document 4.2.2.7.1)

Riociguat (2.4, 24 μ M [final concentration]) was added to the apical (AP) or basolateral (BL) side of Caco-2 cells, and riociguat transport to BL or AP side during 120 minutes was evaluated. The ratio of the apparent permeability coefficient (P_{app}) of riociguat from BL side to AP side to that from AP side to BL side (efflux ratio) was 11 (arithmetic mean) at both concentrations tested. In the presence of 1.0 μ M of ivermectin, an inhibitor of P-glycoprotein (P-gp), the efflux ratio decreased to approximately 0.43 times the efflux ratio in the absence of ivermectin, which suggested that riociguat was a substrate for P-gp. The efflux ratio in the presence of 2 μ M of digoxin was 14.4.

(b) Riociguat transport by P-gp and breast cancer resistance protein (Attached document 4.2.2.7.2, 4.2.2.7.3)

The efflux ratio of riociguat $(1 \ \mu M)$ in P-gp-expressing LLC-PK1 cells was 4.3 times that in non-P-gp-expressing LLC-PK1 cells and, in the presence of 5 μM of ivermectin, a P-gp inhibitor, decreased to the level similar to that in non-P-gp-expressing LLC-PK1 cells. The efflux ratio of dipyridamole (1 μM), a substrate of P-gp, in P-gp-expressing LLC-PK1 cells was 9.5 times that in non-P-gp-expressing LLC-PK1 cells.

The efflux ratio of topotecan (2 μ M), a substrate of breast cancer resistance protein (BCRP), in BCRP-expressing MDCKII cells was 10 times that in non-BCRP-expressing MDCKII cells, and the efflux ratio of riociguat (0.20-10 μ M) in BCRP-expressing MDCKII cells was 3.7 to 6.7 times that in non-BCRP-expressing MDCKII cells. In the presence of a BCRP inhibitor Ko143 (1 μ M), the efflux ratio of riociguat (1 μ M) in BCRP-expressing MDCKII cells decreased to a level similar to that in non-BCRP-expressing MDCKII cells.

(c) Riociguat transport by uptake transporters (Attached document 4.2.2.7.5, 4.2.2.7.6)

Organic anion transporting polypeptide 1B1 (OATP1B1)-expressing HEK cells and non-OATP1B1-expressing HEK cells were incubated in the presence of riociguat (0.2-10 μ M) for 1.5 minutes. The ratio of riociguat uptake into OATP1B1-expressing HEK cells to that in non-expressing HEK cells was 1.0 to 1.2, whereas the uptake ratio of pravastatin (10 μ M), a known substrate of OATP1B1, was 8.9.

Organic anion transporting polypeptide 1B3 (OATP1B3)-expressing HEK cells and non-OATP1B3-expressing HEK cells were incubated in the presence of riociguat (0.2-10 μ M) for 2.5 minutes. As a result, the ratio of uptake of riociguat into OATP1B3-expressing HEK cells to that into non-expressing HEK cells was 1.4 to 1.7. Uptake of riociguat into OATP1B3-expressing HEK cells was not inhibited by 10 μ M of rifamycin, an inhibitor of OATP1B3. When cells were incubated in the presence of pravastatin (10 μ M), a known substrate of OATP1B3, for 1.5 minutes, the ratio of uptake into OATP1B3-expressing HEK cells to that into non-expressing HEK cells was 3.8, and, in the presence of 10 μ M of rifamycin, transport of pravastatin by OATP1B3-expressing HEK cells was 3.8 to approximately 0.18 times the level in the absence of rifamycin.

When organic anion transporter 1 (OAT1)-expressing HEK cells and non-OAT1-expressing HEK cells were incubated in the presence of riociguat (0.3, 3 μ M) for 5 minutes, there was no difference in the intracellular uptake of riociguat between OAT1-expressing HEK cells and non-expressing HEK cells.

When organic anion transporter 3 (OAT3)-expressing HEK cells and non-OAT3-expressing HEK cells were incubated in the presence of riociguat (0.3, 3 μ M) for 5 minutes, there was no difference in the intracellular uptake of riociguat between OAT3-expressing HEK cells and non-expressing HEK cells.

(d) Inhibitory effect of riociguat on P-gp and BCRP (Attached document 4.2.2.7.2, 4.2.2.7.4)

The efflux ratio of digoxin (25 μ M) in P-gp-expressing LLC-PK1 cells in the presence of ivermectin (5 μ M) decreased to approximately 0.2 times the ratio in the absence of ivermectin. The efflux ratio in the presence of riociguat (0.1-100 μ M) was approximately 0.660 to 1.14 times the ratio in the absence of riociguat. The efflux ratio of dipyridamole (1 μ M) in P-gp-expressing LLC-PK1 cells in the presence of riociguat (0.07-20 μ M) was approximately 0.862 to 1.30 times the ratio in the absence of riociguat.

The efflux ratios of BCRP substrates topotecan (2 μ M) and PhiP (2 μ M) in BCRP-expressing MDCKII cells in the presence of BCRP inhibitor Ko143 (1 μ M) decreased to 0.12 and 0.03 times, respectively, the ratios in the absence of Ko143, whereas the efflux ratios in the presence of riociguat (0.10-24 μ M) were similar to those observed in the absence of riociguat.

(e) Inhibitory effect of riociguat on uptake transporters (Attached document 4.2.2.7.5, 4.2.2.7.6)

The uptake of pravastatin (10 μ M) into OATP1B1-expressing HEK cells in the presence of riociguat (1, 10 μ M) was similar to the level observed in the absence of riociguat.

The transport of pravastatin (10 μ M) into OATP1B3-expressing HEK cells decreased to approximately 15% in the presence of rifamycin (10 μ M) compared with the level observed in the absence of rifamycin, but showed little or no change in the presence of riociguat (0.3-10 μ M).

OAT1-expressing HEK cells and non-expressing HEK cells were incubated in the presence of *p*-aminohippuric acid (1, 10 μ M) for 5 minutes, and OAT1-mediated uptake of *p*-aminohippuric acid was calculated by the difference in the transport between OAT1-expressing HEK cells and non-expressing HEK cells. As a result, the OAT1-mediated uptake of 1 and 10 μ M of *p*-aminohippuric acid decreased to 19% and 10%, respectively, in the presence of an OAT1 inhibitor probenecid (100 μ M) compared with the level in the absence, whereas there was no difference in the uptake in the presence of riociguat (0.3-3 μ M) compared with the level in the absence.

OAT3-expressing HEK cells and non-expressing HEK cells were incubated in the presence of estrone 3-sulfate (1, 10 μ M) for 5 minutes; and OAT3-mediated uptake of estrone 3-sulfate decreased to 5% and 7%, respectively, in the presence of an OAT3 inhibitor probenecid (100 μ M). However, there was no difference in the uptake in the presence of riociguat (0.3-3 μ M) compared with the level in the absence of riociguat.

4.(ii).A.(2) Studies in healthy adult subjects

4.(ii).A.(2).1) Japanese single-dose study (Study 12639, Attached document 5.3.3.1.1)

Riociguat (0.5, 1.0, 2.5 mg) was administered orally in a single dose under fasting conditions to 27 Japanese healthy adult male subjects (9 subjects per group). As a result, t_{max} (median [minimum-maximum]) of riociguat was 1.000 [0.500-1.500], 1.000 [0.500-1.500], and 1.500 [0.750-4.000] hours, respectively; C_{max} was 22.89 (31.5%), 49.73 (23.6%), and 126.4 (17.1%) μ g/L, respectively; AUC_∞ was 106.2 (56.4%), 271.9 (101%), and 823.5 (70.9%) μ g·h/L, respectively; and t_{1/2} was 4.15 (46.1%), 6.33 (86.4%), and 7.59 (47.2%) hours, respectively. Also t_{max} (median [minimum-maximum]) of M-1 was 4.000 [4.000-12.000], 4.000 [4.000-12.000], and 4.000 [4.000-12.000] hours, respectively; C_{max} was 10.11 (26.2%), 14.41 (58.5%), and 25.91 (66.2%) μ g/L, respectively; AUC_∞ was 217.7 (11.2%), 341.9 (18.1%), and 690.2 (41.5%) μ g·h/L, respectively; and t_{1/2} was 12.96 (19.0%), 17.56 (22.6%), and 16.26 (21.1%) hours, respectively. In the riociguat 0.5, 1.0, and 2.5 mg groups, the urinary excretion rate of riociguat was

 $6.38\pm3.00\%$ (mean ± standard deviation [SD]), $11.02\pm6.86\%$, and $15.66\pm7.61\%$, respectively; and that of M-1 was $28.85\pm4.04\%$, $27.79\pm4.79\%$, and $25.17\pm7.30\%$, respectively.

4.(ii).A.(2).2) Japanese multiple-dose study (Study 12640, Attached document 5.3.3.1.2) Riociguat (1.0, 1.5 mg) was administered orally in a single dose to 18 Japanese healthy adult male subjects (9 subjects per group) under fasting conditions, followed by a 48-hour washout period, and then riociguat (1.0, 1.5 mg) was administered orally under fasting conditions 3 times daily for 7 days. Tables 3 and 4 show the pharmacokinetic parameters of riociguat and M-1, respectively, obtained in the study.

Dose	Day	t _{max} (h)	C _{max} (µg/L)	AUC* (µg·h/L)	t _{1/2} (h)
1.0 mg	1 (n = 9)	0.750 [0.500-2.000]	45.52 (27.3%)	251.40 (66.5%)	6.55 (72.4%)
1.0 mg	9 (n = 8)	1.500 [0.500-4.000]	59.85 (35.8%)	325.32 (40.3%)	9.69 (28.7%)
1.5 mg	1 (n = 9)	1.500 [0.750-3.000]	88.90 (25.7%)	639.19 (69.8%)	8.47 (54.0%)
1.5 mg	9 (n = 7)	1.500 [0.500-4.000]	100.91 (27.6%)	515.85 (29.3%)	9.17 (25.7%)

 Table 3. Pharmacokinetic parameters of riociguat following multiple dose of riociguat

Geometric mean (CV); t_{max}, median [minimum-maximum]

* AUC on Day 1 indicates AUC $_{\infty}$ after single dose administration. AUC on Day 9 indicates AUC from the first dose on Day 9 to 7 hours later.

Table 4. Pharmacokinetic p	parameters of M-1 following	g multiple dose of riociguat
----------------------------	-----------------------------	------------------------------

Dose	Day	t _{max} (h)	C _{max} (µg/L)	AUC* (µg·h/L)	t _{1/2} (h)
1.0 mg	1 (n = 9)	6.000 [4.000-12.000]	14.16 (42.2%)	352.67 (17.9%)	13.50 (23.4%)
1.0 mg	9 (n = 8)	4.000 [0.500-4.000]	36.81 (25.1%)	223.85 (23.4%)	16.56 (24.6%)
1.5 mg	1 (n = 9)	4.000 [3.000-24.000]	15.82 (58.7%)	474.08 (37.5%)	14.03 (13.9%)
1.5 mg	9 (n = 7)	4.000 [1.500-6.967]	59.53 (31.6%)	368.39 (31.5%)	17.72 (20.0%)

Geometric mean (CV); t_{max}, median [minimum-maximum]

* AUC on Day 1 indicates AUC $_{\infty}$ after single dose administration. AUC on Day 9 indicates AUC from the first dose on Day 9 to 7 hours later.

4.(ii).A.(2).3) Mass balance study (Study 11911, Attached document 5.3.3.1.6 [Reference data])

Following a single oral dose of ¹⁴C-labeled riociguat (1.0 mg) to 4 foreign healthy adult male subjects under fasting conditions, the unchanged riociguat, M-1, and N-glucuronate of M-1 (M-4) were mainly detected in plasma and excreta. In 3 of 4 subjects, the unchanged riociguat accounted for 95% to 99% and 10% to 18% of the radioactivity in the plasma at 15 minutes and 24 hours post-dose, respectively, and M-1 accounted for 1% to 5% and 47% to 90% of the radioactivity in the plasma at 15 minutes and 48 hours post-dose, respectively. Within 216 hours post-dose, 4.49% to 7.58% of the administered radioactivity was excreted in urine in the form of the unchanged riociguat, 18.9% to 23.1% as M-1, and 7.52% to 18.9% as M-4; and 9.03% to 17.5% of the administered radioactivity was excreted in feces in the form of the unchanged riociguat, and 31.2% to 42.7% as M-1. In the remaining 1 subject, the unchanged riociguat accounted for 67% of the radioactivity in the plasma at 48 hours post-dose, and, within 216 hours post-dose, 19.1% of the administered radioactivity was excreted in urine in the form of the administered radioactivity was excreted in urine in the form of the methanged riociguat accounted for 67% of the radioactivity in the plasma at 48 hours post-dose, and, within 216 hours post-dose, 19.1% of the administered radioactivity was excreted in urine in the form of the methanged riociguat accounted for 67% of the radioactivity in the plasma at 48 hours post-dose, and, within 216 hours post-dose, 19.1% of the administered radioactivity was excreted in urine in the form of the methanged riociguat accounted for 67% of the administered radioactivity was excreted in urine in the form of the methanged riociguat accounted for 67% of the radioactivity was excreted in urine in the form of the methanged riociguat accounted for 67% of the administered radioactivity was excreted in urine in the form of the methanged riociguat accounted for 67% of the administered radioactivity was excreted in urine in the form of the metha

unchanged riociguat, 7.36% as M-1, and 4.42% as M-4; and 43.8% of the administered radioactivity was excreted in feces in the form of the unchanged riociguat, and 14.8% as M-1.

4.(ii).A.(3) Effects of intrinsic factors on pharmacokinetics

4.(ii).A.(3).1) Effects of age and sex (Study 11914, Attached document 5.3.3.3.1 [Reference data])

A single oral dose of riociguat (2.5 mg) was administered under fasting conditions to a total of 36 foreign healthy non-elderly (18-45 years old) and elderly (64.5-80 years old) male and female subjects (9 subjects per group). The ratios [90% CI] of the geometric mean of C_{max} , AUC_{∞}, and t_{1/2} of riociguat in the elderly subjects to those in the non-elderly subjects were 1.16 [0.98-1.36], 1.40 [1.06-1.86], and 1.41 [1.08-1.84], respectively, and the ratios [90% CI] of the geometric mean of C_{max}, AUC_{∞}, and t_{1/2} of riociguat in the female subjects to those in the male subjects were 1.35 [1.14-1.59], 1.09 [0.82-1.44], and 1.04 [0.79-1.35], respectively.

4.(ii).A.(3).2) Clinical pharmacology study in patients with renal impairment (Study 15000, Attached document 5.3.3.3.3 [Reference data])

Riociguat (1 mg) was administered orally in a single dose under fasting conditions to 8 foreign patients with mild renal impairment (creatinine clearance $[CL_{CR}] \ge 50$ and ≤ 80 mL/min), 8 patients with moderate renal impairment ($CL_{CR} > 30$ and < 50 mL/min), and 8 healthy adult subjects ($CL_{CR} > 80$ mL/min) matched for sex, age (± 10 years), and body weight (± 10 kg) with renal impairment groups. Riociguat (0.5 mg) was also administered in a similar manner to 8 patients with severe renal impairment ($CL_{CR} \le 30$ mL/min). The ratio of the geometric mean [90% CI] of C_{max} of riociguat, adjusted for dose, in patients with mild, moderate, and severe renal impairment to that in healthy adult subjects was 1.3357 [1.0387-1.7177], 1.0435 [0.8184-1.3305], and 1.1093 [0.8700-1.4144], respectively, and the ratio of the geometric mean [90% CI] of dose-adjusted AUC_∞ of riociguat was 2.0891 [1.2327-3.5407], 2.2383 [1.3445-3.7263], and 1.9327 [1.1609-3.2175], respectively. The ratio of the geometric mean [90% CI] of C_{max} of M-1, adjusted for dose, in patients with mild, moderate, and severe renal impairment to that in healthy adult subjects was 0.6451 [0.4011-1.0376], 0.6457 [0.4080-1.0220], and 0.9328 [0.5894-1.4765], respectively, and the ratio of the geometric mean [90% CI] of M-1 was 1.0463 [0.6970-1.5707], 1.4468 [0.9771-2.1421], and 2.1144 [1.4280-3.1306], respectively.

4.(ii).A.(3).3) Clinical pharmacology study in patients with hepatic impairment (Study 15001, Attached document 5.3.3.35 [Reference data])

Riociguat (1.0 mg) was administered orally in a single dose under fasting conditions to 8 foreign patients with mild hepatic impairment (Child-Pugh class A), 8 foreign healthy adult subjects matched for sex, age (\pm 10 years), and body weight (\pm 10 kg) with the patients with mild hepatic impairment, 8 foreign patients with moderate hepatic impairment (Child-Pugh class B), and 8 foreign healthy adult subjects matched for sex, age (\pm 10 years), and body weight (\pm 10 kg) with the patients with moderate hepatic impairment (Child-Pugh class B), and 8 foreign healthy adult subjects matched for sex, age (\pm 10 years), and body weight (\pm 10 kg) with the patients with moderate hepatic impairment. As a result, the ratio [90% CI] of the geometric mean of C_{max} of riociguat in patients with mild and moderate hepatic impairment to that in healthy adult subjects was 1.2381 [0.9818-1.5613] and 1.0928 [0.8665-1.3780], respectively, and the ratio [90% CI] of the geometric mean of AUC_{∞} of riociguat was 1.7245 [1.1464-2.5942] and 1.6486 [1.0960-2.4800], respectively. The ratio [90% CI] of the geometric mean of C_{max} of M-1 in patients with mild and moderate hepatic impairment to that in healthy adult subjects was 1.2381 [0.9818-1.5613] and 0.6638 [0.4531-0.9723], respectively, and the ratio [90% CI] of the geometric mean of AUC_{∞} of M-1 was 1.2640 [0.8929-1.7893] and 0.9739 [0.6880-1.3786], respectively.

4.(ii).A.(4) Effects of extrinsic factors on pharmacokinetics and pharmacodynamics

4.(ii).A.(4).1) Drug-drug interaction with omeprazole (Study 11262, Attached document 5.3.3.4.1 [Reference data])

A two-treatment, two-period, crossover study was conducted in 12 foreign healthy adult male subjects to investigate the effect of concomitant use with omeprazole on the pharmacokinetics of riociguat (with a wash-out period of \geq 72 hours between the treatment periods). During the administration of riociguat alone, riociguat (2.5 mg) was administered orally in a single dose. During the period of concomitant use, omeprazole (40 mg) was administered orally once daily for 4 days and riociguat (2.5 mg) was administered orally at 2 hours after omeprazole administration on the fifth day. The ratios [90% CI] of the geometric mean of C_{max} and AUC_∞ after concomitant use of riociguat with omeprazole to those after administration of riociguat alone were 0.6517 [0.5426-0.7827] and 0.7361 [0.6478-0.8365], respectively, for riociguat, and 1.074 [0.9118-1.2655] and 0.9725 [0.8945-1.0573], respectively, for M-1.

4.(ii).A.(4).2) Drug-drug interaction with aluminum hydroxide gel/magnesium hydroxide combination (Study 11890, Attached document 5.3.3.4.2 [Reference data])

A two-treatment, two-period, crossover study was conducted in 12 foreign healthy adult male subjects to investigate the effect of concomitant use with aluminum hydroxide gel/magnesium hydroxide combination on the pharmacokinetics of riociguat (with a wash-out period of \geq 5 days between the treatment periods). During the administration of riociguat alone, riociguat (2.5 mg) was administered orally in a single dose. During the period of concomitant use, a 10 mL of suspension of aluminum hydroxide gel/magnesium hydroxide combination was administered orally in a single dose and, immediately after that, riociguat (2.5 mg) was orally administered in a single dose. The ratios [90% CI] of the geometric mean of C_{max} and AUC_∞ after the concomitant use to those after administration of riociguat alone were 0.4391 [0.3396-0.5677] and 0.6645 [0.5621-0.7855], respectively, for riociguat, and 0.5665 [0.4435-0.7236] and 0.6740 [0.5663-0.8022], respectively, for M-1.

4.(ii).A.(4).3) Drug-drug interaction with ketoconazole (Study 11261, Attached document 5.3.3.4.3 [Reference data])

Riociguat (0.5 mg) was administered orally in a single dose to 16 foreign healthy adult male subjects. Subsequentaly, ketoconazole (400 mg) was administered orally once daily for 4 days to the 16 subjects and riociguat (0.5 mg) was administered orally immediately after the oral dose of ketoconazole on the fifth day. The ratios [90% CI] of the geometric mean of C_{max} and AUC_{∞} after concomitant use with ketoconazole to those after administration of riociguat alone were 1.4603 [1.3529-1.5763] and 2.5014 [2.1406-2.9229], respectively, for riociguat, and 0.5115 [0.4389-0.5961] and 0.7634 [0.6737-0.8650], respectively, for M-1.

4.(ii).A.(4).4) Drug-drug interaction with clarithromycin (Study 13284, Attached document 5.3.3.4.4 [Reference data])

A two-treatment, two-period, crossover study was conducted in 14 foreign healthy adult male subjects to investigate the effect of clarithromycin on the pharmacokinetics of riociguat (with a wash-out period of \geq 14 days between the treatment periods). During the administration of riociguat alone, riociguat (1.0 mg) was administered orally in a single dose and, during the period of concomitant use with clarithromycin, clarithromycin (500 mg) was administered orally twice daily for 4 days, followed by oral administration of riociguat (1.0 mg) plus clarithromycin (500 mg) on the fifth day. The ratios [90% CI] of the geometric mean of C_{max} and AUC_∞ after concomitant use of riociguat with clarithromycin to those after administration of riociguat alone were 1.0404 [0.8923-1.2131] and 1.4148 [1.2286-1.6292], respectively, for riociguat, and 1.0576 [0.9544-1.1720] and 1.1897 [1.0974-1.2898], respectively, for M-1.

4.(ii).A.(4).5) Drug-drug interaction with midazolam (Study 14982, Attached document 5.3.3.4.5 [Reference data])

A two-treatment, two-period, crossover study was conducted in 22 foreign healthy adult male subjects to investigate the effect of riociguat on the pharmacokinetics of midazolam (with a washout period of \geq 10 days between the treatment periods). During the administration of midazolam alone, midazolam (7.5 mg) was administered orally in a single dose and, during the period of concomitant use of riociguat, riociguat (2.5 mg) was administered orally daily for 3 days, followed by oral administration of midazolam (7.5 mg) then by riociguat (2.5 mg) 3 times on the fourth day. The ratios [90% CI] of the geometric mean of C_{max} and AUC_∞ of midazolam after concomitant use of riociguat with midazolam to those after administration of midazolam alone were 1.0176 [0.8890-1.1648] and 1.0837 [0.9695-1.2113], respectively.

4.(ii).A.(4).6) Drug-drug interaction with warfarin (Study 11918, Attached document 5.3.3.4.6 [Reference data])

A two-treatment, two-period, crossover study was conducted in 22 foreign healthy adult male subjects to investigate the effect of riociguat on the pharmacokinetics and pharmacodynamics of warfarin (with a wash-out period of 17 days between the treatment periods). During the administration of warfarin alone, a placebo tablet was administered orally 3 times daily for 10 days, and, on the seventh day, warfarin (25 mg) was concomitantly administered orally with the first dose of the placebo tablet. During the period of concomitant use of riociguat and warfarin, riociguat (2.5 mg) was administered orally 3 times daily for 10 days, and, on the seventh day, warfarin (25 mg) was concomitantly administered orally with the first dose of riociguat (2.5 mg) was concomitantly administered orally with the first dose of riociguat (2.5 mg). The ratios [90% CI] of the geometric mean of C_{max} and AUC_∞ after concomitant use of warfarin with riociguat to those after administration of warfarin, and 1.0144 [0.9458-1.0880] and 1.0075 [0.9748-1.0414], respectively, for S-warfarin. The prothrombin time after administration of warfarin alone was similar to that observed after concomitant use of warfarin with riociguat.

4.(ii).A.(4).7) Drug-drug interaction with aspirin (Study 14204, Attached document 5.3.3.4.7 [Reference data])

A three-treatment, three-period, crossover study was conducted in 15 foreign healthy adult male subjects to investigate the effect of aspirin on the pharmacokinetics of riociguat and the effect of riociguat on the pharmacodynamics of aspirin (with a wash-out period of \geq 14 days between the treatment periods). During the administration of riociguat alone, riociguat (2.5 mg) was administered orally in a single dose and, during the administration of aspirin alone, aspirin (500 mg) was administered orally once daily for 2 days. During the period of concomitant use of riociguat and aspirin, aspirin (500 mg) was administered orally once daily for 2 days. During the period of concomitant use of riociguat and aspirin, aspirin (500 mg) was concomitantly administered orally. The ratios [90% CI] of the geometric mean of C_{max} and AUC_∞ after concomitant use of aspirin with riociguat to those after administration of riociguat, and 1.0354 [0.9280-1.1552] and 1.0443 [0.9599-1.1360], respectively, for riociguat, and 1.0354 [0.9280-1.1552] and 1.0443 [0.9599-1.1360], respectively, for M-1. The bleeding time after the concomitant use of riociguat and aspirin was not significantly longer than that observed after the administration of aspirin alone.

4.(ii).A.(4).8) Drug-drug interaction with nitroglycerin (Study 14360, Attached document 5.3.3.4.8 [Reference data])

A two-treatment, two-period, crossover study was conducted in 5 foreign healthy adult male subjects to investigate the effect of riociguat on the pharmacodynamics of nitroglycerin (with a wash-out period of ≥ 6 days between the treatment periods). In the concomitant use of riociguat group, nitroglycerin (0.4 mg) was administered sublingually in a single dose at 24 hours after a single oral dose of riociguat (2.5 mg) on Day 1 and, on Day 3, nitroglycerin (0.4 mg) was administered sublingually in a single oral dose of riociguat (2.5 mg). In the placebo group, placebo was administered orally in place of riociguat. Following a single

sublingual dose of nitroglycerin (0.4 mg) at 8 hours after a single oral dose of riociguat (2.5 mg), the maximum decrease in sitting systolic blood pressure (SBP) from baseline was 16.90 mmHg, which was significantly greater than that observed in the placebo group (5.72 mmHg).

4.(ii).A.(4).9) Drug-drug interaction with sildenafil (Study 11917, Attached document 5.3.3.4.9 [Reference data])

To 7 patients with pulmonary arterial hypertension (PAH) receiving sildenafil (20 mg) 3 times daily, riociguat (0.5, 1.0 mg) was administered orally in a single dose at 3 and 5 hours, respectively, after the first dose of sildenafil of the study day. As a result, there was no significant change either in the mean arterial pressure or in the pulmonary vascular resistance.

4.(ii).A.(5) Population pharmacokinetic analysis (Study 13817, Attached document 5.3.3.5.8)

A population pharmacokinetic (PPK) analysis was conducted using NONMEM (ver. 6), based on the plasma riociguat concentration data obtained from the following studies: Study 11348 (riociguat [0.5-2.5 mg] was administered 3 times daily for 16 weeks to patients with CTEPH); Study 11349 (the long-term extension study of Study 11348); Study 12934 (riociguat [0.5-2.5 mg] was administered 3 times daily for 12 weeks to patients with PAH); and Study 12935 (the long-term extension study of Study 12934). Blood samples were collected at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and/or 7.5 hours after riociguat administration in the following manner: in Study 11348, on Day 1 and at 2, 4, 6, 8, 12, and 16 weeks after study initiation (or at study discontinuation); in Study 12934, on Day 1 and at 2, 4, 6, 8, and 12 weeks after study initiation (or at study discontinuation); and in Studies 11349 and 12935, on Day 1, at 8 weeks after study initiation, and at every 3 months thereafter. A total of 642 patients were included in PPK analysis, with the total number of blood sampling points being 5245. An oral one-compartment model with the first order absorption was selected as the pharmacokinetic model used for PPK analysis. Because of the low plasma concentration in the absorption phase, the first-order absorption rate constant (k_a) was fixed at 2.17 h⁻¹, the value estimated from the data of phase II studies. The characteristics of patients subjected to PPK analysis were summarized as follows: sex, 180 male patients and 518 female patients; ethnicity, 453 Caucasian patients, 196 Asian patients, 32 Hispanic patients, 14 Black patients, and 3 miscellaneous patients; the diagnosis, 438 patients with PAH and 260 patients with CTEPH; smoking habit, 669 non-smokers and 29 smokers. Median [minimummaximum] values of some patient characteristics and related parameters were as follows: age, 56 [18-80] years; body weight, 68 [36-158.3] kg; CL_{CR}, 81.2 [15.4-233] mL/min; and total bilirubin, 0.58 [0.12-3.68] mg/dL. As candidates for covariates of the apparent total body clearance (CL/F), dose, baseline age, body weight, ethnicity, diagnosis, smoking habit, concomitant drugs, CL_{CR}, and total bilirubin were evaluated and, in the final model, smoking habit, concomitant use with bosentan, bilirubin, and CL_{CR} were selected as the covariates. As candidates for covariates of the apparent distribution volume (V/F), dose, baseline age, body weight, ethnicity, diagnosis, and total bilirubin were evaluated and, in the final model, body weight was selected as the covariate.

The mean population parameter value of the final model was 1.81 L/h for CL/F and 32.3 L for V/F, the inter-individual variability (coefficient of variation [CV] [%]) was 41.2% for CL/F and 25.0% for V/F, with the residual error being 34.2%.

4.(ii).A.(6) Studies on QT-prolonging effect

4.(ii).A.(6).1) Study on the validation of ECG assessment (Study 13796, Attached document 5.3.4.1.2)

With the objective of validating the assessment of QTc-interval prolongation conducted in a global phase III study (Study 12934) in patients with PAH, a crossover study was conducted in which moxifloxacin (400 mg) or placebo was administered orally in a single dose to 51 healthy adult male and female subjects, and the effect on QTc interval was investigated (with a wash-out

period of \geq 7 days between the treatment periods). The least squares mean [95% CI] of the difference in the change of QTcF and QTcB from baseline at 3 hours after the study drug administration between moxifloxacin and placebo was 15.4 [11.9-18.8] ms and 15.6 [10.1-21.0] ms, respectively. Based on the results, the applicant discussed that the conditions for ECG assessment used in Study 12934 were sufficiently sensitive to detect the QT-prolonging effect of riociguat.

4.(ii).A.(6).2) Global phase III study in patients with PAH (Study 12934, Attached document 5.3.5.4.1)

In 254 patients in the riociguat dose titration group (0.5-2.5 mg/dose, 3 times daily), 63 patients in the riociguat 1.5 mg group (1.5 mg/dose, 3 times daily), and 126 patients in the placebo group, change in QT interval from baseline was evaluated at 2 to 3 hours after the first dose, at 1 hour before and 2 to 3 hours after the second dose in Week 0; at 1 hour before and 2 to 3 hours after the second dose in Week 0; at 1 hour before and 2 to 3 hours after the first dose in Week 12; and at the last visit. As a result, the mean changes in QT interval, QTcB interval, and QTcF interval from baseline in the combined riociguat group (riociguat dose titration group + riociguat 1.5 mg group) were $\leq 11 \text{ msec}$, $\leq 7 \text{ msec}$, and $\leq 7 \text{ msec}$, respectively. No difference was observed between the riociguat dose titration group or the riociguat 1.5 mg group and the placebo group.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Ethnic difference in the pharmacokinetics of riociguat

PMDA asked the applicant to explain the ethnic difference in the pharmacokinetics of riociguat.

The applicant responded as follows:

Results of the pooled analysis of all phase I studies (339 Caucasian subjects, 7 African American subjects, 12 Chinese subjects, and 112 Japanese subjects; all of whom were non-smokers) showed no significant ethnic difference in dose-adjusted AUC. Based on the PPK model constructed using the data of phase III studies, individual AUC estimates were calculated for each of the patients with CTEPH in the PPK analysis population of phase III studies, and tallied by ethnicity and subjected to comparison, among different ethnic groups, of the geometric mean of AUC at steady state. As a result, the geometric mean of AUC in Caucasian subjects, African American subjects, Chinese subjects, and other ethnic groups was higher by 18%, 23%, 19%, and 15%, respectively, than that in Japanese subjects, while the variability of AUC was similar among ethnic groups. In a similar manner, the geometric mean of AUC at steady state was compared between Japanese patients versus Caucasian patients, African American patients, Chinese patients, and patients in other ethnic groups with PAH in the PPK analysis population in phase III studies. As a result, the geometric mean of AUC at steady state was compared between Japanese patients were subjects at the PPK analysis population in phase III studies. As a result, the geometric mean of AUC in Caucasian patients, African American patients, Chinese patients, and patients in other ethnic groups was higher by 25%, 62%, 49%, and 29%, respectively, than that in Japanese patients, while the variability of AUC was similar among ethnic in Japanese patients, while the variability of AUC was similar among ethnic in Japanese patients, while the variability of AUC was similar among ethnic groups.

Riociguat shows linear pharmacokinetics up to the dose of 2.5 mg. Multiple CYP enzymes (CYP1A1, 2C8, 2J2, 3A4) are involved in the metabolism of riociguat, and these CYP enzymes have no known genetic polymorphism that would cause a definite change in the pharmacokinetics of riociguat. Neither do transporters involved in the biliary excretion of the unchanged riociguat (P-gp, BCRP) have any known such genetic polymorphism. Furthermore, riociguat has pharmacokinetic characteristics insensitive to ethnic factors, such as a high BA (approximately 94%) and a little susceptibility to food.

Therefore, the applicant considers that the pharmacokinetics of riociguat is extremely unlikely to differ among ethnic groups.

PMDA considers as follows:

Results of multiple phase I studies did not show any significant differences in the pharmacokinetic parameters among healthy adult subjects of different ethnic groups. Also, the results of the analysis using the PPK model constructed from blood concentration data of phase III studies showed that the individual estimate of AUC in Japanese patients was distributed within a similar range as that in patients of other ethnic groups, although there is a limitation to the accuracy of the evaluation because of the limited number of Japanese patients studied. Therefore, there is no particular problem from the pharmacokinetic point of view in the phase III studies of riociguat having been conducted as global clinical studies.

4.(ii).B.(2) Factors affecting the pharmacokinetics of riociguat

The applicant explained the factors affecting the pharmacokinetics of riociguat, as follows: Both in healthy adult subjects and in patients with pulmonary hypertension, plasma riociguat concentration peaked at 0.25 to 1.5 hours after administration of up to 2.5 mg 3 times daily, whereas $t_{1/2}$ was longer in patients with pulmonary hypertension (10-12 hours) than in healthy adult subjects (5-9 hours), resulting in an approximately 3 times higher AUC at steady state in these patients compared with healthy adult subjects. Pulmonary hypertension, the underlying disease, may have changed the profiles of renal excretion of riociguat and elimination of riociguat from the hepatobiliary system due to the decreased cardiac output, hepato-systemic shunt, aggravation of the renal function, etc. Results of PPK analysis showed that renal function and bilirubin level, which change in patients with pulmonary hypertension, were factors affecting inter-individual variability in the total body clearance of riociguat. These results suggest that the underlying disease is a factor affecting the pharmacokinetics of riociguat.

N-demethylation of riociguat, the reaction that generates metabolite M-1, is a major oxidative pathway in humans, and results of *in vitro* studies using liver microsomes have shown that CYP1A1 plays a major role in the metabolism of riociguat. CYP1A1 is expressed not only in the liver and the small intestine but also in the lung, and is strongly induced by cigarette smoke, charcoal-grilled meat, and Brassicaceae vegetables. There are *in vitro* findings that the lung microsomes from smokers have 2 to 3-fold higher catalytic activity to generate M-1 from riociguat than the microsomes from non-smokers. Also, there is a report of a clinical study that the total clearance of riociguat in smokers is higher compared with non-smokers. These findings suggest that a smoking habit is also a factor affecting the pharmacokinetics of riociguat. However, both in the population of non-smokers and in the population of smokers, there was a large interindividual variability of the pharmacokinetics of riociguat, suggesting that environment and dietary factors, both of which are considered to induce CYP1A1 activity as smoking is considered to, also affect the pharmacokinetics of riociguat.

In the study on drug-metabolizing enzymes or transporters in healthy adult male subjects (147 Caucasian subjects, 12 Japanese subjects), there were no genetic factors associated with the variations in the pharmacokinetics of riociguat.

PMDA asked the applicant to explain whether or not the severity of pulmonary hypertension or the primary disease of pulmonary hypertension (CTEPH or PAH) possibly affected the pharmacokinetics of riociguat.

The applicant responded as follows:

Individual estimates of pharmacokinetic parameters were compared using the PPK model between patients with PAH and patients with CTEPH, the primary diseases of pulmonary hypertension. As a result, AUC, C_{max} , and C_{trough} were all greater in CTEPH patients. However, considering that mean age of the CTEPH patient population (59.3 years) was higher than that of the PAH patient population (51.1 years), there is no difference in the pharmacokinetics of riociguat due to the difference in the primary disease. The individual estimates of AUC in CTEPH patients calculated similarly using the PPK model were compared among different WHO

functional classes. Results showed that the severity of the disease did not have any significant effects on AUC. Therefore, the applicant considers that the severity of pulmonary hypertension or the primary disease does not directly affect the pharmacokinetics of riociguat.

PMDA considers as follows:

Pharmacokinetics of riociguat may possibly be affected by multiple factors, such as underlying diseases, smoking habit, and environment/dietary factors, and therefore varies widely depending on subject characteristics and other background factors. Taking account of the large individual variability in the pharmacokinetics and of the suggested relationship between the plasma riociguat concentration and the hypotensive effect, it is acceptable that the applicant set the dosage and administration in which the maintenance dose was to be determined individually based on patient SBP. The appropriateness of the proposed dosage and administration will be discussed in "4.(iii).B.(7) Dosage and administration."

4.(ii).B.(3) Pharmacokinetics in patients with renal impairment

As clinical pharmacology studies to investigate the effect of renal impairment on the pharmacokinetics of riociguat, Study 11915 was conducted in both smokers and non-smokers and Study 15000, in non-smokers. Since most of the target patients of riociguat are non-smokers, and smoking affects the pharmacokinetics of riociguat, PMDA reviewed mainly the results of Study 15000.

PMDA considers as follows:

In Study 11910 in which riociguat (1.0 mg) was administered intravenously to healthy adult subjects, the total body clearance was 3.861 L/h and renal clearance was 0.3434 L/h, indicating that renal excretion contributes only minimally to the elimination of riociguat. In Study 15000 in which riociguat was administered orally in a single dose to healthy adult subjects and patients with renal impairment, no correlation was observed between the severity of renal impairment and the extent of AUC increase; however, AUC in patients with renal impairment (regardless of the severity) was approximately twice that in healthy adult subjects, indicating that AUC in patients with renal impairment was affected to a greater extent than expected from the contribution of renal excretion in the elimination of riociguat. Therefore, a lower starting dose of riociguat (0.5 mg 3 times daily) should be considered in patients with renal impairment. A caution statement for patients with renal impairment and necessity of adjusting the starting dose will be discussed furthermore in "4.(iii).B.(4).4) Administration in patients with renal impairment."

4.(ii).B.(4) Pharmacokinetics in patients with hepatic impairment

As clinical pharmacology studies of the effect of hepatic impairment on the pharmacokinetics of riociguat, Study 11916 was conducted in smokers and non-smokers and Study 15001, in non-smokers. Since most of the target patients of riociguat are non-smokers and smoking affects the pharmacokinetics of riociguat, PMDA reviewed mainly the results of Study 15001.

PMDA considers as follows:

The proposed package insert required careful administration to patients with moderate or severe hepatic impairment but did not contain a caution statement concerning patients with mild hepatic impairment. In Study 15001 in which riociguat (1.0 mg) was administered orally in a single dose to healthy adult subjects and to patients with mild or moderate hepatic impairment, approximately a 1.7-fold increase in AUC relative to healthy adult subjects was observed even in patients with mild hepatic impairment. Therefore, careful administration is required even to patients with mild hepatic impairment as is the case to patients with moderate impairment, a patient group who showed a similar extent of increase in AUC (approximately 1.6-fold). However, given the extent of the increase in AUC in patients with mild or moderate hepatic impairment, it is unnecessary to uniformly start at the low dosage regimen of 0.5 mg 3 times daily. A caution statement concerning patients with hepatic impairment and necessity of adjusting the starting dose will be discussed

furthermore in "4.(iii)B.(4).5) Administration in patients with hepatic impairment."

4.(ii).B.(5) Drug-drug interactions

4.(ii).B.(5).1) Interaction with omeprazole

PMDA asked the applicant to explain the cause of the decrease in exposure to riociguat in concomitant use with omeprazole, and to explain whether or not there are other drugs that decrease exposure to riociguat by a similar mechanism.

The applicant responded as follows:

Following concomitant use of riociguat with omeprazole, Cmax of riociguat decreased by 35%, and AUC by 26%, compared with the administration of riociguat alone, whereas $t_{1/2}$ following the concomitant use was 9.0 hours, which was not significantly different from $t_{1/2}$ following the administration of riociguat alone (7.9 hours). These results suggest that omeprazole does not affect CYPs or transporters involved in the metabolism and excretion of riociguat. Since riociguat is a basic compound, the solubility in acid solution (pH 2) is as high as 980 mg/L, but the solubility at pH 5 and 7 is as low as 5 and 3 mg/L, respectively, showing a decrease with the increase in pH. These findings suggest that the decrease in exposure to riociguat observed following the concomitant use with omeprazole was caused by the decrease in solubility of riociguat due to the increase in pH in the stomach following the concomitant use with omeprazole compared with the pH following the administration of riociguat alone, resulting in a decrease in absorption of riociguat. Drugs that increase intragastric pH, such as proton pump inhibitors and H₂ receptor antagonists, may possibly decrease exposure to riociguat by a similar mechanism. Also, following the concomitant use of riociguat with aluminum hydroxide gel/magnesium hydroxide combination, C_{max} of riociguat decreased by 56%, and AUC by 34%, compared with the values observed following the administration of riociguat alone. These results suggest that antacids may also possibly decrease exposure to riociguat by a similar mechanism as that of omeprazole.

Approximately 54% of patients who participated in phase II or III studies received concomitant therapy with acid-reducing agents (antacids, proton pump inhibitors, H₂ receptor antagonists). Plasma riociguat concentration decreased after the concomitant use, but the extent of the decrease was \leq 15%, and no difference was observed in the safety data. As predicted from the *in vitro* solubility data, riociguat absorption is decreased by concomitant use with drugs that increase the pH in the stomach and the upper intestinal tract. However, the applicant considers that it is unnecessary to impose uniform dose titration on all patients receiving concomitant use with acid-reducing agents, other than individualized dose adjustment. Since acid-reducing agents such as aluminum hydroxide/magnesium hydroxide combination decrease the AUC of riociguat, it is cautioned that such acid-reducing agents should be administered \geq 1 hour after riociguat dosing.

The applicant has provided, in the proposed package insert, the data of interaction with omeprazole and cautioned to avoid the simultaneous administration of acid-reducing agents with a potent activity that decreases the AUC of riociguat. Therefore, PMDA considers that the measures taken by the applicant are acceptable.

4.(ii).B.(5).2) Interactions with CYP3A inhibitors

PMDA asked the applicant to explain the appropriateness of the caution statement on the interactions with CYP3A inhibitors, taking account of the study results on the interactions with ketoconazole and clarithromycin.

The applicant responded as follows:

Following the concomitant use with ketoconazole, AUC of riociguat increased approximately 2.5fold in non-smokers and approximately 4-fold in smokers, showing a greater increase in smokers than in non-smokers, whereas the increase in the AUC of riociguat following the concomitant use with clarithromycin was approximately 1.3-fold in non-smokers and approximately 1.6-fold in smokers. The marked effect of ketoconazole observed in smokers was possibly caused by its inhibition of multiple CYP isoforms. It appears that ketoconazole inhibited the CYP1A1-catalyzed metabolism in particular, the main metabolic pathway of riociguat in smokers. Ketoconazole is also a potent inhibitor of CYP3A and P-gp, whereas clarithromycin is a potent and selective CYP3A inhibitor and inhibits P-gp to a slight to moderate extent. Thus, the difference in the extent of the increase in AUC between concomitant use with ketoconazole and that with clarithromycin appears to be due partly to the difference in the activity to inhibit the P-gp/BCRP-mediated excretion route.

Since ketoconazole inhibits multiple CYP isoforms and transporters such as P-gp/BCRP, the pharmacokinetic interactions of riociguat observed in the concomitant use with ketoconazole were the strongest interactions that may occur via the inhibition of CYP isoforms and transporters including P-gp/BCRP. A similar increase in plasma riociguat concentration may occur in concomitant use with azole antifungal agents (e.g., itraconazole) and HIV protease inhibitors (e.g., ritonavir) which inhibit CYP and P-gp/BCRP. Also, clarithromycin, a potent CYP3A inhibitor, increased the plasma riociguat concentration approximately 1.4-fold. This result suggests that concomitant use with erythromycin or telithromycin, drugs that potently or moderately inhibit CYP3A, may also increase the plasma riociguat concentration to a similar extent.

Based on the above, the applicant considers that concomitant use with drugs that potently inhibit multiple pathways of riociguat metabolism/excretion, i.e., CYP and P-gp/BCRP, such as azole antifungal agents (e.g., ketoconazole, itraconazole) and HIV protease inhibitors (e.g., ritonavir) should be contraindicated, but that other CYP inhibitors may be concomitantly administered.

PMDA accepted the applicant's response that concomitant use with azole antifungal agents and HIV protease inhibitors, drugs which simultaneously inhibit multiple metabolic enzymes and transporters involved in the pharmacokinetics of riociguat, should be contraindicated, taking account of the study results on the interaction with ketoconazole. However, the applicant did not provide caution against concomitant use with clarithromycin which potently and selectively inhibits CYP3A and at the same time inhibits P-gp to a slight to mild extent. An increase in plasma riociguat concentration caused by concomitant drugs may enhance the hypotensive action of riociguat, an effect correlated with the plasma riociguat concentration, which, as a result, may affect the riociguat dose which is to be adjusted based on SBP. Therefore, potent CYP3A inhibitors should be defined as drugs requiring precautions for concomitant use in the package insert to ensure careful administration. Also, since there were no subjects who continuously used potent CYP3A inhibitors in the phase III comparative studies, safety information on the concomitant use of such drugs should be collected after the market launch.

4.(ii).B.(5).3) Interactions with tyrosine kinase inhibitors

PMDA asked the applicant to explain the appropriateness of the caution statement in concomitant use of riociguat with tyrosine kinase inhibitors, taking account of the fact that the inhibition of riociguat metabolism by tyrosine kinase inhibitors is time-dependent.

The applicant explained as follows:

Using human liver microsomes and selective inhibitors of CYP isoforms, contribution of each CYP isoform to the demethylation reaction to generate M-1 was investigated. Results showed that multiple CYP isoforms, including CYP3A4/5, CYP2C8, CYP2J2, and CYP1A1, were involved in the metabolism of riociguat. In the *in vitro* study on the inhibition of demethylation reaction using recombinant CYP1A1 and human liver microsomes, tyrosine kinase inhibitors (erlotinib, gefitinib, imatinib, sorafenib) strongly inhibited the recombinant CYP1A1, while their inhibitory activity against human liver microsomes was weaker than against the recombinant CYP1A1. These results suggest that, even if CYP1A1 is inhibited by tyrosine kinase inhibitors, other CYP isoforms catalyze demethylation reactions in place of CYP1A1. In contrast, ketoconazole

exhibited inhibitory activities against recombinant CYP1A1 and against human liver microsomes to similar extent, which suggests that ketoconazole potently inhibits not only CYP1A1 but also other CYP isoforms present in the liver microsomes.

Since tyrosine kinase inhibitors time-dependently inhibitat most only CYP1A1, it is considered that the activity of other CYP isoforms involved in demethylation (CYP2C8, 2J2, 3A4/5) to metabolize riociguat remains intact. Also, the extent of the increase in plasma riociguat concentration caused by CYP1A1 inhibition due to concomitant use with a tyrosine kinase inhibitor will be less than that caused by concomitant use with ketoconazole which inhibits not only CYP1A1 but also other CYP isoforms involved in riociguat metabolism. Therefore, although it is necessary to provide caution that the plasma riociguat concentration may be increased by tyrosine kinase inhibitors, it is not necessary to set a rule, such as riociguat dose reduction, as far as riociguat is administered according to the regimen of dose titration for individual patients.

PMDA considers as follows:

It is impossible to explain the extent of the increase in the plasma riociguat concentration due to the time-dependent inhibition of CYP1A1 metabolism by tyrosine kinase inhibitors, based on the results of the *in vitro* study and on the extent of the increase in the plasma riociguat concentration following the concomitant use with ketoconazole. It is unknown to what extent the plasma riociguat concentration will increase following the concomitant use with a tyrosine kinase inhibitor and, therefore, the starting dose or the maximum dose of riociguat cannot be specified for such a therapy. At the current moment, it may only be feasible at most to provide caution for careful administration upon providing the information that concomitant use with a tyrosine kinase inhibitor may increase the plasma riociguat concentration, as proposed by the applicant; however, safety information etc., of such concomitant use should be collected after the market launch.

4.(ii).B.(6) QT/QTc evaluation in riociguat administration

The applicant explained the reason for not having conducted a study to evaluate QT/QTc in riociguat administration as follows:

In phase I studies in healthy adult subjects, adverse events related to the pharmacological action of riociguat were frequently observed after a single-dose administration of riociguat at 5.0 mg, showing a poor tolerability at doses of >2.5 mg. Therefore, it was considered inappropriate for safety reason to conduct a QT/QTc evaluation study of riociguat in healthy adult subjects, based on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (PFSB/ELD Notification No. 1023-1 dated October 23, 2009). Instead of the QT/QTc evaluation study, QT evaluation was conducted by an independent centralized measurement in an expanded ECG monitoring in Study 12934 in patients with PAH. Results of Study 12934 did not show any difference in changes in the QT interval, QTcB interval, or QTcF interval from baseline between the riociguat dose titration group or the riociguat 1.5 mg group and the placebo group. In order to analyze the sensitivity of ECG evaluation to be performed in Study 12934, Study 13796 was conducted in medical institutions where Study 12934 was to be conducted. In Study 13796, ECG was measured and evaluated according to the same methods as used in Study 12934. Results demonstrated that the evaluation method employed in Study 12934 was sufficiently sensitive to detect clinically significant changes in the QT interval after riociguat administration. Based on the above, the applicant considers that there are no findings suggestive of clinically significant prolongation of QT interval by riociguat.

PMDA considers as follows:

In addition to the applicant's explanation that it is inappropriate for safety reason to administer riociguat at a dose of >2.5 mg to healthy adult subjects, it is also inappropriate to administer at a dose of \geq 5 mg of riociguat to patients with pulmonary hypertension, because of the potential risk of hypotension [see "4.(iii).B.(7) Dosage and administration"]. Therefore, it is acceptable that no QT/QTc evaluation study was conducted using riociguat. The applicant conducted a study to

analyze the sensitivity of ECG evaluation performed in Study 12934. As a result, the effect of a single-dose administration of moxifloxacin on QT/QTc was able to be evaluated by the same ECG evaluation method as in Study 12934. Therefore, it is considered possible to evaluate the QT-prolonging effect of riociguat in Study 12934. Based on the above, PMDA accepted the explanation of the applicant that there are no findings suggestive of the QT-prolonging effect of riociguat.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

Results of the following 11 studies were submitted as evaluation data: 4 Japanese clinical pharmacology studies, 2 global phase III studies, 2 long-term extension studies, 2 foreign clinical pharmacology studies, and 1 phase I/II study [for data of BE and pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. The main clinical study results supporting the present application are summarized below.

4.(iii).A.(1) Japanese clinical pharmacology studies

4.(iii).A.(1).1) Single-dose study (Study 12639, Attached document 5.3.3.1.1; Study period, to the total study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study (Study 12639, Attached document 5.3.3.1.1; Study period, total study (Study 12639, Attached document 5.3.3.1.1; Study 12639, Attached document 5.3.3.1.1; Study (Study 12639, Attached document 5.3.3.1]; Study 12639, Attached document 5.3.3.1]; Study 12639, Attached document 5.3.3.1]; Study 12639, Attached Study 12639, Attached Atta

A single-blind, dose-titration study was conducted at a single center in Japan to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of riociguat following single dose administration. In this study, riociguat (0.5, 1.0, 2.5 mg) or placebo was administered orally in a single dose under fasting conditions to 36 healthy adult male subjects (12 subjects in each dose step [9 subjects in the riociguat group, 3 subjects in the placebo group]). All 36 subjects treated with the study drug completed the study.

The incidence of treatment-emergent adverse events (TEAEs) was 0% (0 of 9 subjects) in the placebo group, 0% (0 of 9 subjects) in the 0.5 mg group, 44.4% (4 of 9 subjects) in the 1.0 mg group, and 100% (9 of 9 subjects) in the 2.5 mg group. TEAEs reported by \geq 2 subjects in any group were flushing (0 subjects in the placebo group, 0 subjects in the 0.5 mg group, 0 subjects in the 1.0 mg group, 6 subjects in the 2.5 mg group), conjunctival hyperaemia (0 subjects, 0 subjects, 0 subjects, 5 subjects, respectively), orthostatic hypotension (0 subjects, 0 subjects, 3 subjects, respectively), headache (0 subjects, 0 subjects, 0 subjects, 3 subjects, respectively), and feeling abnormal (0 subjects, 0 subjects, 2 subjects, 0 subjects, respectively). No death or serious TEAE was observed.

No clinically significant changes were observed in laboratory test values. As regards vital signs, the mean change in pulse rate from baseline was greater in all riociguat groups compared with the placebo group up to 12 hours after administration.

4.(iii).A.(1).2) Multiple-dose study (Study 12640, Attached document 5.3.3.1.2; Study period, to to to to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study period, to be a study (Study 12640, Attached document 5.3.3.1.2; Study 12640, Attached document 5.3.3.1; Study 12640, Attached document 5.

A single-blind, dose-titration study was conducted at a single center in Japan to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of riociguat following multiple dose administration. In this study, riociguat (1.0, 1.5, 2.5 mg) or placebo was to be administered orally under fasting conditions 3 times daily for 7 days (Day 3 to Day 9 of study treatment) to healthy adult male subjects (target sample size, 12 subjects in each dose step [9 subjects in the riociguat group, 3 subjects in the placebo group]). Additionally, a single dose of the study drug was to be administered orally on Day 1 of each step. Evaluation of the results of Step 1 (1.0 mg 3 times daily) and Step 2 (1.5 mg 3 times daily) in this study showed that, in the 1.5 mg group, (i) TEAEs considered related to the study drug were observed in approximately half of the subjects, (ii) definite increase in heart rate and decrease in blood pressure were observed, and (iii) the exposure level was sufficiently high compared with the results in foreign clinical studies. Therefore, the

applicant cancelled Step 3 (2.5 mg 3 times daily). The study drug was administered to a total of 24 subjects in Steps 1 and 2, and the study was discontinued in 1 subject in the 1.0 mg group (consent withdrawal) and in 2 subjects in the 1.5 mg group (due to TEAEs).

The incidence of TEAEs was 0% in the placebo group (0 of 6 subjects), 22.2% in the 1.0 mg group (2 of 9 subjects), and 44.4% in the 1.5 mg group (4 of 9 subjects). TEAEs reported by ≥ 2 subjects in any group were headache (0 subjects in the placebo group, 2 subjects in the 1.0 mg group, 2 subjects in the 1.5 mg group) and nausea (0 subjects, 0 subjects, 2 subjects, respectively). No death or serious TEAE was observed. TEAEs leading to treatment discontinuation were reported by 2 subjects in the 1.5 mg group (AST increased, ALT increased; nausea).

The decreases in SBP and diastolic blood pressure (DBP) from baseline were greater in the riociguat groups compared with the placebo group. The mean changes in SBP and DBP on Day 9 from baseline were -0.50 and 0.00 mmHg, respectively, in the placebo group, -3.13 and -2.38 mmHg, respectively, in the 1.0 mg group, and -9.14 and -7.57 mmHg, respectively, in the 1.5 mg group. The increase in heart rate from baseline was greater in the 1.5 mg group compared with the placebo group or the 1.0 mg group, with the change in the heart rate from baseline on Day 9 being -5.17/min in the placebo group, -2.63/min in the 1.0 mg group, and 3.14/min in the 1.5 mg group.

4.(iii).A.(1).3) BE between formulation for clinical studies and to-be-marketed formulation (0.5 mg tablets) (Study 14769, Attached document 5.3.1.2.2; Study period, to to the studies of the studies of

An open-label, two-treatment, two-period, crossover study was conducted at a single center in Japan to evaluate the BE between the formulation for clinical studies (0.5 mg tablet) and to-be-marketed formulation (0.5 mg tablet) administered orally in a single dose under fasting conditions to 24 Japanese healthy adult male subjects (with a wash-out period of \geq 7 days between the treatment periods). One subject withdrew his consent before the administration of the study drug (formulation for clinical studies) in the second period, and was withdrawn from the study.

TEAEs were reported by 2 subjects after administration of the formulation for clinical studies (diarrhoea, vomiting, feeling abnormal, feeling hot, pyrexia, gastroenteritis rotavirus, C-reactive protein increased, neutrophil percentage increased, white blood cell count increased, hyperglycaemia, syncope; blood bilirubin increased) and by 3 subjects after administration of the to-be-marketed formulation (atrioventricular block first degree; abdominal pain; feeling hot, neutrophil percentage increased, white blood cell count increased). Neither death nor serious TEAE was observed.

No clinically significant changes were observed in laboratory test values, vital signs, or ECG.

4.(iii).A.(1).4) BE between formulation for clinical studies and to-be-marketed formulation (1.0 mg tablets) (Study 14845, Attached document 5.3.1.2.3; Study period, to to to to the state of the state

An open-label, two-treatment, two-period, crossover study was conducted at a single center in Japan to evaluate the BE between the formulation for clinical studies (1.0 mg tablet) and the tobe-marketed formulation (1.0 mg tablet) administered orally in a single dose under fasting conditions to 24 Japanese healthy adult male subjects (with a wash-out period of \geq 7 days between the treatment periods). All 24 subjects treated with the study drug completed the study.

TEAEs were reported by 2 subjects after administration of the formulation for clinical studies (atrioventricular block first degree; aspartate aminotransferase [AST] increased) and by 2 subjects after administration of the to-be-marketed formulation (Epstein-Barr virus infection, alanine

aminotransferase [ALT] increased, blood lactate dehydrogenase increased; blood creatine phosphokinase increased). Neither death nor serious TEAE was observed.

No clinically significant changes were observed in laboratory test values, vital signs, or ECG.

4.(iii).A.(2) Foreign clinical pharmacology studies (Study 13010, Attached document 5.3.1.1.4; Study period, to (19)

In an open-label, two-treatment, two-period, crossover study at a single center overseas, riociguat (2.5 mg, formulation for clinical studies) was administered orally in a single dose to 24 foreign healthy adult male subjects under fasting conditions and after a high fat diet to evaluate the food effect on the pharmacokinetics of riociguat and the safety of riociguat (with a wash-out period of approximately 1 week between the treatment periods). One subject discontinued the study before the first dose of the study drug because of an adverse event.

The incidence of TEAEs was 43% (10 of 23 subjects) after fasted administration and 35% (8 of 23 subjects) after fed administration. TEAEs reported by ≥ 2 subjects in either administration period were headache (6 subjects after fasted administration and 2 subjects after fed administration), nasal congestion (4 subjects and 3 subjects, respectively), flushing (3 subjects and 0 subjects, respectively), and catheter site pain (0 subjects and 2 subjects, respectively). Neither death nor serious TEAE was observed.

No clinically significant changes were observed in laboratory test values.

An open-label, uncontrolled study was conducted at 16 centers overseas to evaluate the safety and tolerability of the riociguat dose adjustment based on SBP in foreign patients with pulmonary hypertension (target sample size, 60 patients).

The primary treatment period was defined as the first 12 weeks of treatment. The treatment was started at 1.0 mg/dose 3 times daily (interval of approximately 8 hours) (TID). Then, the dose was to be determined every 2 weeks within the dose range of 1.0 to 2.5 mg TID, according to the following criteria. If 1.0 mg TID was intolerable, dose reduction to 0.5 mg TID was permitted.

- If the trough SBP is >100 mmHg, increase the dose by 0.5 mg from the current dose.
- If the trough SBP is in the range of 90 to 100 mmHg, maintain the current dose.
- If the trough SBP is <90 mmHg but no hypotensive signs or symptoms are observed, decrease the dose by 0.5 mg from the current dose.
- If, regardless of the time point, the SBP is <90 mmHg, and hypotensive signs or symptoms such as dizziness and presyncope are observed, discontinue riociguat, and resume the administration after 24 hours at the reduced dose (by 0.5 mg from the current dose).

The primary treatment period was followed by the long-term extended treatment period (patients were allowed to voluntarily participate until the approval of riociguat or until the discontinuation of the development) in which administration was continued according to the same dose titration method as used in the primary treatment period.

The main inclusion criteria were patients aged 18 to 75 years with PAH or CTEPH who had pulmonary vascular resistance (PVR) and the mean pulmonary arterial pressure (PAPmean) exceeding 300 dyn·sec·cm⁻⁵ and 25 mmHg, respectively, and were classified as WHO functional class II or III (CTEPH patients were limited to those who were ineligible for pulmonary endarterectomy [PEA], refused to receive PEA, or were not absolutely indicated for urgent PEA).

Initially, concomitant use with therapeutic agents for pulmonary hypertension (e.g., calcium channel blockers, endothelin receptor antagonists [ERAs], prostacyclin, phosphodiesterase-5 (PDE-5) inhibitors) had been prohibited. Pursuant to protocol revisions, concomitant use with calcium channel blockers was permitted (**1**, **1**) and continued use of bosentan was permitted if the patient had been treated with the drug before the initiation of the study (**1**, **1**).

4.(iii).A.(3).1) Primary treatment period

A total of 75 patients (33 patients with PAH, 42 patients with CTEPH) who were treated with the study drug during the primary treatment period were included in the safety analysis population. Of these, 72 patients (31 patients and 41 patients, respectively) excluding 3 patients withdrawn from the study, were included in the pharmacodynamics analysis population. All 3 patients (2 patients and 1 patient, respectively) discontinued the study because of adverse events. The WHO functional class of patients in the pharmacodynamics analysis population was class II in 15 patients (5 patients and 10 patients, respectively), class III in 56 patients (25 patients and 31 patients, respectively), and class IV in 1 patient (1 patient and 0 patients, respectively). Bosentan was concomitantly administered to 6 patients.

The daily dose at the end of the primary treatment period was 1.5 mg/day in 1% of patients (1 of 75 patients), 3.0 mg/day in 8% (6 of 75 patients), 4.5 mg/day in 11% (8 of 75 patients), 6.0 mg/day in 11% (8 of 75 patients), 7.5 mg/day in 68% (51 of 75 patients), and 9.0 mg/day⁵) in 1% (1 of 75 patients).

As regards the pharmacodynamic effects, changes in PVR from baseline to Week 12 (data obtained within 4 weeks before the initiation of the study or at baseline) were as shown in Table 5. Changes in six-minute walking distance (6MWD) from baseline to Week 12 were as shown in Table 6.

	Patients with PAH	Patients with CTEPH	
Baseline	847 ± 428 (N = 20)	732 ± 287 (N = 30)	
Week 12	521 ± 243 (N = 19)	531 ± 239 (N = 29)	
Change	-323 ± 285 (N = 19)	-207 ± 124 (N = 29)	

 Table 5. Change in PVR (dyn·sec·cm⁻⁵) from baseline to week 12

 $(mean \pm SD)$

Table 6.	Change i	in 6MWD	(m) from	baseline to	week 12
----------	----------	---------	----------	-------------	---------

	Patients with PAH	Patients with CTEPH
Baseline	316.7 ± 127.4 (N = 31)	382.9 ± 88.1 (N = 41)
Week 12	390.2 ± 129.5 (N = 31)	447.6 ± 95.8 (N = 39)
Change	73.5 ± 84.0 (N = 31)	64.3 ± 62.0 (N = 39)

 $(\text{mean} \pm \text{SD})$

⁵⁾ One patient erroneously treated with a higher-than-planned dose of riociguat

As regards safety, the incidence of TEAEs was 88% (29 of 33 patients) in patients with PAH and 86% (36 of 42 patients) in patients with CTEPH. Table 7 shows TEAEs with an incidence of \geq 10% in either patient group.

	Patients with PAH	Patients with CTEPH
	(N = 33)	(N = 42)
Dyspepsia	15 (5)	31 (13)
Hypotension	3 (1)	24 (10)
Tachycardia	0 (0)	21 (9)
Oedema peripheral	9 (3)	14 (6)
Abdominal pain upper	6 (2)	12 (5)
Vertigo	3 (1)	12 (5)
Headache	24 (8)	10 (4)
Gastroenteric infection	0 (0)	10 (4)
Respiratory tract infection	0 (0)	10 (4)
Fatigue	12 (4)	7 (3)
Nasopharyngitis	12 (4)	0 (0)

Table 7. TEAEs with	an incidence of >10%	in either patient group
		m onnor pattorn group

% (number of patients)

One patient with CTEPH died of right ventricular failure, but a causal relationship to the study drug was ruled out for the death. The incidence of serious TEAEs was 14.7% (11 of 75 patients) and the serious TEAE reported by ≥ 2 patients was cardiac failure (3%, 2 patients). A causal relationship to the study drug was ruled out for all the TEAEs.

TEAEs leading to treatment discontinuation were reported by 3 patients (pulmonary oedema, rash, and right ventricular failure in 1 patient each).

4.(iii).A.(3).2) Long-term extended treatment period

Of 72 patients (31 patients with PAH, 41 patients with CTEPH) who completed the primary treatment period, 68 patients (27 patients and 41 patients, respectively) proceeded to the long-term extended treatment period, and all of them were included in the safety analysis population. At the time point of the data cut-off, 21 patients were discontinued from the study, with the main reasons for the discontinuation being adverse events (7 patients), death (5 patients), discretion of the physician (3 patients), and consent withdrawal (3 patients).

The mean treatment duration in the long-term extended treatment period was 36.5 months. The daily dose at the data cut-off or at study discontinuation was 0 mg/day in 1.5% of patients (1 of 68 patients), 1.5 mg/day in 1.5% (1 of 68 patients), 3.0 mg/day in 7.4% (5 of 68 patients), 4.5 mg/day in 11.8% (8 of 68 patients), 5.0 mg/day in 1.5% (1 of 68 patients), 6.0 mg/day in 5.9% (4 of 68 patients), and 7.5 mg/day in 70.6% (48 of 68 patients).

As regards safety, the incidence of TEAEs in 68 patients included in safety analysis was 91.2% (62 patients). TEAEs with an incidence of \geq 10% were nasopharyngitis in 45.6% (31 patients), oedema peripheral in 30.9% (21 patients), pulmonary hypertension in 23.5% (16 patients), respiratory tract infection and cough in 20.6% (14 patients) each, oedema and dizziness in 19.1% (13 patients) each, syncope and hypotension in 17.6% (12 patients) each, pulmonary arterial hypertension in 13.2% (9 patients), anaemia, right ventricular failure, diarrhoea, dyspepsia, gastrooesophageal reflux disease, and vomiting in 11.8% (8 patients) each, and bronchitis, pneumonia, hypokalaemia, and headache in 10.3% (7 patients) each.

Death occurred in 7 patients (right ventricular failure and cor pulmonale [2 patients each], cardiac failure, hepatic neoplasm malignant, sudden death [1 patient each]), but a causal relationship to

the study drug was ruled out for all events. The incidence of serious TEAEs was 69.1% (47 patients). Serious TEAEs with an incidence of \geq 5% were syncope in 17.6% (12 patients), right ventricular failure in 11.8% (8 patients), pulmonary arterial hypertension in 10.3% (7 patients), cardiac failure in 8.8% (6 patients), pulmonary hypertension in 7.4% (5 patients), and atrial flutter and pneumonia in 5.9% (4 patients) each.

The incidence of TEAEs leading to treatment discontinuation was 11.8% (8 patients). The TEAE that was reported by ≥ 2 patients and resulted in treatment discontinuation was pulmonary hypertension in 2.9% of patients (2 patients).

Global phase III study in patients with CTEPH (Study 11348, Attached 4.(iii).A.(4) document 5.3.5.1.1; Study period, to

A randomized, double-blind, parallel group, comparative study was conducted at 89 centers in 26 countries including Japan to evaluate the efficacy and safety of riociguat in patients with CTEPH (target sample size, 270 patients in total: 180 patients in the riociguat group; 90 patients in the placebo group).

The dose titration period was defined as the first 8 weeks in the 16 weeks of study drug treatment period. In the riociguat group, the initial dose was to be started at 1.0 mg TID (interval of approximately 6-8 hours). Then, the dose was to be adjusted every 2 weeks according to the following criteria to determine the maintenance dose within the range of 0.5 to 2.5 mg TID. In the placebo group, the dose was to be adjusted in a similar manner to determine the maintenance dose.

- If the trough SBP is \geq 95 mmHg, increase the dose by 0.5 mg from the current dose.
- If the trough SBP is in the range of 90 to 94 mmHg, maintain the current dose.
- If the trough SBP is <90 mmHg but no hypotensive signs or symptoms are observed, decrease the dose by 0.5 mg from the current dose.
- If, regardless of the time point, the SBP is <90 mmHg, and hypotensive signs or symptoms such as dizziness and presyncope are observed, discontinue riociguat and resume the administration after 24 hours at the reduced dose (by 0.5 mg from the current dose).

The primary treatment period was defined as the 8 weeks after the end of the dose titration period, in which riociguat was administered at the same dose as at the end of the dose titration period. Dose reduction for safety reasons was permitted.

The main inclusion criteria were patients aged 18 to 80 years with CTEPH who had 6MWD of 150 to 450 m^{6} at screening and at baseline (at the initiation of study drug treatment period) and met either of the following criteria.

- Inoperable⁷⁾ CTEPH with PVR⁸⁾ and PAPmean exceeding 300 dyn·sec·cm⁻⁵ and 25 mmHg, respectively, measured at \geq 90 days after the initiation of anticoagulant therapy
- Persistent or recurrent pulmonary hypertension after PEA (PVR⁸⁾ >300 dyn·sec·cm⁻⁵ at \geq 180 days after operation)⁹⁾

In this study, patients were randomized in a 2:1 ratio to the riociguat group or the placebo group in each country/region.

⁶⁾ The upper limit of 450 m was defined to clarify the inclusion/exclusion criteria.

⁷⁾ Operability was judged by a skilled surgeon before assignment.

 ⁸⁾ Changed from >480 dyn·sec·cm⁻⁵ to >300 dyn·sec·cm⁻⁵, considering the study feasibility. (19)
 ⁹⁾ If pulmonary hypertension persisted or recurred after PEA, operability judgment for this study was not performed.

Concomitant use of oral anticoagulants, diuretics, digitalis, calcium channel blockers, oxygen therapy, etc., was permitted. Anticoagulants were to be started at least 90 days prior to study drug administration, and the dose of diuretics was to be stabilized for at least 30 days prior to study drug administration. Patients who were being treated with nitric oxide (NO) donor (e.g., nitrates) and patients who had previously been treated with PAH drugs (e.g., ERA, prostacyclin derivatives, PDE-5 inhibitors) were to be excluded from the study (NO donors should not be administered within 90 days prior to study drug administration). Patients who experienced unacceptable adverse reactions, or did not respond, to PAH drugs were allowed to be enrolled in the study after discontinuation of PAH drugs \geq 30 days before the right heart catheterization test at baseline.

4.(iii).A.(4).1) Results of the entire study

Of 262 randomized patients (174 patients in the riociguat group, 88 patients in the placebo group), 261 patients (173 patients and 88 patients, respectively) who received at least 1 dose of the study drug were included in the safety analysis population and the intent-to-treat (ITT) population, and the ITT population was used for the primary efficacy analysis. Of the randomized patients, 19 patients (14 patients, 5 patients) discontinued the study; the main reasons for the discontinuation were adverse events in 6 patients (4 patients, 2 patients) and death in 4 patients (2 patients, 2 patients). Table 8 shows the WHO functional class, clinical classification of CTEPH, and country/region of patients in the ITT population.

Table 6. Dasenne and disease characteristics of subjects (entire population, 111)				
		Riociguat group	Placebo group	
		(N = 173)	(N = 88)	
WHO functional class	Ι	1.7 (3)	0 (0)	
	II	31.8 (55)	28.4 (25)	
	III	61.8 (107)	68.2 (60)	
	IV	4.6 (8)	2.3 (2)	
	Unknown	0 (0)	1.1 (1)	
Clinical classification	Inoperable CTEPH	69.9 (121)	77.3 (68)	
of CTEPH	Postoperative CTEPH	30.1 (52)	22.7 (20)	
Country/region	North America	8.7 (15)	10.2 (9)	
	South America	8.7 (15)	6.8 (6)	
	Europe	60.1 (104)	60.2 (53)	
	China	12.1 (21)	12.5 (11)	
	Asia/Oceania	10.4 (18)	10.2 (9)	

Table 8. Baseline and disease characteristics of subjects (entire population, ITT)

% (number of patients)

The daily dose of riociguat at Week 16 (the last visit) was 1.5 mg/day in 0.6% (1 of 160 patients), 3.0 mg/day in 3.8% (6 of 160 patients), 4.5 mg/day in 6.3% (10 of 160 patients), 6.0 mg/day in 12.5% (20 of 160 patients), and 7.5 mg/day in 76.9% (123 of 160 patients).

As regards efficacy, changes in 6MWD from baseline to Week 16, the primary endpoint, were as shown in Table 9, showing a significant difference between the riociguat group and the placebo group (P < 0.0001; Wilcoxon test stratified by country/region).

	Riociguat group	Placebo group
	(N = 173)	(N = 88)
Baseline		
Mean (SD)	342.3 (81.9)	356.0 (74.7)
Median (minimum-maximum)	360.0 (150-557)	372.0 (152-474)
Change from baseline to Week 16 ^a		
Mean (SD)	38.9 (79.3)	-5.5 (84.3)
Median (minimum-maximum)	42.0 (-376 to 335)	5.0 (-389 to 226)
Between-group comparison of change	Riociguat group	– placebo group
Difference of least squares mean [95% CI] ^b	45.69 [24.74-66.63]	
P value (analysis of covariance ^b)	< 0.0001	
<i>P</i> value (stratified Wilcoxon test ^c)	< 0.0	0001

Table 9. Change in 6MWD (m) from baseline to Week 16 (entire population, ITT)

a: The last measured value up to Week 16 in subjects who completed or discontinued the study In subjects who did not make a visit at discontinuation because of death or clinical aggravation, or did not have 6MWD measured at the visit at discontinuation, missing values were imputed by the worst value (0 m). b: Analysis of covariance using baseline values as the covariate and the treatment group and country/region as the main effects

c: Wilcoxon test stratified by country/region

Since the results of Shapiro-Wilk test for the normality of residuals in analysis of covariance were statistically significant (P = 0.0001), the P value obtained by the stratified Wilcoxon test was handled as the results of the formal significance test according to the pre-determined rule.

Changes in PVR from baseline to Week 16, the secondary endpoint, were as shown in Table 10.

Table 10. Changes in PVR (dyn-sec-cm ³)	from baseline to week 16 (er	tire population, ITT)
	Riociguat group	Placebo group
	(N = 151)	(N = 82)
Baseline		
Mean (SD)	790.68 (431.57)	779.32 (400.94)
Median (minimum-maximum)	711.11 (195.2-3942.0)	691.39 (258.1-2046.8)
Change from baseline to Week 16 ^a		
Mean (SD)	-225.68 (247.52)	23.07 (273.53)
Median (minimum-maximum)	-175.94 (-1753.2 to 511.0)	14.89 (-679.6 to 969.2)
Between-group comparison of change ^b	Riociguat group	– placebo group
Difference of least squares mean [95% CI] ^c	-246.43 [-303.33 to -189.53]	
<i>P</i> value (analysis of covariance ^c)	< 0.0001	
<i>P</i> value (stratified Wilcoxon test ^d)	< 0.0	001

T-11. 10 CL 5. 0 -1 . 4 .

a: The last measured value after baseline measurement

b: Only if significant difference was observed in the primary endpoint 6MWD, significance test on the secondary endpoint was to be conducted.

c: Analysis of covariance using baseline values as the covariate and the treatment group and country/region as the main effects

d: Wilcoxon test stratified by country/region

Since the results of Shapiro-Wilk test for the normality of residual in analysis of covariance were statistically significant (P = 0.0001), the P value obtained by the stratified Wilcoxon test was handled as the results of the formal significance test according to the pre-determined rule.

As regards safety, the incidence of TEAEs was 91.9% (159 of 173 patients) in the riociguat group and 86.4% (76 of 88 patients) in the placebo group. TEAEs with an incidence of \geq 5% in either group were as shown in Table 11.

	·	
	Riociguat group (N = 173)	Placebo group (N = 88)
Headache	24.9 (43)	13.6 (12)
Dizziness	22.5 (39)	12.5 (11)
Dyspepsia	17.9 (31)	8.0(7)
Oedema peripheral	15.6 (27)	20.5 (18)
Nasopharyngitis	15.0 (26)	9.1 (8)
Nausea	11.0 (19)	8.0(7)
Diarrhoea	9.8 (17)	4.5 (4)
Vomiting	9.8 (17)	3.4 (3)
Hypotension	9.2 (16)	3.4 (3)
Upper respiratory tract infection	5.8 (10)	4.5 (4)
INR increased	5.8 (10)	4.5 (4)
Constipation	5.8 (10)	1.1 (1)
Cough	5.2 (9)	18.2 (16)
Dyspnoea	4.6 (8)	13.6 (12)
Back pain	4.0 (7)	5.7 (5)
Insomnia	2.3 (4)	6.8 (6)
Pain in extremity	1.7 (3)	5.7 (5)
Blood creatinine increased	1.7 (3)	5.7 (5)

Table 11. TEAEs with an incidence of ≥5% in either group

% (number of patients); INR, International normalized ratio

Death occurred in 1.2% (2 of 173 patients) in the riociguat group (cardiac failure in 1 patient; anaemia, catheter site haemorrhage, and renal failure acute in 1 patient) and in 3.4% (3 of 88 patients) in the placebo group (cardiac arrest in 2 patients; cardiopulmonary failure in 1 patient). Except for renal failure acute, a causal relationship to the study drug was ruled out. Renal failure acute occurred on Day 54 after the treatment start, and the subject died because of the event on Day 64. The incidence of serious TEAEs was 19.7% (34 of 173 patients) in the riociguat group and 15.9% (14 of 88 patients) in the placebo group. Serious TEAEs reported by \geq 2 patients in either group were right ventricular failure (3.5% [6 patients] in the riociguat group, 3.4% [3 patients] in the placebo group), syncope (2.3% [4 patients] and 3.4% [3 patients], respectively), haemoptysis (1.7% [3 patients] and 0% [0 patients], respectively), cardiac arrest (0% [0 patients] and 2.3% [2 patients], respectively), gastritis, catheter site haemorrhage, renal failure chronic, pulmonary hypertension, and respiratory failure (1.2% [2 patients] each, 0% [0 patients] each, respectively). Among these, a causal relationship to the study drug could not be ruled out for syncope (3 patients and 1 patient, respectively) or gastritis (1 patient and 0 patients, respectively). The outcome of syncope was resolved/disappeared, and the outcome of gastritis was improved.

The incidence of TEAEs leading to treatment discontinuation was 2.9% (5 patients) in the riociguat group and 2.3% (2 patients) in the placebo group, and a TEAE that was reported by ≥ 2 patients in either group and resulted in treatment discontinuation was right ventricular failure (0.6% [1 patient] and 2.3% [2 patients], respectively).

4.(iii).A.(4).2) Results in Japanese population

At 15 centers in Japan where the study was conducted, 16 Japanese patients were randomized into the treatment groups (11 patients in the riociguat group, 5 patients in the placebo group). All patients received at least 1 dose of the study drug and were included in the safety analysis population and in the ITT population. Two patients (2 patients and 0 patients, respectively) discontinued the study because of lack of efficacy in 1 patient and consent withdrawal in 1 patient. The WHO functional class was II in 6 patients (5 patients, 1 patient) and III in 10 patients (6 patients, 4 patients), and the clinical classification of CTEPH was inoperable CTEPH in 14 patients (9 patients, 5 patients) and postoperative CTEPH in 2 patients (2 patients, 0 patients).

The daily dose of riociguat in Week 16 (the last visit) was 3.0 mg/day in 22.2% (2 of 9 patients), 6.0 mg/day in 33.3% (3 of 9 patients), and 7.5 mg/day in 44.4% (4 of 9 patients).

As regards efficacy, changes in 6MWD and PVR in the Japanese population from baseline to Week 16 were as shown in Tables 12 and 13, respectively.

Table 12. Changes in 6MWD (m) from baseline to Week 16 (Japanese population, ITT)			
	Riociguat group	Placebo group	
	(N = 11)	(N = 5)	
Baseline			
Mean (SD)	375.5 (52.5)	368.4 (40.0)	
Median (minimum-maximum)	378.0 (276-489)	362.0 (310-415)	
Change from baseline to Week 16 ^a			
Mean (SD)	31.9 (148.6)	36.0 (36.4)	
Median (minimum-maximum)	64.0 (-376 to 217)	14.0 (6-85)	
	1 . 1 . 1 . 1	1 1	

a: The last measured value up to Week 16 in subjects who completed or discontinued the study In subjects who did not make a visit at discontinuation because of death or clinical aggravation, or did not have 6MWD measured at the visit at discontinuation, missing values were imputed by the worst value (0 m).

Table 13. Changes in PVR (dyn·sec·cm⁻⁵) from baseline to Week 16 (Japanese population, ITT)

	Riociguat group	Placebo group
	(N = 9)	(N = 5)
Baseline		
Mean (SD)	598.18 (302.52)	596.66 (280.05)
Median (minimum-maximum)	503.77 (388.8-1379.7)	532.25 (301.9-1018.9)
Change from baseline to Week 16 ^a		
Mean (SD)	-129.61 (122.49)	15.72 (120.81)
Median (minimum-maximum)	-159.16 (-291.5 to 146.8)	-14.18 (-125.6 to 205.1)
a. The last measured value after baseline measurement		

a: The last measured value after baseline measurement

As regards safety, the incidence of TEAEs was 100% (11 of 11 patients) in the riociguat group and 100% (5 of 5 patients) in the placebo group. TEAEs reported by ≥ 2 patients in either group were as shown in Table 14.

	Riociguat group	Placebo group
	(N = 11)	(N = 5)
Nasopharyngitis	36.4 (4)	40.0 (2)
Back pain	27.3 (3)	0 (0)
Dyspepsia	18.2 (2)	0 (0)
Dizziness	18.2 (2)	0 (0)
Headache	18.2 (2)	0 (0)
Hypotension	18.2 (2)	20.0(1)

Table 14. TEAEs reported by ≥ 2 patients in either group (Japanese population)

% (number of patients)

No death occurred. Serious TEAEs were reported by 2 patients in the riociguat group (atrial flutter, pulmonary hypertension) and by 1 patient in the placebo group (right ventricular failure). A causal relationship to the study drug was ruled out for all events.

There was no TEAE leading to treatment discontinuation.

4.(iii).A.(5) Global long-term extension study in patients with CTEPH (Study 11349: Attached document 5.3.5.1.2, 5.3.5.1.5; Study period, to ongoing; data cut-off,

An open-label, uncontrolled study in patients who had completed the 16-week treatment in Study 11348 was conducted at 71 centers in 25 countries including Japan to evaluate the efficacy and safety of riociguat in patients with CTEPH.

During the 8-week dose titration period after the end of Study 11348, the same dose as used in Study 11348 was administered continuously in patients who had been in the riociguat group in Study 11348; and in patients who had been in the placebo group, the maintenance dose was determined according to the same method as used during the dose titration period of Study 11348.¹⁰ After the end of the dose titration period, the time until the market launch of riociguat following the marketing approval in the country of each center was defined as the primary treatment period. During the primary treatment period, it was allowed to adjust the dose within the range of 0.5 to 2.5 mg TID at the discretion of the investigator/subinvestigator regardless of the treatment group in Study 11348, by taking account of the blood pressure of patients, expected adverse drug reactions, and progression of CTEPH.

The main inclusion criterion was patients who completed the 16-week administration in Study 11348. Concomitant use with NO donors or with PDE-5 inhibitors was prohibited throughout the study, while the concomitant use with ERA and/or prostacyclin derivatives was permitted during the primary treatment period.

4.(iii).A.(5).1) Results of the entire study

Of 243 patients (160 patients in the riociguat group, 83 patients in the placebo group) who completed Study 11348, a total of 237 patients (155 patients and 82 patients, respectively) proceeded to the present study and all of these 237 patients were subjected to the interim evaluation; the study was discontinued in 26 patients (16 patients and 10 patients, respectively), with the main reasons being death in 12 patients (9 patients and 3 patients, respectively) and adverse events in 7 patients (3 patients and 4 patients, respectively).

The mean treatment duration in the study (excluding the period in Study 11348) was 582.2 days.

As regards efficacy, change in 6MWD from baseline (at the initiation of study drug administration in Study 11348) to Week 12 in this study was 61.1 ± 58.9 m (mean \pm SD) in the riociguat-riociguat group (N = 145) and 50.5 ± 64.2 m in the placebo-riociguat group (N = 75), and the change from baseline to 12 months was 58.6 ± 57.6 m in the riociguat-riociguat group (N = 114) and 36.8 ± 68.9 m in the placebo-riociguat group (N = 58).

As regards safety, the incidence of TEAEs was 96.8% (150 of 155 patients) in the riociguatriociguat group and 95.1% (78 of 82 patients) in the placebo-riociguat group. TEAEs with an incidence of \geq 5% in either group were as shown in Table 15.

¹⁰⁾In order to maintain the blindness of the assignment to Study 11348, the information on riociguat dose was revealed neither to the physicians nor to the patients during the dose titration period, and was unblinded after the end of the dose titration period.

	Riociguat-riociguat group	Placebo-riociguat group	
	(N = 155)	(N = 82)	
Nasopharyngitis	23.9 (37)	22.0 (18)	
Dizziness	18.7 (29)	19.5 (16)	
Oedema peripheral	15.5 (24)	23.2 (19)	
Diarrhoea	13.5 (21)	14.6 (12)	
Cough	12.9 (20)	14.6 (12)	
Bronchitis	12.3 (19)	6.1 (5)	
Arthralgia	12.3 (19)	6.1 (5)	
Dyspnoea	11.6 (18)	11.0 (9)	
Upper respiratory tract infection	11.6 (18)	9.8 (8)	
Back pain	9.7 (15)	11.0 (9)	
Dyspepsia	9.7 (15)	9.8 (8)	
Chest pain	9.0 (14)	4.9 (4)	
Nausea	7.1 (11)	13.4 (11)	
Constipation	7.1 (11)	7.3 (6)	
INR increased	7.1 (11)	6.1 (5)	
Vomiting	7.1 (11)	4.9 (4)	
Pain in extremity	7.1 (11)	3.7 (3)	
Epistaxis	6.5 (10)	9.8 (8)	
Syncope	6.5 (10)	8.5 (7)	
Respiratory tract infection	6.5 (10)	7.3 (6)	
Anaemia	6.5 (10)	6.1 (5)	
Urinary tract infection	6.5 (10)	4.9 (4)	
Hypotension	5.8 (9)	7.3 (6)	
Right ventricular failure	5.8 (9)	4.9 (4)	
APTT prolonged	5.8 (9)	1.2 (1)	
Pulmonary hypertension	5.2 (8)	8.5 (7)	
Abdominal pain upper	5.2 (8)	6.1 (5)	
Contusion	5.2 (8)	3.7 (3)	
Headache	4.5 (7)	12.2 (10)	
Palpitations	4.5 (7)	7.3 (6)	
Musculoskeletal pain	3.9 (6)	7.3 (6)	
Oedema	3.2 (5)	8.5 (7)	
Hypokalaemia	3.2 (5)	7.3 (6)	
Influenza	3.2 (5)	6.1 (5)	
Fatigue	2.6 (4)	9.8 (8)	
Insomnia	1.3 (2)	9.8 (8)	
Нурохіа	1.3 (2)	7.3 (6)	

Table 15. TEAEs with an incidence of \geq 5% in either group

% (number of patients); APTT, Activated partial thromboplastin time; INR, International normalized ratio

Death occurred in 5.8% (9 of 155 patients) in the riociguat-riociguat group and in 4.9% (4 of 82 patients) in the placebo-riociguat group; a causal relationship to the study drug was ruled out for all deaths. The incidence of serious TEAEs was 40.6% (63 patients) in the riociguat-riociguat group and 45.1% (37 patients) in the placebo-riociguat group. Serious TEAEs observed in $\geq 2\%$ of all treated patients were syncope (6.5% [10 patients] in the riociguat-riociguat group, 8.5% [7 patients] in the placebo-riociguat group), right ventricular failure (5.2% [8 patients] and 4.9% [4 patients], respectively), pulmonary hypertension (3.9% [6 patients] and 6.1% [5 patients], respectively), pneumonia (3.2% [5 patients] and 3.7% [3 patients], respectively), cardiac arrest, gastrointestinal haemorrhage, catheterization cardiac (2.6% [4 patients] each, 1.2% [1 patient] each, respectively), and atrial fibrillation (1.3% [2 patients] and 3.7% [3 patients], respectively); of these, a causal relationship to the study drug could not be ruled out for syncope (2 patients and 2 patients, respectively) or pulmonary hypertension (1 patient and 0 patients, respectively), but the outcome was resolved/disappeared for both TEAEs.

The incidence of TEAEs leading to treatment discontinuation was 1.9% (3 patients) in the riociguat-riociguat group and 6.1% (5 patients) in the placebo-riociguat group, and a TEAE that was reported by ≥ 2 patients and resulted in treatment discontinuation in either group was pulmonary hypertension (1.3% [2 patients] and 1.2% [1 patient], respectively).

4.(iii).A.(5).2) Results in Japanese population

All 14 Japanese patients (9 patients in the riociguat group, 5 patients in the placebo group) who completed Study 11348 proceeded to this study and were subjected to the interim evaluation; the study was discontinued in 2 patients (0 patients and 2 patients, respectively) because of adverse events in 1 patient and consent withdrawal in 1 patient.

The mean treatment duration with riociguat (excluding the period in Study 11348) in this study in the Japanese population was 655.4 days.

As regards efficacy, the change in 6MWD from baseline (at the initiation of the study drug administration in Study 11348) to Week 12 was 72.0 ± 58.3 m (mean \pm SD) in the riociguat-riociguat group (N = 7) and 80.8 ± 26.0 m in the placebo-riociguat group (N = 4), and the change from baseline to 12 months was 60.6 ± 51.2 m (N = 9) and 70.0 ± 47.4 m (N = 3), respectively.

As regards safety, the incidence of TEAEs was 100% (9 of 9 patients) in the riociguat-riociguat group and 100% (5 of 5 patients) in the placebo-riociguat group. TEAEs reported by \geq 2 patients in either group were as shown in Table 16.

	Riociguat-riociguat group	Placebo-riociguat group
	(N = 9)	(N = 5)
Nasopharyngitis	66.7 (6)	80.0 (4)
Dizziness	33.3 (3)	40.0 (2)
Constipation	33.3 (3)	20.0 (1)
Dental caries	33.3 (3)	0 (0)
Bronchitis	22.2 (2)	20.0 (1)
Back pain	22.2 (2)	20.0 (1)
Hypotension	22.2 (2)	20.0 (1)
Diarrhoea	22.2 (2)	20.0 (1)
Dyspepsia	22.2 (2)	0 (0)
Face oedema	22.2 (2)	0 (0)
Contusion	22.2 (2)	0 (0)
Decreased appetite	22.2 (2)	0 (0)
Musculoskeletal pain	22.2 (2)	0 (0)
Musculoskeletal stiffness	22.2 (2)	0 (0)
Epistaxis	22.2 (2)	0 (0)
Нурохіа	0 (0)	40.0 (2)

Table 16. TEAEs reported by ≥2 patients in either group (Japanese population)

% (number of patients)

No death occurred. Serious TEAEs reported by 2 patients in the riociguat-riociguat group (bile duct stone; dizziness) and by 2 patients in the placebo-riociguat group (Prinzmetal angina; right ventricular failure, angiogram pulmonary, syncope, angioplasty). Among these, a causal relationship to the study drug could not be ruled out for dizziness or Prinzmetal angina; the outcome of these events was resolved/disappeared and improved, respectively.

A TEAE leading to treatment discontinuation was reported by 1 patient in the placebo-riociguat group (Prinzmetal angina).

4.(iii).A.(6) Global phase III study in patients with PAH (Study 12934: Attached document 5.3.5.4.1; Study period, to be a study)

A randomized, double-blind, parallel group, comparative study was conducted at 124 centers in 30 countries including Japan to evaluate the efficacy and safety of riociguat in patients with PAH (target sample size, 438 patients in total: 250 patients in the dose titration group; 125 patients in the placebo group; and 63 patients in the 1.5 mg TID group).

Of the 12-week period of study drug administration, the first 8 weeks was defined as the dose titration period. Administration was to be started at the dose of 1.0 mg TID (interval of approximately 6-8 hours), after which the dose was to be adjusted every 2 weeks according to criteria similar to those in Study 11348. The maintenance dose was to be determined within the range of 0.5 to 2.5 mg TID in the dose titration group and within the range of 0.5 to 1.5 mg TID group. In the placebo group, the dose was to be adjusted in a similar manner to determine the maintenance dose.

The primary treatment period was defined as the 4 weeks after the end of the dose titration period, in which riociguat was administered at the same dose as at the end of the dose titration period. Dose reduction for safety reasons was permitted.

The main inclusion criteria were patients aged 18 to 80 years with PAH who had 6MWD of 150 to 450 m at the screening and at baseline (at the initiation of treatment period), PVR of >300 dyn·sec·cm⁻⁵, and PAPmean of >25 mmHg. In this study, patients were stratified by use/non-use of PAH drugs (ERA, prostacyclin derivatives), and randomly assigned in a ratio of 4:2:1 to the dose titration group, the placebo group, or the 1.5 mg TID group in each country/region.

Concomitant use with oral anticoagulants, diuretics, digitalis, calcium channel blockers, oxygen therapy, etc., was permitted. Anticoagulants were to be started from at least 30 days prior to the study drug administration, and the dose of diuretic was to be stabilized for at least 30 days prior to the study drug administration. Among PAH drugs (e.g., ERA, prostacyclin derivatives, PDE-5 inhibitors), ERA and prostacyclin derivatives (except intravenous preparations) were allowed to be concomitantly administered if there had been no change in the type of drug or daily dose for at least 90 days^{*} prior to the study drug administration.

4.(iii).A.(6).1) Results of the entire study

Of 445 randomized patients (254 patients in the dose titration group, 127 patients in the placebo group, 64 patients in the 1.5 mg TID group), 443 patients (254 patients, 126 patients, and 63 patients, respectively) who were treated with at least 1 dose of the study drug were included in the safety analysis population and in the ITT population. The ITT population was used for the primary efficacy analysis. Of the randomized patients, 40 patients (17 patients, 16 patients, and 7 patients, respectively) discontinued the study. The main reasons for discontinuation were adverse events in 16 patients (8 patients, 7 patients, and 1 patient, respectively) and consent withdrawal in 11 patients (6 patients, 3 patients, and 2 patients, respectively). In the ITT population at baseline, 222 patients (131 patients, 60 patients, and 31 patients, respectively) were previously treated with PAH drugs, while 221 patients (123 patients, 66 patients, and 32 patients, respectively) were not; 194 patients (113 patients, 54 patients, and 27 patients, respectively) were concomitantly treated with ERA and 31 patients (20 patients by country/region was 40 patients (24 patients, 11 patients, and 5 patients, respectively) in North America, 207 patients (23 patients, 59 patients, and 30 patients, respectively) in South America, 207 patients (118 patients, 59 patients, and 30 patients,

^{*} Oral beraprost sodium preparation approved in Japan was allowed to be concomitantly administered if the drug had been continuously used at the daily dose of $\leq 180 \ \mu g$ since $\geq 270 \ days$ prior to the study drug administration.

respectively) in Europe, 77 patients (43 patients, 24 patients, and 10 patients, respectively) in China, and 75 patients (46 patients, 18 patients, and 11 patients, respectively) in Asia/Oceania.

The daily dose of riociguat at Week 12 (at the last visit) was 1.5 mg/day in 1.7% (4 of 236 patients), 3.0 mg/day in 2.5% (6 of 236 patients), 4.5 mg/day in 5.9% (14 of 236 patients), 6.0 mg/day in 15.3% (36 of 236 patients), and 7.5 mg/day in 74.6% (176 of 236 patients) in the dose titration group; and 3.0 mg/day in 5.3% (3 of 57 patients) and 4.5 mg/day in 94.7% (54 of 57 patients) in the 1.5 mg TID group.

As regards efficacy, changes in 6MWD from baseline to Week 12, the primary endpoint, were as summarized in Table 17, showing a significant difference between the dose titration group and the placebo group (P < 0.0001; Wilcoxon test stratified by use/non-use of concomitant PAH drugs and by country/region).

Table 17. Change in 6MWD (m) from baseline to Week	12 (entire po	pulation, ITT)
		D1 1	1.7

	Dose titration Placebo		1.5 mg TID
	group	group	group
	(N = 254)	(N = 126)	(N = 63)
Baseline			
Mean (SD)	361.4 (67.7)	367.8 (74.6)	363.2 (66.6)
Median (minimum-maximum)	374.5 (160-468)	391.0 (150-450)	385.0 (158-448)
Change from baseline to Week 12 ^a			
Mean (SD)	29.6 (65.8)	-5.6 (85.5)	31.1 (79.3)
Median (minimum-maximum)	30.0 (-430 to 279)	8.5 (-400 to 204)	32.0 (-415 to 190)
Between-group comparison of change	Dose titration group – placebo group		
Difference of least squares mean [95% CI] ^b	^b 35.78 [20.06-51.51]		
<i>P</i> value (analysis of covariance ^b)	< 0.0001		
<i>P</i> value (stratified Wilcoxon test ^c)	< 0.0001		

a: The last measured value up to Week 12 in subjects who completed or discontinued the study

In subjects who did not make a visit at discontinuation because of death or clinical aggravation, or did not have 6MWD measured at the visit at discontinuation, missing values were imputed by the worst value (0 m).

b: Analysis of covariance using baseline values as the covariate and the treatment group, country/region, and use/non-use of concomitant PAH drugs as the main effects

c: Wilcoxon test stratified by use/non-use of concomitant PAH drugs and by country/region

Since the results of Shapiro-Wilk test for the normality of residual in analysis of covariance were statistically significant (P = 0.0001), the *P* value obtained by the stratified Wilcoxon test was handled as the results of the formal significance test according to the pre-determined rule.

Changes in PVR from baseline to Week 12, the secondary endpoint, were as shown in Table 18.

	Dose titration group	Placebo group	1.5 mg TID group
	(N = 232)	(N = 107)	(N = 58)
Baseline			
Mean (SD)	790.96 (452.60)	834.06 (476.71)	847.81 (548.17)
Median (minimum-maximum)	685.24 (241.5-2613.3)	740.00 (286.1-2545.5)	729.72 (258.1-3617.4)
Change from baseline to Week 12 ^a			
Mean (SD)	-223.29 (260.09)	-8.89 (316.57)	-167.79 (320.22)
Median (minimum-maximum)	-182.95 (-1297.8 to	-28.56 (-885.7 to	-147.12 (-1092.4 to
	712.0)	1434.0)	975.5)
Between-group comparison of change ^b	Dose titration grou	ıp – placebo group	
Difference of least squares mean [95% CI] ^c	-225.72 [-281]		
<i>P</i> value (analysis of covariance ^c)	< 0.0001		
<i>P</i> value (stratified Wilcoxon test ^d)	< 0.	0001	

a: The last measured value after baseline measurement

b: Only if significant difference was observed in the primary endpoint 6MWD, a significance test on the secondary endpoint was to be conducted.

c: Analysis of covariance using baseline values as the covariate and the treatment group, country/region, and use/non-use of concomitant PAH drugs as the main effects

d: Wilcoxon test stratified by use/non-use of concomitant PAH drugs and by country/region

Since the results of Shapiro-Wilk test for the normality of residual in analysis of covariance were statistically significant (P = 0.0001), the *P* value obtained by the stratified Wilcoxon test was handled as the results of the formal significance test according to the pre-determined rule.

As regards safety, the incidence of TEAEs was 89.4% (227 of 254 patients) in the dose titration group, 85.7% (108 of 126 patients) in the placebo group, and 92.1% (58 of 63 patients) in the 1.5 mg TID group. TEAEs with an incidence of \geq 5% in any group were as shown in Table 19.

	Dose titration group $(N = 254)$	Placebo group (N = 126)	1.5 mg TID group (N = 63)
Headache	27.2 (69)	19.8 (25)	31.7 (20)
Dyspepsia	18.9 (48)	7.9 (10)	12.7 (8)
Oedema peripheral	17.3 (44)	11.1 (14)	22.2 (14)
Nausea	15.7 (40)	12.7 (16)	15.9 (10)
Dizziness	15.7 (40)	11.9 (15)	23.8 (15)
Diarrhoea	13.8 (35)	10.3 (13)	9.5 (6)
Nasopharyngitis	10.2 (26)	11.1 (14)	9.5 (6)
Vomiting	10.2 (26)	8.7 (11)	11.1 (7)
Hypotension	9.8 (25)	2.4 (3)	3.2 (2)
Anaemia	8.3 (21)	2.4 (3)	1.6(1)
Palpitations	7.9 (20)	4.8 (6)	7.9 (5)
Chest pain	7.1 (18)	8.7 (11)	6.3 (4)
Dyspnoea	6.3 (16)	11.1 (14)	6.3 (4)
Gastrooesophageal reflux disease	5.5 (14)	3.2 (4)	6.3 (4)
Cough	4.7 (12)	10.3 (13)	4.8 (3)
Nasal congestion	4.3 (11)	2.4 (3)	6.3 (4)
Tachycardia	3.5 (9)	5.6 (7)	0 (0)
Pyrexia	3.1 (8)	3.2 (4)	9.5 (6)
Fatigue	2.8 (7)	6.3 (8)	0 (0)
Chest discomfort	2.4 (6)	8.7 (11)	6.3 (4)
Flushing	2.0 (5)	5.6 (7)	3.2 (2)
Gastritis	1.6 (4)	0 (0)	6.3 (4)

Table 19. TEAEs with an incidence of $\geq 5\%$ in any group

% (number of patients with the event)

Death occurred in 0.8% (2 of 254 patients) in the dose titration group (sepsis and haemoptysis in 1 patient each), in 2.4% (3 of 126 patients) in the placebo group (pulmonary arterial hypertension in 1 patient, anxiety in 1 patient, respiratory failure and circulatory collapse in 1 patient), and in 1.6% (1 of 63 patients) in the 1.5 mg TID group (right ventricular failure and pulmonary arterial hypertension in 1 patient). A causal relationship to the study drug was ruled out for all deaths. The incidence of serious TEAEs was 11.4% (29 patients) in the dose titration group, 18.3% (23 patients) in the placebo group, and 17.5% (11 patients) in the 1.5 mg TID group. TEAEs reported by ≥ 2 patients in any group were as follows: syncope (1.2% [3 patients] in the dose titration group, 4.0% [5 patients] in the placebo group, 0% [0 patients] in the 1.5 mg TID group); right ventricular failure (0.8% [2 patients], 0.8% [1 patient], and 4.8% [3 patients], respectively); chest pain (0.8% [2 patients], 0.8% [1 patient], and 0% [0 patients], respectively); pneumonia (0.8% [2 patients], and 0% [0 patients], and 1.6% [1 patient], respectively); PAH (0.4% [1 patient], 1.6% [2 patients], and 1.6% [1 patient], respectively); and renal failure acute and haemoptysis (0.8% [2 patients], 0% [0 patients], and 0% [0 patients] each, respectively). Of these, a causal relationship to the study drug could not be ruled out for syncope (3 patients, 1 patient, and 0 patients, respectively), PAH (0 patients, 1 patient, and 0 patients, respectively), or renal failure acute (1 patient, 0 patients, and 0 patients, respectively), but the outcome was resolved/disappeared in all of them.

The incidence of TEAEs leading to treatment discontinuation was 3.1% (8 patients) in the dose titration group, 7.1% (9 patients) in the placebo group, and 1.6% (1 patient) in the 1.5 mg TID group. No TEAE reported by ≥ 2 patients in any group resulted in treatment discontinuation.

4.(iii).A.(6).2) Results in Japanese population

At 15 centers in Japan where the study was conducted, 27 Japanese patients were randomized into the treatment groups (16 patients in the dose titration group, 8 patients in the placebo group, 3 patients in the 1.5 mg TID group), of whom 26 patients (16 patients, 7 patients, and 3 patients, respectively) received at least 1 dose of the study drug. Therefore, these 26 patients were included in the safety analysis population and in the ITT population. Of the randomized patients, 4 patients (1 patient, 2 patients, and 1 patient, respectively) discontinued the study. The reasons for discontinuation were lack of efficacy in 1 patient (0 patients, 1 patient, and 0 patients, respectively), non-compliance in 1 patient (1 patient, 0 patients, and 0 patients, respectively), protocol deviation in 1 patient (0 patients, 1 patient, and 0 patients, respectively), and consent withdrawal in 1 patient (0 patients, 0 patients, and 1 patient, respectively). At baseline, PAH drugs had been administered to 18 patients (11 patients, 4 patients, and 3 patients, respectively) but not to 8 patients (5 patients, 3 patients, and 0 patients, respectively); ERA had been concomitantly administered to 13 patients (7 patients, 3 patients, and 3 patients, respectively); and prostacyclin derivatives to 7 patients (5 patients, 2 patients, and 0 patients, respectively).

The daily dose of riociguat in Week 12 (at the last visit) was 1.5 mg/day in 13.3% (2 of 16 patients), 4.5 mg/day in 13.3% (2 of 16 patients), 6.0 mg/day in 13.3% (2 of 16 patients), and 7.5 mg/day in 60% (9 of 16 patients) in the dose titration group; and 4.5 mg/day in 100% (2 of 2 patients) in the 1.5 mg TID group.

As regards efficacy, the changes in 6MWD and PVR from baseline to Week 12 (the last visit) in the Japanese population were as shown in Tables 20 and 21, respectively.

	Dose titration group (N = 16)	Placebo group $(N = 7)$	1.5 mg TID group (N = 3)
Baseline			
Mean (SD)	345.8 (64.2)	346.0 (69.1)	390.7 (85.6)
Median (minimum-maximum)	346.5 (217-446)	370.0 (214-402)	435.0 (292-445)
Change from baseline to Week 12 ^a			
Mean (SD)	21.4 (35.7)	40.1 (49.4)	0.3 (4.6)
Median (minimum-maximum)	23.0 (-71 to 78)	32.0 (-30 to 106)	3.0 (-5 to 3)

Table 20.	Change in 6M	VD (m) from	n baseline to	Week 12	(Japanese p	opulation, ITT)
-----------	--------------	-------------	---------------	---------	-------------	-----------------

a: The last measured value up to Week 12 in subjects who completed or discontinued the study In subjects who did not make a visit at discontinuation because of death or clinical aggravation, or did not have 6MWD measured at the visit at discontinuation, missing values were imputed by the worst value (0 m).

Table 21. Changes in PVR (dvn·sec·cm ⁻⁵) fro	m baseline to Week 12	(Japanese pop	oulation. ITT)
--	-----------------------	---------------	----------------

	Dose titration group	Placebo group	1.5 mg TID group
	(N = 16)	(N = 7)	(N = 3)
Baseline			
Mean (SD)	618.93 (177.69)	874.34 (437.58)	692.34 (248.67)
Median (minimum-maximum)	588.81 (401.5-975.6)	936.76 (337.3-1589.2)	666.67 (457.5-952.9)
Change from baseline to Week 12 ^a			
Mean (SD)	-160.55 (161.74)	-73.94 (163.13)	-134.13 (119.42)
Median (minimum-maximum)	-163.26 (-451.5 to	-125.35 (-315.3 to	-82.49 (-270.7 to -49.2)
	101.4)	166.7)	

a: The last measured value after baseline measurement

As regards safety, the incidence of TEAEs was 87.5% (14 of 16 patients) in the dose titration group, 71.4% (5 of 7 patients) in the placebo group, and 100% (3 of 3 patients) in the 1.5 mg TID group. TEAEs reported by ≥ 2 patients in any group were as shown in Table 22.

b			
	Dose titration group	Placebo group	1.5 mg TID group
	(N = 16)	(N = 7)	(N = 3)
Nasopharyngitis	25.0 (4)	14.3 (1)	0 (0)
Nausea	18.8 (3)	0 (0)	0 (0)
Headache	12.5 (2)	14.3 (1)	66.7 (2)
Palpitations	12.5 (2)	14.3 (1)	0 (0)
Anaemia	12.5 (2)	0 (0)	0 (0)
Hypotension	12.5 (2)	0 (0)	0 (0)
Chest discomfort	0 (0)	14.3 (1)	66.7 (2)

Table 22. TEAEs reported by ≥ 2 patients in any group (Japanese population)

% (number of patients with the event)

No death occurred. Serious TEAEs were reported by 2 patients in the dose titration group (cardiomegaly, dizziness), in 1 patient in the placebo group (syncope), and in 1 patient in the 1.5 mg TID group (gastritis). Of these, dizziness in the dose titration group and gastritis in the 1.5 mg TID group were considered related to the study drug, but the outcome was resolved/disappeared for both TEAEs.

There was no TEAE leading to treatment discontinuation.

4.(iii).A.(7) Global long-term extension study in patients with PAH (Study 12935: Attached document 5.3.5.4.2, 5.3.5.4.12; Study period, to ongoing; data cut-off,

An open-label, uncontrolled study in patients who had completed the 12-week administration in Study 12934 was conducted at 97 centers in 27 countries including Japan to evaluate the efficacy and safety of riociguat in patients with PAH.

During the 8-week dose titration period following the end of Study 12934, the dose of riociguat was determined depending on the treatment group assigned in Study 12934 as follows. During the primary treatment period, it was allowed to adjust the dose within the range of 0.5 to 2.5 mg TID at the discretion of the investigator/subinvestigator regardless of the treatment group in Study 12934, by taking account of the blood pressure of patients, expected adverse drug reactions, and progression of PAH.

- Dose titration group: the same dose as in Study 12934
- Placebo group: the dose was to be determined in a similar manner as in the dose titration period of Study 12934.
- 1.5 mg TID group: if the dose at the end of Study 12934 was 1.5 mg TID, the treatment was to be started at 1.5 mg TID, and the dose was to be determined in a similar manner as in the dose titration period of Study 12934; if the dose at the end of Study 12934 was 1.0 or 0.5 mg TID, dose reduction was allowed while no increase was allowed.

The main inclusion criterion was patients who completed 12-week administration in Study 12934. Concomitant use of NO donors and PDE-5 inhibitors was prohibited throughout the study. Concomitant use of ERA and prostacyclin derivatives was permitted during the primary treatment period in patients who did not use these drugs in Study 12934. In patients who had been concomitantly treated with these drugs from the time of enrollment in Study 12934, the dose and the type of drug were allowed to be changed.

4.(iii).A.(7).1) Results of the entire study

Of 405 patients (237 patients in the dose titration group, 111 patients in the placebo group, 57 patients in the 1.5 mg group) who completed Study 12934, a total of 396 patients (231 patients, 109 patients, and 56 patients, respectively) proceeded to this study, all of whom were subjected to the interim evaluation; the study was discontinued in 72 patients (43 patients, 21 patients, 8 patients), with the main reasons being adverse events in 33 patients (21 patients, 8 patients) and death in 19 patients (10 patients, 6 patients, 3 patients).

The mean treatment duration (excluding the period in Study 12934) in this study was 662.7 days.

As regards efficacy, the change in 6MWD from baseline (at the initiation of the study drug administration in Study 12934) to Week 12 was 52.3 ± 60.7 m (mean \pm SD) in the dose titration group (N = 218), 51.9 ± 66.7 m in the placebo-riociguat group (N = 103), and 55.4 ± 67.1 m in the 1.5 mg TID-dose titration group (N = 54), and the change from baseline to 12 months was 52.7 ± 70.1 m in the dose titration group (N = 192), 45.7 ± 75.9 m in the placebo-riociguat group (N = 85), and 55.9 ± 87.5 m in the 1.5 mg TID-dose titration group (N = 50).

As regards safety, the incidence of TEAEs was 96.1% (222 of 231 patients) in the dose titration group, 98.2% (107 of 109 patients) in the placebo-riociguat group, and 98.2% (55 of 56 patients) in the 1.5 mg TID-dose titration group. TEAEs with an incidence of \geq 10% in any group were as shown in Table 23.

	Dese tituetien energy	Placebo-riociguat	1.5 mg TID-dose
	Dose titration group	group	titration group
	(N = 251)	(N = 109)	(n = 56)
Nasopharyngitis	23.8 (55)	24.8 (27)	23.2 (13)
Dizziness	22.9 (53)	25.7 (28)	21.4 (12)
Cough	22.5 (52)	18.3 (20)	10.7 (6)
Oedema peripheral	21.6 (50)	22.9 (25)	25.0 (14)
Nausea	17.7 (41)	17.4 (19)	10.7 (6)
Headache	14.3 (33)	24.8 (27)	14.3 (8)
Diarrhoea	13.9 (32)	24.8 (27)	19.6 (11)
Vomiting	13.0 (30)	17.4 (19)	14.3 (8)
Upper respiratory tract infection	12.6 (29)	15.6 (17)	14.3 (8)
Dyspepsia	12.6 (29)	9.2 (10)	14.3 (8)
Dyspnoea	12.1 (28)	11.0 (12)	19.6 (11)
Back pain	12.1 (28)	7.3 (8)	3.6 (2)
Chest pain	11.3 (26)	12.8 (14)	10.7 (6)
Pulmonary arterial hypertension	10.4 (24)	9.2 (10)	12.5 (7)
Hypotension	10.4 (24)	6.4 (7)	10.7 (6)
Anaemia	10.0 (23)	11.9 (13)	8.9 (5)
Epistaxis	9.5 (22)	11.0 (12)	17.9 (10)
Bronchitis	8.7 (20)	11.9 (13)	12.5 (7)
Respiratory tract infection	8.7 (20)	9.2 (10)	7.1 (4)
Fatigue	7.4 (17)	11.0 (12)	7.1 (4)
Hypokalaemia	7.4 (17)	9.2 (10)	14.3 (8)
Gastroenteritis	6.1 (14)	4.6 (5)	10.7 (6)
Haemoptysis	5.6 (13)	6.4 (7)	3.6 (2)
Gastrooesophageal reflux disease	4.8 (11)	10.1 (11)	5.4 (3)
Abdominal discomfort	4.3 (10)	5.5 (6)	10.7 (6)
Urinary tract infection	3.9 (9)	9.2 (10)	10.7 (6)
Influenza	3.9 (9)	3.7 (4)	10.7 (6)
Pneumonia	2.6 (6)	3.7 (4)	10.7 (6)

Table 23. TEAEs with an incidence of ≥10% in any group

% (number of patients with the event)

Death occurred in 6.1% (14 of 231 patients) in the dose titration group, in 6.4% (7 of 109 patients) in the placebo-riociguat group, and in 5.4% (3 of 56 patients) in the 1.5 mg TID-dose titration group. A causal relationship to the study drug could not be ruled out for death in 2 patients in the dose titration group (pulmonary haemorrhage, pneumonia; PAH). The patient with pulmonary haemorrhage/pneumonia developed acute pulmonary haemorrhage and was hospitalized at Day 715 after treatment initiation. The patient received oxygen and cyclocapron inhalation, but developed pneumonia on Day 717 and died on Day 718. The patient with PAH showed aggravation of PAH at Day 407 after treatment initiation and was treated with other PAH drugs, but died on Day 418. The incidence of serious TEAEs was 49.4% (114 patients) in the dose titration group, 55.0% (60 patients) in the placebo-riociguat group, and 53.6% (30 patients) in the 1.5 mg TID-dose titration group. TEAEs with an incidence of $\geq 2\%$ in the entire study population were as follows: PAH (8.2% [19 patients] in the dose titration group, 5.5% [6 patients] in the placebo-riociguat group, 12.5% [7 patients] in the 1.5 mg TID-dose titration group); syncope (6.5% [15 patients], 9.2% [10 patients], and 5.4% [3 patients], respectively); right ventricular failure (6.9% [16 patients], 4.6% [5 patients], and 7.1% [4 patients], respectively); catheterization cardiac (5.2% [12 patients], 2.8% [3 patients], and 5.4% [3 patients], respectively); pulmonary hypertension (3.5% [8 patients], 1.8% [2 patients], and 3.6% [2 patients], respectively); and anaemia (1.7% [4 patients], 4.6% [5 patients], and 0% [0 patients], respectively). Of these, a causal relationship to the study drug could not be ruled out for syncope (6 patients, 3 patients, and 0 patients, respectively) or PAH (1 patient, 0 patients, and 1 patient, respectively). The outcome of syncope was resolved/disappeared in all patients, whereas the outcome of PAH was death in the dose titration group and not resolved/not disappeared in the 1.5 mg TID-dose titration group.

The incidence of TEAEs leading to treatment discontinuation was 10.8% (25 patients) in the dose titration group, 6.4% (7 patients) in the placebo-riociguat group, and 7.1% (4 patients) in the 1.5 mg TID-dose titration group; TEAEs reported by \geq 2 patients in any group were PAH (1.7% [4 patients], 0% [0 patients], 3.6% [2 patients]), pulmonary hypertension (1.3% [3 patients], 0.9% [1 patient], 0% [0 patients]), and death and hypoxia (0.9% [2 patients], 0% [0 patients], 0% [0 patients]), 0% [0 patients]).

4.(iii).A.(7).2) Results in Japanese population

Of 23 Japanese patients (15 patients in the dose titration group, 6 patients in the placebo group, 2 patients in the 1.5 mg TID group) who completed Study 12934, a total of 21 patients (14 patients, 5 patients, and 2 patients, respectively) proceeded to this study, all of whom were subjected to interim evaluation; the study was discontinued in 7 patients (4 patients, 2 patients, 1 patient), with the reasons for discontinuation being adverse events in 3 patients (1 patient, 1 patient), 1 patient, 1 patient, 0 patients), lack of efficacy, protocol deviation, and consent withdrawal in 1 patient each (1 patient, 0 patients, and 0 patients each, respectively).

The mean treatment duration (excluding the period in Study 12934) of the Japanese population in this study was 629.8 days.

As regards efficacy, the change in 6MWD from baseline (at the initiation of the study drug administration in Study 12934) to Week 12 was 44.3 ± 27.5 m (mean \pm SD) in the dose titration group (N = 12), 120.5 \pm 122.9 m in the placebo-riociguat group (N = 4), and 32.5 ± 31.8 m in the 1.5 mg TID-dose titration group (N = 2), and the change at 12 months from baseline was 45.2 ± 39.0 m in the dose titration group (N = 13), 71.7 ± 60.9 m in the placebo-riociguat group (N = 3), and 50.0 ± 49.5 m in the 1.5 mg TID-dose titration group (N = 2).

As regards safety, the incidence of TEAEs was 100% (14 of 14 patients) in the dose titration group, 100% (5 of 5 patients) in the placebo-riociguat group, and 100% (2 of 2 patients) in the 1.5 mg TID-dose titration group. TEAEs reported by \geq 2 patients in any group were as shown in Table 24.

	Dose titration group (N = 14)	Placebo-riociguat group (N = 5)	1.5 mg TID-dose titration group (N = 2)
Nasopharyngitis	64.3 (9)	60.0 (3)	50.0 (1)
Dizziness	28.6 (4)	0 (0)	0 (0)
Diarrhoea	21.4 (3)	40.0 (2)	50.0 (1)
Insomnia	21.4 (3)	20.0 (1)	0 (0)
Нурохіа	21.4 (3)	20.0 (1)	0 (0)
Anaemia	21.4 (3)	0 (0)	0 (0)
Iron deficiency anaemia	21.4 (3)	0 (0)	0 (0)
Skin ulcer	21.4 (3)	0 (0)	0 (0)
Right ventricular failure	14.3 (2)	20.0 (1)	0 (0)
Nausea	14.3 (2)	20.0 (1)	0 (0)
Pyrexia	14.3 (2)	20.0 (1)	0 (0)
Pulmonary arterial hypertension	14.3 (2)	0 (0)	50.0 (1)
Palpitations	14.3 (2)	0 (0)	0 (0)
Constipation	14.3 (2)	0 (0)	0 (0)
Oedema	14.3 (2)	0 (0)	0 (0)
Catheterisation cardiac	14.3 (2)	0 (0)	0 (0)
Rash	14.3 (2)	0 (0)	0 (0)
Influenza	7.1 (1)	0 (0)	100 (2)
Gastrooesophageal reflux disease	0 (0)	40.0 (2)	0 (0)
Weight increased	0 (0)	0 (0)	100 (2)
Systemic lupus erythematosus	0 (0)	0 (0)	100 (2)

Table 24. TEAEs reported by ≥ 2 patients in any group (Japanese population)

% (number of patients)

Death occurred in 1 patient in the placebo group (sudden cardiac death). A causal relationship to the study drug was ruled out for the death. The incidence of serious TEAEs was 78.6% (11 of 14 patients) in the dose titration group, 60.0 (3 of 5 patients) in the placebo-riociguat group, and 50.0% (1 of 2 patients) in the 1.5 mg TID-dose titration group. The serious TEAE reported by ≥ 2 patients in any group was catheterization cardiac (14.3% [2 of 14 patients] in the dose titration group, 0% [0 of 5 patients] in the placebo-riociguat group, and 0% [0 of 2 patients] in the 1.5 mg TID-dose titration group, and 0% [0 of 2 patients] in the 1.5 mg TID-dose titration group. A causal relationship to the study drug was ruled out for all events.

TEAE leading to treatment discontinuation was reported by 1 patient in the dose titration group (hypoxia), by 1 patient in the placebo-riociguat group (pericardial effusion), and by 1 patient in the 1.5 mg TID-dose titration group (PAH).

4.(iii).B Outline of the review by PMDA

As the evaluation data for the application, the data of studies on patients with PAH were submitted in addition to the data of studies on patients with CTEPH, the proposed indication of riociguat. In the review, the efficacy of riociguat was evaluated mainly based on the results of the studies on patients with CTEPH, while the safety was evaluated based on the study results in patients with CTEPH and on those in patients with PAH.

4.(iii).B.(1) Clinical positioning of riociguat

PMDA asked the applicant to explain the choice between riociguat and PEA or percutaneous transluminal pulmonary artery dilatation (balloon pulmonary angioplasty [BPA]) and the choice between riociguat and other medical therapies (e.g., anticoagulant therapy, oxygen inhalation, cardiotonic agents, diuresis, pulmonary vasodilators), based on the guidelines and treatment algorithms established in Japan and other countries, and to explain the clinical positioning of riociguat in CTEPH treatment.
The applicant responded as follows:

The treatment algorithm for CTEPH stipulated in the Guidelines for Treatment of Pulmonary Hypertension (JCS 2012) (Guidelines for the Diagnosis and Treatment of Cardiovascular Diseases [2011 Joint Working Group Report]), Japanese guideline, recommends the following procedures: first make a definitive diagnosis and evaluate the severity accurately; then start anticoagulant therapy, which is expected to prevent disease progression; and perform, as necessary, inferior vena cava filter placement, measures against hypoxemia and right heart failure; after which consider the necessity and appropriateness of PEA. PEA is considered to be wellindicated for proximal CTEPH with the organized thrombus of which the proximal end is located in the main pulmonary artery to proximal part of the segmental arteries. However, whether indication of PEA is feasible or not depends on the experience of the operating facility; PEA is difficult in patients with a markedly high PVR incompatible with the amount of the thrombus at the central side or in patients with peripheral CTEPH localized to segmental or subsegmental arteries, and is unlikely to be indicated for elderly patients or patients with disorders in other organs. For patients in whom PEA is deemed inappropriate, BPA is recommended as an alternative method to remove the physical stenosis and obstruction of pulmonary arteries by the Guidelines for Treatment of Pulmonary Hypertension (JCS 2012). Since it is suggested that BPA is more effective than drug therapies, BPA is performed with an increasing frequency in Japan. However, because pulmonary oedema is frequently observed after BPA and fatal cases have been reported as well, future investigations regarding the standardization of the therapeutic procedure for BPA are required. For patients for whom neither PEA nor BPA is indicated and for patients with postoperative persistent pulmonary hypertension, consideration is given to vasodilation therapy with PAH drugs in addition to medical treatment. However, there are currently no pulmonary vasodilators for CTEPH approved in Japan, and conventional vasodilators are used without confirmation of the efficacy. ESC/ERS guideline (2009) (Galie N et al., Eur Heart J. 2009;30(20):2493-2537) and ACCF/AHA 2009 expert consensus (McLaughlin VV et al., Circulation. 2009;119:2250-2294), which are referred to regarding CTEPH therapy in Europe and the US, recommend the same therapeutic procedures as the Japanese guideline, except for no BPA therapy mentioned in them.

Riociguat caused improvements in efficacy parameters such as exercise tolerance and hemodynamics in patients with PEA-ineligible or postoperative persistent or recurrent CTEPH, and demonstrated acceptable safety profile. Based on the above, the applicant considers that riociguat can be qualified as the first-line drug for the medical treatment for patients with PEA-ineligible or postoperative persistent or recurrent CTEPH in and out of Japan.

PMDA considers as follows:

PEA has been performed for CTEPH, and the Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thrombosis and Deep Vein Thrombosis (JCS 2009) in Japan (Guidelines for the Diagnosis and Treatment of Cardiovascular Diseases, [2008 report of Joint Working Group]) reported that PEA is effective for proximal CTEPH with the lesion localized in the main pulmonary artery to interlobar arteries and proximal part of the segmental arteries, with the postoperative survival rate being 75% after 6 years and 86% after 5 years. However, PEA has some drawbacks: prognosis is poor in patients with postoperative persistent pulmonary hypertension; and no effective operation can be performed for distal CTEPH with obstructive lesion localized mainly in the distal part of segmental arteries to subsegmental arteries. In recent years, effectiveness of BPA in peripheral thrombus was reported (Guidelines for Treatment of Pulmonary Hypertension [JCS 2012]). However, taking account of the fact that the report is based on the experiences in a limited number of specialized facilities, the difficulty of judgment of indication of BPA, and the difficulty of the operating procedure, it is hard to say that BPA is a well-established and widely adopted treatment method at the current moment.

In light of the facts that currently there is no drug indicated for CTEPH either in Japan or elsewhere and that PAH drugs are used off-label in actual clinical practice, it is of significance to supply to clinical settings riociguat, which has shown efficacy, including improved exercise tolerance and hemodynamics [see "4.(iii).B.(3) Efficacy"] and an acceptable safety profile [see "4.(iii).B.(4) Safety"] in patients with PEA-ineligible, or postoperative persistent or recurrent CTEPH. Also, PMDA accepts the applicant's claim that riociguat can be qualified as the first-line drug for patients with inoperable CTEPH including those with distal CTEPH and with various complications, and for postoperative persistent or recurrent pulmonary hypertension.

4.(iii).B.(2) Evaluation of global clinical studies

4.(iii).B.(2).1) Intrinsic and extrinsic ethnic factors among regions

PMDA asked the applicant to explain the similarity and dissimilarity of the intrinsic and extrinsic ethnic factors among regions that participated in Study 11348, including the similarity and dissimilarity of clinical environments related to surgical and medical treatment of CTEPH, and to explain the appropriateness of conducting Study 11348 as a global clinical study.

The applicant responded as follows:

(a) Intrinsic ethnic factors

The epidemiologic data on CTEPH in Japan and overseas are very limited. The annual incidence in foreign countries is reported to be 1.75 to 3.7 per million (Kiely D et al., *BMJ*. 2013;346:f2028), whereas in Japan, the annual incidence of CTEPH is calculated to be 0.5 to 0.8 per million from the surveillance on the patient registration based on the personal clinical questionnaire (Clinical Manual for Pulmonary Hypertension – Latest guideline aimed at radical treatment, 2012 revised edition). In foreign countries, it was reported that there is no sex difference in the incidence of CTEPH, whereas a higher incidence in women was reported in Japan (Guidelines for Treatment of Pulmonary Hypertension [JCS 2012]). Comparison of baseline characteristics (e.g., sex, age, clinical classification of CTEPH, WHO functional class) among regions that participated in Study 11348 showed that age, clinical classification of CTEPH (operated/unoperated), or PVR value showed differences in some regions such as China and South America compared with other regions. However, because of the limited number of patients studied in each region (Table 8), the observed differences in the baseline characteristics appear to be accidental. Therefore, the applicant considers that the intrinsic ethnic factors were similar as a whole among the regions, including Japan.

(b) Extrinsic ethnic factors

In the treatment of CTEPH, Guidelines for Treatment of Pulmonary Hypertension (JCS 2012) is mainly referred to in Japan, ESC/ERS guideline (2009) in Europe, and ACCF/AHA 2009 expert consensus in the US. As discussed in (1) above, the contents of guidelines in Japan and in other countries are basically the same. When Study 11348 was conducted, BPA treatment was not recommended by the then available Guidelines for Treatment of Pulmonary Hypertension (JCS 2006). Therefore, BPA was not permitted in Study 11348 and, as a result, there were no Japanese subjects who underwent BPA during Study 11348. In other regions such as China, CTEPH treatment followed the guidelines of Europe and the US and, as a result, the treatment procedure for CTEPH is basically the same among Japan, Europe, the US, and other regions. Indication for PEA was judged centrally based on established criteria at the evaluation committee consisting of surgeons skilled in PEA, and only those who were judged as ineligible for PEA were to be enrolled in Study 11348 as patients with inoperable CTEPH.

In all participating regions including Japan, Europe, and the US, there were no drugsapproved for CTEPH, and concomitant use with PAH drugs (ERA, PDE-5 inhibitors, prostacyclin derivatives) was prohibited during Study 11348. In fact, only 2 patients (1.2%) in the riociguat group were treated with a PAH drug (ERA) in Study 11348; in one of them, bosentan was started to be administered because of worsening of clinical conditions during the study.

Regarding the medical treatment (anticoagulants, cardiotonic agents, diuretics, oxygen inhalation therapy, calcium channel blockers) at the initiation of study drug administration in Study 11348, anticoagulants were used to similar extent in approximately 80% to 100% of patients in any region. Oxygen inhalation therapy was used slightly more frequently in North America (33.3% in the riociguat group, 44.4% in the placebo group) than in other regions, but in no patient in China. The cardiotonic agent (digitalis) was not used in North America, but tended to be used at a slightly higher frequency in South America (26.7% in the riociguat group, 16.7% in the placebo group) and in China (33.3% in the riociguat group, 27.3% in the placebo group). Diuretics tended to be used at a slightly lower frequency in Asia/Oceania. Calcium channel blockers did not show any significant differences in the frequency of use among the regions. As regards oxygen inhalation therapy, it was stipulated that the primary endpoint 6MWD was to be measured under the same conditions as those at baseline (use/non-use of oxygen inhalation therapy, conditions for oxygen administration, etc.) regardless of whether or not oxygen inhalation therapy was newly introduced or the conditions for the inhalation were changed during Study 11348. It should be taken into consideration that these medical treatments are not specific to CTEPH and the only anticoagulant therapy has received a class I recommendation.

Based on the above, the applicant considers that there is no clear difference either in intrinsic or extrinsic ethnic factors among participating regions that would affect the evaluation of efficacy or safety of riociguat, and therefore that it was appropriate to have conducted and evaluated Study 11348 as a global clinical study.

PMDA considers as follows:

Regarding intrinsic ethnic factors, differences in age, presence/absence of previous operation, and PVR value were observed among CTEPH patients in different regions in Study 11348. However, the differences in age, presence/absence of previous operation, and PVR value observed among regions where Study 11348 was conducted are unlikely to have affected the evaluation of efficacy or safety of riociguat in the entire study because there seems to be no ethnic difference in the pathology of CTEPH per se. As regards extrinsic ethnic factors, there were differences in the concomitant therapies other than pulmonary vasodilators (e.g., oxygen inhalation therapy, cardiotonic agent, diuretics) among some regions, and there appeared to be differences in the judgment of the indication for operation among centers. However, in the treatment of CTEPH, there was no difference between Japan and other countries that would affect the evaluation of efficacy or safety of riociguat, for the following reasons: (i) patients were allowed to be enrolled only when long-term oxygen inhalation therapy and use of diuretics had been stabilized since before the administration of the study drug, (ii) in Study 11348, indication for operation was judged centrally based on established criteria, and (iii) treatment was performed according to the almost identical guidelines both in Japan and in other countries. In addition, there are no particular problems, from a pharmacokinetic point of view, in collectively evaluating the data from the Japanese population and other populations [see "4.(ii).B.(1) Ethnic difference in the pharmacokinetics of riociguat"]. Based on the above, it is acceptable to evaluate the efficacy and safety of riociguat based on the results of the global clinical study.

4.(iii).B.(3) Efficacy

PMDA asked the applicant to explain the appropriateness of the change in 6MWD from baseline as the primary endpoint in Study 11348, based on the clinical significance of the improvement of 6MWD in patients with CTEPH.

The applicant responded as follows:

According to a study in 84 patients with inoperable CTEPH (Saouti N et al., *Respir Med.* 2009;103(7):1013-1019), 6MWD was the only factor correlated with survival among factors investigated by the multivariate analysis, and the difference of 6MWD by 50 m causes the

decrease in the hazard ratio of all deaths to 0.779 [95%CI, 0.640-0.947], based on the results of univariate analysis. These results infer that the improvement of exercise tolerance shown by 6MWD contributes to the improvement of the survival rate.

In addition, 6MWD is shown to have a highly positive correlation with WHO functional class and with survival in patients with PAH which is a disease that shows pulmonary hypertension as is the case with CTEPH and has pathology similar to that (Benza RL et al., *Circulation*. 2010;122(2):164-172). Improvement of 6MWD, a parameter for exercise tolerance that can be tested non-invasively, is a factor correlated with hemodynamics, pulmonary vascular resistance index (PVRI) in particular. The relationship between PVRI and 6MWD can be explained by the fact that improvement in PVRI increases exercise cardiac output and thereby improves exercise capacity. Thus, the improvement of exercise tolerance following the short-term treatment suggests improved pulmonary hemodynamics.

PMDA considers as follows:

Although 6MWD has been used as the primary endpoint in many clinical studies on PAH drugs approved in and out of Japan, questions have been raised about the relationship between change in 6MWD and survival rate, based on the results of the meta-analysis of 16 clinical studies on PAH (Macchina A et al., *Am Heart J.* 2007;153:1037-1047). However, it is appropriate at the current moment to use the change in 6MWD from baseline as the primary endpoint in clinical studies to evaluate the clinical effect on CTEPH as is the case with PAH, for the following reasons: (i) it is reported that 6MWD is correlated with the severity of PAH and with the life prognoses in patients with PAH (Miyamoto S et al., *Am J Respir Crit Care Med.* 2000;161(2 Pt 1):487-492), (ii) American College of Cardiology (ACC) recommends 6MWD as the primary endpoint for PAH drugs (Hoeper M et al., *J Am Coll Cardiol.* 2004;43:48S-55S), and (iii) it is suggested that both in idiopathic pulmonary arterial hypertension (IPAH) and CTEPH, pulmonary vascular remodeling is a serious contributing factor for pulmonary hypertension at their terminal stages (Moser KM et al., *Chest.* 1993;103(3):685-692.).

In Study 11348, the null hypothesis on the normality of the distribution of residual was rejected by the analysis of covariance regarding the changes of the primary endpoint 6MWD and the secondary endpoint PVR (P = 0.0001, Shapiro-Wilk test). Therefore, according to the predetermined rule, the P value obtained by the stratified Wilcoxon test, a non-parametric analysis, was to be handled as the result of the formal significance test. Therefore, 6MWD, PVR, and PVRI in Study 11348 are mainly evaluated based on the median values. The median (range) change in 6MWD from baseline to Week 16 observed in Study 11348 was 42.0 (-376 to 335) m in the riociguat group and 5.0 (-389 to 226) m in the placebo group, verifying the superiority of the riociguat group to the placebo group (P < 0.0001, Wilcoxon test stratified by country/region). The difference between the riociguat group and the placebo group exceeded 30 m, the between-group difference in the change of 6MWD assumed at the planning of the study, from which PMDA concludes that riociguat caused a clinically significant improvement in 6MWD. The efficacy of riociguat is also supported by the results of the sensitivity analysis performed separately using multiple methods for imputing missing values of the primary endpoint. Furthermore, in the longterm extension study (Study 11349), the changes in 6MWD from the initiation of study drug administration in Study 11348 to Week 12 and 12 months in Study 11349 were 61.1 ± 58.9 m (mean \pm SD) and 58.6 \pm 57.6 m, respectively, in the riociguat-riociguat group and 50.5 \pm 64.2 m and 36.8 ± 68.9 m, respectively, in the placebo-riociguat group, showing a certain persistent improvement in exercise tolerance in the long-term administration. Moreover, results of the investigation of PVRI, an additional and important endpoint in Study 11348, showed that the median (range) change from baseline to Week 16 was -306.48 (-2714.3 to 961.3) dyn·sec·cm⁻⁵·m² in the riociguat group and 32.00 (-1289.8 to 1903.1) dyn·sec·cm⁻⁵·m² in the placebo group. Improved PVRI in the riociguat group compared with the placebo group supports the efficacy of riociguat.

Based on the above, PMDA concludes that Studies 11348 and 11349 demonstrated the clinically significant efficacy of riociguat in patients with CTEPH.

4.(iii).B.(4) Safety

4.(iii).B.(4).1) Syncope

The applicant explained syncope as follows:

Syncope is a symptom frequently observed in patients with pulmonary hypertension. According to a recent study (Le RJ et al., *J Am Coll Cardiol.* 2011;58(8):863-867), 12% of patients whose PAH was newly diagnosed had a history of syncope, and syncope is an independent strong factor for poor prognosis. Since riociguat may affect syncope by the vasodilation, syncope was defined as "an adverse event of special interest" in Studies 11348 and 12934.

In the combined analysis of Studies 11348 and 12934, the incidence of TEAEs suggestive of syncope¹¹⁾ was 3.3% (16 of 490 patients) in the riociguat group and 4.7% (10 of 214 patients) in the placebo group, with 1 patient each in both groups discontinuing the study because of syncope. A half of syncope cases observed in the riociguat group and all of syncope cases in the placebo group were considered to be serious TEAEs, but the outcome was "recovered/disappeared" in all cases. No relationship was observed between syncope and exposure to riociguat or the increase/decrease of the dose of riociguat during the dose titration period. Subpopulation analysis by patient characteristics did not identify any subpopulations in which the risk of syncope was increased by riociguat administration.

Thus, results of the phase III comparative studies did not show any increases in the incidence of syncope-related events in subjects receiving riociguat compared with subjects receiving placebo. Therefore, the applicant considers that riociguat administration is not directly related with syncope and that syncope-related events are symptoms of the underlying diseases.

PMDA considers as follows:

Syncope is a symptom commonly observed in patients with pulmonary hypertension. In the combined analysis of Studies 11348 and 12934, the incidence of TEAEs suggesting syncope in the riociguat group was not higher compared with the placebo group. In addition, results of the subpopulation analysis did not identify any subpopulations with increased risk for syncope. Thus, there are no data suggesting that riociguat administration has a clear risk of syncope. However, given the mechanism of action of riociguat (vasodilating effect) and serious consequences of syncope in daily life, it is critical to raise caution against syncope. Therefore, the following measures proposed by the applicant is considered appropriate: (i) listing "syncope" in the "Other adverse reactions" section of the package insert (draft); and (ii) providing caution to take necessary measures, including discontinuation of administration, as necessary in case of syncope. Appropriateness of the caution statement regarding syncope in riociguat administration will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).2) Hypotension

The applicant explained hypotension as follows:

In the combined analysis of Studies 11348 and 12934, the incidence of TEAEs suggestive of hypotension¹²) was 10.0% (49 of 490 patients) in the riociguat group and 3.7% (8 of 214 patients) in the placebo group, and the outcome was "resolved/disappeared" in a majority of subjects in both groups. Serious TEAEs suggesting hypotension were observed in 2 patients in the riociguat

¹¹⁾TEAEs suggestive of syncope: loss of consciousness, presyncope, and syncope

¹²⁾TEAEs suggesting hypotension: blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure orthostatic decreased, blood pressure systolic decreased, blood pressure systolic inspiratory decreased, hypotension, orthostatic hypotension, and diastolic hypotension

group, and administration of the study drug was discontinued because of hypotension in 1 subject in the riociguat group. The mean duration of TEAEs suggesting hypotension was longer in the riociguat group than in the placebo group (50.971 hours and 1.057 hours, respectively). TEAEs suggesting hypotension tended to occur within 1 hour after riociguat administration, while there was no tendency of increase in the frequency of TEAEs suggesting hypotension with the increase in the dose of riociguat.

PMDA considers as follows:

In the clinical studies of riociguat, TEAEs suggesting hypotension were observed as were the cases with other pulmonary vasodilators, requiring caution against the risk of hypotension. The risk of hypotension will be controlled to a certain extent by requiring, in the package insert, to adjust the dose of riociguat according to SBP and hypotension, and to administer riociguat with caution to patients with hypotension with SBP of <95 mmHg (patients excluded in Studies 11348 and 12934) and patients with specific underlying diseases that may be aggravated by the vasodilating action of riociguat (e.g., decreased body fluid, severe left ventricle outflow tract obstruction, dysautonomia). Appropriateness of dose adjustment based on blood pressure and of administering riociguat to patients with SBP of <95 mmHg will be discussed in "4.(iii).B.(7) Dosage and administration."

4.(iii).B.(4).3) Other adverse events of concern

The applicant explained adverse events commonly observed in clinical studies, as follows: In Study 11348, TEAEs that occurred at \geq 5% higher incidence in the riociguat group compared with the placebo group were headache (24.9% in the riociguat group, 13.6% in the placebo group), dizziness (22.5% and 12.5%, respectively), dyspepsia (17.9% and 8.0%, respectively), nasopharyngitis (15.0% and 9.1%, respectively), diarrhoea (9.8% and 4.5%, respectively), vomiting (9.8% and 3.4%, respectively), and hypotension (9.2% and 3.4%, respectively). In Study 12934, TEAEs that occurred at \geq 5% higher incidence in the riociguat dose-titration group compared with the placebo group were headache (27.2% and 19.8%, respectively), dyspepsia (18.9% and 7.9%, respectively), oedema peripheral (17.3% and 11.1%, respectively), anaemia (8.3% and 2.4%, respectively), and hypotension (9.8% and 2.4%, respectively). Thus, the safety profile was largely consistent between the 2 studies.

Comparison of Study 11348 and Study 12934 showed that the incidence of oedema peripheral was higher in the placebo group (20.5%) than in the riociguat group (15.6%) in Study 11348 (patients with CTEPH), whereas the incidence was higher in the riociguat dose-titration group (17.3%) than in the placebo group (11.1%) in Study 12934 (patients with PAH). Also, the incidence of anemia in the riociguat group (3.5%) in Study 11348 was lower compared with the incidence in the dose titration group (8.3%) in Study 12934.

Thus, many of the adverse events frequently observed in clinical studies were predictable from the mechanism of action of riociguat (direct stimulation of sGC in smooth muscle cells) and common to other PAH drugs with a vasodilating action.

PMDA considers as follows:

Adverse events commonly observed following riociguat administration, such as headache, dyspepsia, oedema peripheral, dizziness, diarrhoea, vomiting, and nasopharyngitis, are known events that are also reported to occur with other pulmonary vasodilators, and are considered to occur due to the smooth muscle relaxing effect, including the vasodilating action of riociguat. Taking account of the fact that many of these adverse events related to the mechanism of action of riociguat are nonserious, the safety of riociguat is clinically acceptable. Also, the risk caused by the vasodilation can be controlled by providing, in the package insert, a caution statement to administer riociguat carefully to patients with hypotension and to patients with specific underlying diseases that may be aggravated by the vasodilating action of riociguat (e.g., decreased

body fluid, severe left ventricle outflow tract obstruction, dysautonomia).

Appropriateness of the above conclusions of PMDA and of the caution statement related to these events will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).4) Administration in patients with renal impairment

Taking account of the observations that AUC of riociguat was approximately twice as high in patients with mild to severe renal impairment as in subjects with normal renal function, and that the blood riociguat concentration is correlated with the hemodynamic effect of riociguat, PMDA asked the applicant to explain whether or not administration of riociguat in patients with renal impairment should be started at a lower dose.

The applicant responded as follows:

In Studies 11348 and 12934, only patients with $CL_{CR} \ge 30$ mL/min were to be enrolled, and the starting dose was 1.0 mg TID regardless of renal function. The disposition of subjects treated with riociguat in each study by baseline CL_{CR} was as shown in Table 25.

		Number	CL _{CR} (mL/min)			
Study	Treatment group	of	<30	≥ 30 and	\geq 50 and	>80
		patients		<50	≤ 80	
Study 11348	Riociguat group	173	1.7 (3)	13.9 (24)	47.4 (82)	32.4 (56)
Study 11349	Placebo-riociguat group	82	0 (0)	14.6 (12)	39.0 (32)	39.0 (32)
Study 12934	Dose titration group and 1.5 mg TID group	317	0.3 (1)	9.1 (29)	32.5 (103)	53.0 (168)
Study 12935	Placebo-riociguat group	109	0 (0)	5.5 (6)	26.6 (29)	63.3 (69)

Table 25. Disposition of subjects treated with riociguat in each study by baseline CL_{CR}

% (number of patients)

The number of subjects who had to decrease the dose to 0.5 mg during the period from the treatment initiation at the first visit until the second visit (2 weeks after treatment initiation) was 3 patients in Study 11348 (baseline CL_{CR} : 44 mL/min, 64 mL/min, 124 mL/min), 2 patients in Study 11349 (baseline CL_{CR} in Study 11348: 41 mL/min, 90 mL/min), 10 patients in Study 12934 (baseline CL_{CR} : <30 mL/min, 0 patients; \geq 30 and <50 mL/min, 2 patients; \geq 50 and \leq 80 mL/min, 5 patients; \geq 80 mL/min, 3 patients), and 6 patients in Study 12935 (baseline CL_{CR} : \geq 50 and \leq 80 mL/min, 3 patients; \geq 80 mL/min, 3 patients). TEAEs leading to treatment discontinuation during the period from the first to the second visit were observed in 1 patient in Study 11348 (baseline CL_{CR} , 53 mL/min), 3 patients in Study 12934 (baseline CL_{CR} : 51 mL/min, 179 mL/min, 107 mL/min), 1 patient in Study 12935 (baseline CL_{CR} , 83 mL/min), and none in Study 11349.

In Studies 11348 and 12934, there were in whole only a small number of patients in whom riociguat was discontinued or reduced because of the action of riociguat after treatment initiation, and no increased risk was suggested in patients with renal impairment even at the starting dose of 1.0 mg TID. In the clinical pharmacology study in patients with renal impairment (Study 15000), AUC of riociguat was approximately twice higher in patients with mild to severe renal impairment than in subjects with normal renal function. However, the decrease in CL_{CR} and the increase in exposure to riociguat are not necessarily correlated; the exposure level in subjects with $CL_{CR} < 30$ mL/min was not significantly different from the level in patients in other classes of renal impairment. Therefore, the applicant determined that patients with $CL_{CR} < 30$ mL/min can be treated at the starting dose of 1.0 mg TID, as with patients with CL_{CR} of ≥ 30 and < 80 mL/min.

On the other hand, combined analysis of Studies 11348 and 12934 throughout their entire period showed that the incidence of TEAE suggestive of hypotension tended to increase with the

decrease in renal function in the riociguat group compared with the placebo group ($CL_{CR} < 30$) mL/min, 25% [1 of 4 patients] in the riociguat group, 0% [0 of 1 patient] in the placebo group; CL_{CR} ≥30 and <50 mL/min, 15.8% [9 of 57 patients], 0% [0 of 24 patients], respectively; CL_{CR} ≥50 and ≤80 mL/min, 9.9% [17 of 172 patients], 5.9% [4 of 68 patients], respectively; CL_{CR} >80 mL/min, 5.6% [13 of 233 patients], 0.9% [1 of 109 patients], respectively). Therefore, in patients with renal impairment, the balance of risk versus benefit should be evaluated extremely carefully throughout the dose titration period and the maintenance period. For this purpose, the package insert will include a caution statement for "Careful Administration" in patients with renal impairment with CL_{CR} of ≥ 15 and < 80 mL/min to raise caution. Also, in the use-results survey on all treated patients, safety information on patients with renal impairment will be collected and analyzed, and appropriateness of the starting dose will be investigated at the same time. In patients with severe renal impairment ($CL_{CR} < 15 \text{ mL/min}$) and patients on dialysis, blood riociguat concentration may increase and there is no clinical experience with riociguat in these patients. Therefore, the following caution statement will be added in the "Contraindications" section: "Patients with severe renal impairment (creatinine clearance <15 mL/min) and patients on dialysis (No clinical experience, Blood riociguat concentration may increase markedly)."

PMDA considers as follows:

Although the relationship between the decrease in CL_{CR} and the increase in exposure to riociguat is unclear, the clinical pharmacology study in patients with renal impairment (Study 15000) showed the following results: AUC of riociguat in patients with renal impairment was approximately twice as high regardless of the level of renal function as in subjects with normal renal function; and the incidence of hypotension increased more with the decrease in renal function in the riociguat group than in the placebo group. In addition, only a limited number of patients with CL_{CR} <30 mL/min were enrolled in clinical studies, precluding the sufficient evaluation of the safety of starting with 1.0 mg TID. Taking account of the above, it is desirable to require careful administration in patients with renal impairment with CL_{CR} of ≥ 15 and < 80mL/min, and to increase the dose while paying attention to hypotensive symptoms, considering a lower starting dose (0.5 mg TID). The applicant's proposal to contraindicate riociguat in patients with severe renal impairment (CL_{CR} <15 mL/min) and patients on dialysis is appropriate, taking account of the following facts concerning these patients: blood riociguat concentration may increase; there is no clinical experience with riociguat; and hypotension-related risk may be enhanced with the increase in exposure to riociguat. Appropriateness of the caution statement regarding patients with renal impairment will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).5) Administration in patients with hepatic impairment

PMDA asked the applicant to explain whether or not administration of riociguat in patients with hepatic impairment should be started at a lower dose because of the following reasons: AUC of riociguat was approximately 1.6 to 1.7 times higher in patients with mild to moderate hepatic impairment than in subjects with normal hepatic function; and the blood riociguat concentration is correlated with the hemodynamic effect of riociguat.

The applicant responded as follows:

It was shown that AUC of riociguat increases in patients with mild to moderate hepatic impairment, but data vary from subject to subject.

In Studies 11348 and 12934, patients with the following baseline values were excluded: ALT >3 times the normal upper limit; bilirubin > twice the normal upper limit; and/or sign of severe hepatic impairment. In Studies 11348 and 12934, the percentage of patients who showed baseline AST, ALT, or total bilirubin exceeding the normal upper limit was as low as 5.9% to 18.3%. Among patients in whom the dose of riociguat had to be reduced or discontinued during the period from the first to the second visit (2 weeks after the treatment initiation), those who showed

abnormally high baseline value (exceeding the normal upper limit) of AST, ALT, or total bilirubin were none in the riociguat group of Study 11348, 1 patient in the placebo-riociguat group of Study 11349, 2 patients in the riociguat group (dose titration group and 1.5 mg TID group) of Study 12934, and 1 patient in the placebo-riociguat group of Study 12935. Thus, in Studies 11348 and 12934 combined, only a few patients resulted in dose reduction or discontinuation immediately after treatment initiation. These results suggest that 1.0 mg TID is a safe starting dose even in patients with mild to moderate hepatic impairment.

However, in Study 15001 in which the effect of hepatic impairment on the pharmacokinetics of riociguat was investigated, the exposure level increased to a similar extent in patients with mild and moderate hepatic impairment compared with subjects with normal hepatic function. Therefore, the following description will be included in the "Careful Administration" section of the package insert (draft): patients with mild or moderate hepatic disorder (Child-Pugh class A or B) (Increase in blood riociguat was observed. During the dose titration period, riociguat should be administered with caution while monitoring the patient condition) (see "Pharmacokinetics"). As regards the patients with severer hepatic impairment (Child-Pugh class C), there is no experience of riociguat in clinical studies in patients with pulmonary hypertension. In addition, results of the clinical pharmacology study showed that exposure to riociguat will be contraindicated in patients with severe hepatic impairment.

PMDA considers as follows:

There is only limited information on the efficacy and safety of riociguat when administered to pulmonary hypertension patients with hepatic impairment. In Study 15001, the exposure level increased in patients with mild to moderate hepatic impairment compared with subjects with normal hepatic function, as much as 1.6 to 1.7 times. In addition, there were only a small number of patients in whom the dose of riociguat had to be reduced or discontinued immediately after treatment initiation in the phase III comparative studies. Based on the above, it is appropriate that the applicant explained to require careful administration in patients with mild to moderate hepatic impairment (Child-Pugh class A or B) and to allow starting the treatment at the dose of 1.0 mg TID. In patients with severe hepatic impairment, exposure to riociguat is expected to increase, but it is difficult to predict the extent of the increase. In addition, there is no information on the pharmacokinetics, efficacy, or safety of riociguat in patients with severe hepatic impairment. Moreover, hypotension-related risk may be enhanced with the increase in exposure to riociguat. Taking account of the above, it is appropriate that the applicant proposed contraindication of riociguat in patients with severe hepatic impairment (Child-Pugh class C). Appropriateness of the caution statement regarding patients with hepatic impairment will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).6) Effect of concomitant drugs

PMDA asked the applicant to explain the safety of each PAH drug when used concomitantly because patients with CTEPH are expected to be treated with concomitant use of riociguat with PAH drugs.

The applicant responded as follows:

There are no PAH drugs approved for CTEPH. In Study 11348 in patients with CTEPH, concomitant use with PAH drugs was prohibited during the period of study drug administration. In Study 11349, only those subjects who completed the dose titration period were allowed to use ERA and prostacyclin derivatives. However, by the cut-off date of **M M**, approximately 90% of subjects had been receiving treatment with riociguat alone. Therefore, there are only limited data available on the concomitant use of PAH drugs with riociguat in patients with CTEPH. The percentage of patients who received concomitant use with PAH drugs in Study 11349 was 7.2% (17 patients) for ERA, 4.6% (11 patients) for prostacyclin derivatives, and 1.3% (3 patients) for

PDE-5 inhibitors (which were prohibited in the study).

After the initiation of concomitant use with these drugs in these subjects, followings TEAEs occurred. After the initiation of concomitant use with ERA, 157 TEAEs occurred in 16 patients, and 2 events in 2 patients were considered to be causally related to the study drug. There were 30 serious TEAEs in 12 patients, but the relationship of all the events to the study drug was ruled out. TEAEs leading to treatment discontinuation were reported by 2 patients (2 events), both of which were related to aggravation of the primary disease. After the initiation of concomitant use with prostacyclin derivatives, 75 TEAEs were reported by 10 patients, none of which were considered to be related to the study drug. A total of 18 serious TEAEs were reported by 8 patients, most of which were events often observed with the primary disease. However, 4 haemorrhagic events occurred in 2 patients, and one of them had a fatal outcome. This patient had been assigned to the placebo group in Study 11348, and developed serious asthma on Day 15 of Study 11349, followed by renal failure acute, pneumonia, and aggravation of pulmonary hypertension. Iloprost¹³⁾ and sildenafil were started on Day 24. On Day 25, the patient had gastrointestinal haemorrhage and pulmonary haemorrhage, and died on Day 31, but the relationship of all the events to the study drug was ruled out. There was 1 patient who discontinued the administration of the study drug because of TEAE, which was aggravation of the primary disease. After the initiation of concomitant use with PDE-5 inhibitors, 14 TEAEs were reported by 3 patients. None of them were considered to be related to the study drug. A serious TEAE was reported by 1 patient, the same patient who received iloprost concomitantly as mentioned above. There were no TEAEs leading to treatment discontinuation.

Thus, adverse events observed during concomitant use of riociguat with PAH drugs were not different from those observed in patients not receiving any PAH drugs concomitantly. Since none of the commercially available PAH drugs are indicated for CTEPH, concomitant use of riociguat with these drugs is not necessarily recommended in patients with CTEPH. However, concomitant use of riociguat with ERA or prostacyclin derivatives is expected to have a certain additive effect in patients with CTEPH as is observed in patients with PAH, and is considered to be acceptable from the safety point of view as well.

Taking account of the applicant's explanation that concomitant use of riociguat with sildenafil is expected to have an additive effect on the pulmonary and systemic circulation, PMDA asked the applicant to explain with referring to specific risks of concomitant use of riociguat with sildenafil whether or not it is sufficient to handle the concomitant use as a treatment requiring just "precautions for concomitant use."

The applicant responded as follows:

PDE-5 inhibitors such as sildenafil suppress the degradation of cGMP in vascular smooth muscle cells, whereas riociguat increases cGMP production via sGC activation. Despite these differences in the mechanism of action, both riociguat and PDE-5 inhibitors cause vasodilation by increasing the intracellular cGMP. Therefore, concomitant use of sildenafil with riociguat is expected to have an additive effect on the pulmonary and systemic circulation. In a placebo-controlled drug-drug interaction study of riociguat (Study 15096) conducted in patients with symptomatic PAH receiving a certain dose of sildenafil, safety of riociguat was favorable during the 12-week primary treatment period, but, during the subsequent period of uncontrolled long-term extended treatment (mean treatment duration, approximately 10 months), the incidence of adverse events leading to treatment discontinuation was higher than in the primary treatment period, with most of the causes being hypotension. Because of the limited number of subjects evaluated, no conclusion can be drawn regarding the efficacy. However, in Study 15096, the benefit of concomitant use of riociguat with sildenafil did not outweigh the risk. Therefore, such

¹³⁾Not approved in Japan.

combination therapy in patients with PAH is not recommended, based on the currently available data. As for CTEPH, no PDE-5 inhibitors are indicated for it, and concomitant use with PDE-5 inhibitors was prohibited in Studies 11348 and 11349. Therefore, there is little data on concomitant use of riociguat with PDE-5 inhibitors in patients with CTEPH. As is the case with PAH, such concomitant use is not recommended.

At the current moment, there are no data to strongly support contraindication of concomitant use of PDE-5 inhibitors. However, NO donors, drugs that increase cGMP in the similar manner as PDE-5 inhibitors do, are to be contraindicated because of the additive effect on blood pressure decrease. Therefore, the applicant determined that it is appropriate to contraindicate PDE-5 inhibitors as well, and therefore PDE-5 inhibitors will be included in the "Contraindications for coadministration" section in the package insert (draft).

PMDA considers as follows:

At the current moment, there are no drugs approved for CTEPH, neither is there any information or evidence on combination therapy for CTEPH in Japanese or foreign guidelines. However, for the treatment of severe PAH, a disease that shows pulmonary hypertension as is the case with CTEPH, combination therapy using multiple drugs with different mechanisms of action, such as prostacyclin derivatives, ERA, and PDE-5 inhibitors, has been proposed. Additionally, although the number of patients treated was limited, the study of concomitant use of riociguat with PAH drugs (ERA, prostacyclin derivatives) does not suggest any clinically significant safety problems. Based on the above, it is plausible that, in future, concomitant use of riociguat with existing PAH drugs may be used for the treatment of CTEPH as well, and the efficacy and safety of such concomitant use will become clear with the accumulation of practical clinical experience. Therefore, relevant information should be actively collected and made available after the market launch. In contrast, in the drug-drug interaction study on sildenafil and riociguat, many patients discontinued the study during the long-term administration because of hypotension, with the benefit of the combination therapy failing to outweigh the risk. Therefore, the applicant's proposal to contraindicate PDE-5 inhibitors is appropriate.

4.(iii).B.(5) Consistency of data between entire population and Japanese population

The applicant explained the consistency in efficacy and safety data between the entire population and the Japanese population in Study 11348, as follows:

1) Efficacy

Efficacy results in Study 11348 were investigated for consistency between the entire population and the Japanese population, regarding particularly important efficacy parameters 6MWD and PVRI. As regards the change in 6MWD from baseline to Week 16, the primary endpoint, in the entire population, the change in median (range) was 42.0 (-376 to 335) m in the riociguat group and 5.0 (-389 to 226) m in the placebo group, and the change in median (range) was 64.0 (-376 to 217) m in the riociguat group and 14.0 (6-85) m in the placebo group, and the change in mean was 31.9 m and 36.0 m, respectively. As for the change in median (range) was -306.48 (-2714.3 to 961.3) dyn·sec·cm^{-5·m²} in the riociguat group and 32.00 (-1289.8 to 1903.1) dyn·sec·cm^{-5·m²} in the placebo group, and the change in median (range) was -251.40 (-450.1 to 225.8) dyn·sec·cm^{-5·m²} in the riociguat group and -20.51 (-245.0 to 294.7) dyn·sec·cm^{-5·m²} in the placebo group, and the change in mean was -209.23 dyn·sec·cm^{-5·m²} and 9.73 dyn·sec·cm^{-5·m²}.

In order to minimize bias in between-group comparison, all subjects who received the study drug after the randomization were included in the population for the primary efficacy and safety analysis. For subjects in whom measurement at Week 16 was not done, missing data were imputed

according to the pre-determined method. The Japanese population included 1 subject in the riociguat group who dropped out of the study because of the aggravation of the clinical conditions and did not make a visit to discontinue the treatment. In this subject, the missing value of 6MWD at Week 16 was imputed by the worst value (0 m) according to the pre-determined rule; this may have greatly affected the results of the Japanese population consisting of only a limited number of patients. The mean and median changes in 6MWD from baseline to Week 16 in Japanese subjects, calculated using the actually observed data alone, were 80.8 and 70.0 m, respectively, in the riociguat group (9 subjects), and 36.0 and 14.0 m, respectively, in the placebo group (5 subjects).

Because of the limited number of patients in the Japanese population, there were large variations in data. The change in 6MWD, the primary endpoint, did not show any significant differences between the 2 treatment groups in the mean value, whereas the median value tended to improve significantly in the riociguat group. Hemodynamic parameters including PVRI showed the improving effect of riociguat consistent between the entire population and the Japanese population. Based on the above, the applicant considers that the efficacy demonstrated in the entire population can be expected in the Japanese population as well.

2) Safety

Safety data in Study 11348 were investigated for consistency between the entire population and the Japanese population, regarding the occurrence of TEAEs.

The incidence of TEAEs was 91.9% (159 of 173 patients) in the riociguat group and 86.4% (76 of 88 patients) in the placebo group in the entire population; and 100.0% (11 of 11 patients) and 100.0% (5 of 5 patients), respectively, in the Japanese population. Among TEAEs reported by ≥ 2 patients in the riociguat group of the Japanese population, those with $\geq 3\%$ higher incidence compared with the entire population were nasopharyngitis (15.0% [26 patients] in the entire population, 36.4% [4 patients] in the Japanese population), back pain (4.0% [7 patients] and 27.3% [3 patients], respectively), and hypotension (9.2% [16 patients] and 18.2% [2 patients], respectively). All of these TEAEs were mild to moderate in severity. In the Japanese population, hypotension occurred with a higher incidence but was mild in all cases, and the absolute number of the affected patients was limited, which suggests that the incidence of TEAEs is not significantly different between the entire population and the Japanese population. Also, occurrences of deaths and serious TEAEs in each treatment group were similar between the entire population and the Japanese population. Among adverse events of special interest other than hypotension (TEAEs suggesting syncope, haemorrhagic TEAEs), haemorrhagic TEAEs occurred in 13.3% (23 patients) in the riociguat group and in 11.4% (10 patients) in the placebo group in the entire population, showing a similar incidence between the riociguat group and the placebo group. The haemorrhagic TEAE with a high incidence was haemoptysis (2.3% [4 patients] in the riociguat group, 0% [0 patients] in the placebo group). In the Japanese population, haemorrhagic TEAEs were observed only in 2 patients in the placebo group (gingival bleeding and puncture site haemorrhage in 1 patient each, non-serious in both events). In the entire population, TEAEs suggesting syncope were observed in 3.5% (6 patients) in the riociguat group and 3.4% (3 patients) in the placebo group, showing a similar incidence between the riociguat group and the placebo group. No TEAEs suggesting syncope were observed in the Japanese population.

Evaluation of laboratory test values showed that, in the entire population, the mean hemoglobin and hematocrit values tended to decrease in the riociguat group compared with the placebo group, whereas in the Japanese population, there was no significant difference in the mean change in hemoglobin and hematocrit between the riociguat group and the placebo group. The mean change in SBP from baseline to Week 16 was -10.49 mmHg in the riociguat group and -5.28 mmHg in the placebo group in the entire population; and -16.45 mmHg in the riociguat group and -3.20 mmHg in the placebo group in the Japanese population, showing a slightly greater change in the

Japanese population. The effect of riociguat on ECG or on blood gas parameters was not observed either in the entire population or in the Japanese population.

Thus, TEAEs commonly observed in the entire population and in the Japanese population were adverse events due to the vasodilating action of riociguat and gastrointestinal symptoms due to smooth muscle relaxation. There was no significant difference in the incidence of serious TEAEs between the entire population and the Japanese population. The mean change in SBP from baseline was slightly greater in the Japanese population compared with the entire population, while TEAEs suggesting hypotension in the riociguat group of the Japanese population (hypotension, blood pressure decreased) were mild in all cases. Results of other safety parameters were also similar between the Japanese population and the entire population.

Based on 1) and 2) above, the applicant considered that riociguat is as effective in the Japanese population as in the entire population, its safety and tolerability are favorable, and that study results were consistent between the entire population and the Japanese population.

PMDA considers as follows:

Even though unavoidable since CTEPH is a rare disease, only a limited number of Japanese patients with CTEPH were able to be enrolled in Study 11348 that was conducted as a global clinical study. Therefore, there is a limitation to the comparison of data between the entire population and the Japanese population, and to the detailed investigation of data obtained from the Japanese population. Comparison of the safety and efficacy, including the secondary endpoint, to the greatest extent possible under such conditions showed that there was no significant disparity in data between the entire population and the Japanese population. Neither did examination of individual data in the Japanese population. Based on the above, consistent data were obtained on the efficacy and safety of riociguat in both the entire population and the Japanese population. Therefore, riociguat is clinically effective in Japanese patients with CTEPH and the safety is acceptable.

4.(iii).B.(6) Indication

The applicant jsutified the proposed indication of riociguat as follows:

Study 11348 was conducted to evaluate the efficacy and safety of riociguat in patients with CTEPH. In the study, superiority of riociguat to placebo was investigated in the change in 6MWD from baseline to Week 16, the primary efficacy endpoint, in patients with inoperable CTEPH and CTEPH patients with postoperative persistent or recurrent pulmonary hypertension. Secondary endpoints such as PVR also showed improvement in the riociguat group compared with the placebo group, supporting the efficacy of riociguat. As regards safety, Study 11348 demonstrated the favorable safety profile and Study 12934 conducted in patients with PAH also showed a similar tendency, as discussed in "4.(iii).B.(4) Safety" above.

Subpopulation analysis was conducted on the treatment effect in 6MWD for each clinical class of CTEPH. As a result, the treatment effect (difference in changes from baseline to Week 16 between the riociguat group and the placebo group) was 53.92 m [95% CI, 28.53-79.31 m] in the inoperable patients (189 patients) and 26.72 m [95% CI, -9.68 to 63.13 m] in patients with post-operative persistent or recurrent pulmonary hypertension (72 patients).¹⁴⁾ The change in PVR from baseline to Week 16, the particularly important secondary endpoint, was also evaluated for each clinical class of CTEPH as a subpopulation analysis. Although the treatment effect was low in the postoperative persistent or recurrent cases, the results showed a greater improvement in the riociguat group (-257.12 \pm 279.42 dyn·sec·cm⁻⁵ [mean \pm SD] in inoperable cases, -153.90 \pm

¹⁴⁾Calculated by analysis of covariance model with baseline value as the covariate and treatment group as the main effect

127.32 dyn·sec·cm⁻⁵ in postoperative persistent or recurrent cases) than in the placebo group $(33.36 \pm 291.78 \text{ dyn·sec·cm}^{-5}, -11.03 \pm 204.58 \text{ dyn·sec·cm}^{-5}, \text{ respectively})$, regardless of the clinical class of CTEPH.

Based on the above, the applicant determined that it was appropriate to propose the indication as "inoperable or postoperative persistent or recurrent chronic thromboembolic pulmonary hypertension."

PMDA asked the applicant to explain the appropriateness of indicating riociguat for inoperable or postoperative persistent or recurrent CTEPH regardless of WHO functional class.

The applicant responded as follows:

Table 26 shows the changes in 6MWD and PVRI from baseline to Week 16 in Study 11348 by baseline WHO functional class.

WHO		6MWD (m)		PVRI (dyn·sec·cm ⁻⁵ ·m ²)		
functional class		Riociguat	Placebo	Riociguat	Placebo group	
		group group		group	r nacebo group	
	N	3	_	3	-	
Class I	Baseline	394.0 (76.3)	_	1877.89 (1000.24)	_	
	Change at Week 16	48.7 (10.0)	_	-623.92 (608.17)	_	
	Ν	55	25	45	24	
Class II	Baseline	386.6 (59.2)	386.3 (63.9)	1367.42 (562.22)	1307.56 (759.50)	
	Change at Week 16	45.3 (82.3)	19.9 (50.5)	-387.16 (385.95)	33.01 (466.63)	
	Ν	107	60	98	55	
Class III	Baseline	325.9 (81.4)	345.3 (73.1)	1402.97 (774.02)	1483.10 (632.54)	
	Change at Week 16	37.8 (75.4)	-16.9 (95.0)	-339.54 (441.45)	63.89 (552.27)	
	Ν	8	2	5	2	
Class IV	Baseline	238.6 (53.3)	237.5 (6.4)	1631.05 (511.35)	729.34 (67.51)	
	Change at Week 16	5.4 (119.6)	20.0 (12.7)	-288.81 (402.14)	113.33 (21.10)	

Table 26. Changes in 6MWD and PVRI from baselin to Week 16 by b	aseline WHO functional class

Mean (SD)

Subjects in classes II and III showed a tendency of improvement in 6MWD in the riociguat group compared with the placebo group. There were only a small number of subjects in class I or IV, with no class I subjects in the placebo group. Among class IV subjects in the riociguat group, 1 subject dropped out of the study because of aggravation of clinical conditions and missing 6MWD value was imputed with the worst value (0 m). Therefore, caution is required in the interpretation of the data of classes I and IV.

As regards PVRI, although the comparison is difficult because of the absence of class I subjects in the placebo group, subjects in class II or higher showed a greater improvement in PVRI in the riociguat group compared with the placebo group, suggesting the efficacy in each of these classes.

As regards TEAEs by WHO functional class in Study 11348, no serious TEAEs were reported by subjects in class I, although comparison was difficult because of the small number of class I subjects and no subjects in the placebo group. In class II subjects, the incidence of TEAEs (96.4% in the riociguat group, 76.0% in the placebo group) and the incidence of serious TEAEs (12.7%, 4.0%, respectively) tended to be higher in the riociguat group compared with the placebo group. The only fatal TEAE observed in class II patients was cardiac failure in 1 patient (1.8%) in the riociguat group. In classes III and IV, no imbalance was observed in the incidence, severity, or seriousness of TEAE between the riociguat group and the placebo group. In class III, a fatal TEAE occurred in 1 patient (0.9%) in the riociguat group and in 3 patients in the placebo group (5.0%),

showing a lower incidence in the riociguat group. In class IV, no fatal TEAE occurred in either group.

Among TEAEs by WHO functional class in Study 11348, TEAEs with \geq 5% higher incidence in the riociguat group compared with the placebo group were as follows: in class II, palpitations (5.5% in the riociguat group, 0% in the placebo group), constipation (5.5% and 0%, respectively), diarrhoea (7.3% and 0%, respectively), dyspepsia (12.7% and 4.0%, respectively), dysphagia (5.5% and 0%, respectively), gastritis (5.5% and 0%, respectively), nausea (12.7% and 4.0%, respectively), vomiting (12.7% and 0%, respectively), chest discomfort (5.5% and 0%, respectively), respiratory tract infection (5.5% and 0%, respectively), upper respiratory tract infection (9.1% and 4.0%, respectively), activated partial thromboplastin time prolonged (10.9% and 4.0%, respectively), dizziness (21.8% and 8.0%, respectively), headache (32.7% and 4.0%, respectively), flushing (7.3% and 0%, respectively), and hypotension (7.3% and 0%, respectively); and in class III, dyspepsia (21.5% and 8.3%, respectively).

The above results suggest, that riociguat was consistently effective in improving 6MWD and PVRI, efficacy parameters of particular importance, regardless of WHO functional class, although the number of subjects in classes I and IV was limited. As regards safety, no serious TEAEs were observed in class I. In class II, although the incidence of TEAEs was higher in the riociguat group than in the placebo group, TEAEs more frequently observed in the riociguat group were mainly those induced by the pharmacological effect of riociguat, such as the vasodilating action and gastrointestinal disorder. In addition, the fatal TEAE in class II was observed only in 1 subject (1.8%) in the riociguat group, which did not show any clear imbalances between the groups. The safety profiles in classes III and IV were comparable between the riociguat group and the placebo group. Based on the above, the applicant considers that it is appropriate to indicate riociguat for all patients with inoperable or postoperative persistent or recurrent CTEPH regardless of WHO functional class.

PMDA considers as follows:

In Study 11348, the change in 6MWD from baseline, the primary efficacy endpoint, showed efficacy of riociguat against placebo in the entire population, whereas the treatment effect was lower in postoperative persistent or recurrent cases compared with the inoperable cases. Also, the treatment effect assessed by the change in PVR from baseline, the important secondary endpoint, wasalso lower in the postoperative persistent or recurrent cases. However, given that postoperative persistent or recurrent pulmonary hypertension is clinically more severe and unlikely to respond to treatment, that there is no additional therapeutic options for these cases, and that efficacy of riociguat has been demonstrated, compared with placebo, in postoperative persistent or recurrent CTEPH.

As regards WHO functional classes for which riociguat can be indicated, efficacy and safety of riociguat were suggested in both classes II and III, in which most of the patients enrolled in Study 11348 were classified. As regards patients in classes I or IV, it is understandable that only a small number of patients with CTEPH in classes I or IV were enrolled, given the following situation: (i) class I patients have no symptoms, which results in delayed diagnosis, and it is difficult for nonspecialists in CTEPH to make a definitive diagnosis at the stage of class I, and (ii) class IV patients are likely to have started receiving treatment including off-label treatment, and there are not many of those who meet the inclusion criteria of the clinical study where concomitant use with other PAH drugs is restricted. Although no class I patients were assigned to the placebo group, precluding the between-group comparison, comparison of data in the riociguat group between pre- and post-treatment showed a tendency of improvement in 6MWD and PVRI. In

class IV, the mean change in 6MWD from baseline in the riociguat group was only 5.4 m, which was inferior to the data in the placebo group, whereas the mean change in PVRI from baseline showed improvement, exceeding the data in the placebo group. In addition, by taking account of the fact that CTEPH is a progressive, serious disease, it is of clinical significance to provide an option of treatment with riociguat to patients in classes I and IV.

Based on the above, PMDA considers it acceptable for riociguat to be indicated for "inoperable or postoperative persisting or recurrent chronic thromboembolic pulmonary hypertension" regardless of disease type or WHO functional class.

4.(iii).B.(7) Dosage and administration

4.(iii).B.(7).1) Appropriateness of selecting the dose of 0.5 to 2.5 mg 3 times daily The applicant justified the dosage and administration of riociguat as follows:

In the foreign phase I single-dose study in Caucasian healthy adult subjects (Study 11258), riociguat (0.25-5.0 mg) was administered in a single dose. As a result, the incidence of adverse events related to the pharmacological effect of riociguat increased at 5.0 mg, precluding the conclusion that 5.0 mg was well tolerated in healthy adult subjects. Therefore, in subsequent studies, riociguat was not administered to healthy adult subjects at doses of >2.5 mg. In the foreign phase I multiple dose study in Caucasian healthy adult subjects (Study 11260), riociguat administered at 1.0 to 2.5 mg TID was safe and well tolerated, whereas, at 2.5 mg TID, the incidence of adverse events was higher compared with lower doses. In foreign phase I studies, the mean $t_{1/2}$ of riociguat was 8 hours (5-10 hours). Therefore, 3 times daily administration was selected to minimize the variation of plasma riociguat concentration between peak and trough, thereby to maintain the constant pharmacodynamic effect. In the proof-of-concept study in patients with pulmonary hypertension (Study 11874), the effect on the hemodynamics was demonstrated at 1.0 mg TID, and asymptomatic hypotension was observed at 5.0 mg TID in patients with pulmonary hypertension as was the case with healthy adult subjects. In addition, a clear correlation was observed between blood riociguat concentration and hemodynamics, and riociguat was shown to decrease not only PVR but also systemic vascular resistance (SVR). Furthermore, a large interindividual variability was observed in pharmacokinetics. Therefore, dose adjustment by gradual dose escalation was selected.

Based on the above results, the foreign phase I/II study (Study 12166) was conducted according to the dosage and administration in which treatment was given with the starting dose of 1.0 mg TID, followed by stepwise increase at 2-week intervals by 0.5 mg at a time up to 2.5 mg TID based on the systemic blood pressure and tolerability of each subject. As a result, the safety and tolerability were favorable, and efficacy endpoints evaluated by an exploratory manner showed improvement from baseline. Therefore, the applicant considered that the dosage and administration of dose titration by 0.5 mg at a time every 2 weeks was appropriate.

Study 11348 in patients with CTEPH was conducted with the starting dose of 1.0 mg TID, and the dose was adjusted based on the systolic blood pressure and tolerability of each subject, with the maximum dose of 2.5 mg TID [see "4.(iii).A.(4) Global phase III study in patients with CTEPH"]. Results demonstrated the efficacy of riociguat as described in (3) above. In Study 11348, the unit dose at Week 8, the end of the dose titration period, was 2.5 mg in 78.8% (130 of 165 subjects), 2.0 mg in 10.9% (18 of 165 subjects), 1.5 mg in 6.1% (10 of 165 subjects), 1.0 mg in 3.6% (6 of 165 subjects) and 0.5 mg in 0.6% (1 of 165 subjects). The percentages of subjects treated with each unit dose at Week 16, were not significantly different from those at Week 8 although the subjects received their maintenance dose for another 8 weeks, showing that the treatment improved 6MWD.

As regards safety, most adverse events commonly observed in the riociguat group compared with the placebo group in Study 11348 were events caused by the pharmacological effects of riociguat,

namely vasodilating action and smooth muscle relaxant effect, as described in (4) above. Thus, riociguat showed a favorable safety profile, including the occurrence of serious adverse events and of adverse events leading to treatment discontinuation.

Based on the above, the applicant considers that the maximum efficacy is expected in each patient while ensuring safety and tolerability when riociguat is administered 3 times daily with the starting unit dose of 1.0 mg, and the dose is adjusted for each patient within the range from 0.5 to 2.5 mg, by increasing or decreasing by 0.5 mg at a time every 2 weeks, using the systolic blood pressure as the index.

PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration being applied to Japanese patients as well as to foreign patients.

The applicant responded as follows:

Table 27 shows the distribution of the maintenance dose in the entire population and in the Japanese population at the end of the dose titration (Week 8) in Study 11348.

Unit dose	Entire population	Japanese population
(mg)	N = 165	N = 10
0	0 (0)	0 (0)
0.5	0.6 (1)	0 (0)
1.0	3.6 (6)	20.0 (2)
1.5	6.1 (10)	0 (0)
2.0	10.9 (18)	20.0 (2)
2.5	78.8 (130)	60.0 (6)

 Table 27. Maintenance doses for entire population and Japanese population at Week 8 in Study 11348 (riociguat group)

% (number of patients)

In the entire population, 78.8% of subjects had reached the maximum unit dose of 2.5 mg TID. In the Japanese population, a slightly lower percentage, 60%, of subjects had reached the unit dose of 2.5 mg TID. Table 28 shows the efficacy results (changes in 6MWD and PVRI) in the entire population and in the Japanese population by the maintenance dose.

in entire population and Japanese population									
	Entire population				Japanese population				
	6	5MWD]	PVRI		6MWD		PVRI	
		(m)	(dyn•s	ec·cm ⁻⁵ ·m ²)		(m)	(dyn•se	$c \cdot cm^{-5} \cdot m^2$)	
Unit dose (mg)	Ν	Median Mean	Ν	Median Mean	Ν	Median Mean	Ν	Median Mean	
Placebo	87	5.0 -1.1	82	32.00 48.26	5	14.0 36.0	5	-20.51 9.73	
0.5	1	32.0 32.0	1	-373.10 -373.10	0	_	0	_	
1.0	6	93.5 106.3	6	-170.47 -234.41	2	104.5 104.5	2	-305.80 -305.80	
1.5	10	31.5 36.2	9	-226.50 -305.52	0	_	0	_	
2.0	18	53.5 15.1	14	-439.04 -643.26	2	67.0 67.0	2	-320.02 -320.02	
2.5	130	42.0 45.3	121	-301.52 -383.12	6	48.0 1.3	5	-208.21 -126.28	

Table 28. Changes in 6MWD and PVRI by maintenance dose in entire population and Japanese population

In Study 11348, most subjects were able to receive increased dose up to 2.5 mg TID, resulting in only a small number of subjects ending up with the maintenance dose of \leq 2.0 mg TID in each population. With this reservation, no clear dose-response correlation was observed either in 6MWD or PVRI, resulting in a consistent treatment effect of riociguat at all maintenance doses. In the Japanese population, data varied significantly because of the small number of subjects studied. As regards the change in 6MWD, the mean value failed to show an improvement in the riociguat group compared with the placebo group, whereas the median value suggested a tendency of a greater improvement in the riociguat group at all maintenance doses compared with the placebo group. The 2.5 mg TID subgroup in the riociguat group included 1 Japanese subject who dropped out of the study because of the aggravation of clinical conditions and failed to make the visit at study discontinuation. Missing data in this subject was imputed by the worst value (0 m), which may have significantly affected the mean value in the Japanese population with the limited number of subjects. Similarly, the change in PVRI from baseline also suggested efficacy at all maintenance doses in the Japanese population as in the entire population.

As regards TEAEs by maintenance dose, those observed at \geq 5% higher incidence in the 2.5 mg TID group than the other riociguat dose groups and at a higher incidence in the riociguat group than in the placebo group were gastrooesophageal reflux disease (0% in the 0.5-2.0 mg TID group, 5.4% in the 2.5 mg TID group, 0% in the placebo group), urinary tract infection (0%, 6.2%, and 2.3%, respectively), and activated partial thromboplastin time prolonged (0%, 5.4%, and 1.1%, respectively). As regards adverse events of special interest, i.e., TEAEs suggesting syncope, TEAEs suggesting hypotension, and haemorrhagic TEAEs, the incidence of TEAEs suggesting syncope was 10% in the 1.5 mg TID group, 11.1% in the 2.0 mg TID group, 2.3% in the 2.5 mg TID group, and 3.4% in the placebo group; the incidence of TEAEs suggesting hypotension was 100% in the 0.5 mg TID group, 16.7% in the 1.0 mg TID group, 30.0% in the 1.5 mg TID group, 27.8% in the 2.0 mg TID group, 6.2% in the 2.5 mg TID group, and 4.6% in the placebo group; and the incidence of haemorrhagic TEAEs was 10% in the 1.5 mg TID group, 22.2% in the 2.0 mg TID group, 13.1% in the 2.5 mg TID group, and 11.5% in the placebo group. Thus, no clear tendency of correlation was observed between the incidences of these adverse events of special interest and the maintenance dose. Similarly to the entire population, no clear tendency of correlation between the incidences and the maintenance dose was observed in the Japanese population.

The results thus proved the assumption that it is possible to select the maintenance dose that is safe and expected to achieve the maximum improvement in the hemodynamics in individual subjects from the range of the maintenance dose (0.5-2.5 mg TID) employed in Study 11348. Also, based on the above results, the applicant considered that it is appropriate to use the same dosage and administration in Japanese patients as in foreign patients.

4.(iii).B.(7).2) Appropriateness of administering riociguat to patients with systolic blood pressure of <95 mmHg

The proposed dosage and administration requires that systolic blood pressure (SBP) before treatment be \geq 95 mmHg. Therefore, PMDA asked the applicant to explain whether or not patients with CTEPH who have SBP of <95 mmHg before treatment can be eligible for treatment with riociguat and, if such is the case, how the dosage and administration should be adjusted.

The applicant responded as follows:

In Study 11348, subjects with SBP of <95 mmHg before riociguat administration were not to be assigned to treatment groups according to the exclusion criteria. Therefore, there is no clinical experience of administering riociguat to such subjects. Also, since riociguat may cause hypotension by its pharmacological effect, it is not recommended to administer riociguat to patients with SBP of <95 mmHg. However, given the poor prognosis of patients with inoperable or postoperative persistent or recurrent CTEPH and the extremely limited treatment options

available for such patients with CTEPH, there may possibly be cases where administration of riociguat should be allowed even in patients with SBP of <95 mmHg, aftrer thorough consideration of the benefit available from riociguat against the possible risk of administration, including hypotension.

Because of no clinical experience of administering riociguat to patients with SBP of <95 mmHg in the clinical studies, there are no data available for selecting the special dosage and administration for such patients. Therefore, there is no rationale to select other starting dose than 1.0 mg TID as is the case with other patients. However, since it is expected that hypotension and accompanying symptoms are more prone to occur at the early stage of riociguat treatment in these patients compared with those with SBP of \geq 95 mmHg, it will be necessary to monitor these patients very carefully from the treatment initiation. For patients with SBP of <95 mmHg, safety information will be collected and analyzed in the use-results survey covering all patients treated and, at the same time, the appropriateness of the starting dose will be evaluated.

Based on 1) and 2) above, PMDA considers as follows:

Although the percentage of patients treated with the maximum maintenance dose (2.5 mg TID) was slightly lower in the Japanese population (60%) than in the entire population (78.8%), more than half of patients in the Japanese population reached the maintenance dose of 2.5 mg TID. In addition, in Study 11348 conducted using the same dosage and administration as proposed in the application, efficacy of riociguat at each maintenance dose was demonstrated in patients including the Japanese population, and no particular safety problem was observed. Therefore, it is appropriate to select the dosage and administration employed in Study 11348.

Although there are no data supporting the dose adjustment based on SBP for patients with SBP of <95 mmHg, who were excluded from Study 11348, it is not considered appropriate to exclude these patients from treatment with riociguat, and there is no problem in administering riociguat carefully to these patients after thorough individual consideration of the balance of risks and benefits of riociguat administration, because there are currently no drugs indicated for CTEPH, and the disease conditions of CTEPH are unlikely to abruptly change once SBP falls below 95 mmHg.

The proposed dosage and administration includes descriptions concerning interval of riociguat administration (6-8 hours), measures to be taken in case of a missed dose, and measures to be taken after interruption of administration. These are supplementary information for the proper use of riociguat and thus inappropriate to be included in "DOSAGE AND ADMINISTRATION."

Based on the above, PMDA has concluded that the following description should be included in "DOSAGE AND ADMINISTRATION" and "Precautions for Dosage and Administration" section. Appropriateness of the conclusion of PMDA and details of the description in the package insert will be finalized, taking account of comments raised in the Expert Discussion.

[DOSAGE AND ADMINISTRATION]

Dose titration period

The usual initial dosage in adults is 1.0 mg of riociguat administered orally 3 times daily (with a dosing interval of approximately 6-8 hours) for 2 consecutive weeks. If the systolic blood pressure remains at \geq 95 mmHg and the patient shows no signs or symptoms of hypotension, the dose should be increased by 0.5 mg at 2-week intervals up to the maximum daily dose of 2.5 mg 3 times daily. If the systolic blood pressure is <95 mmHg but the patient shows no signs or symptoms of hypotention, the current dosage should be maintained. If the patient shows any signs or symptoms of hypotention, the dose should be reduced by 0.5 mg 3 times daily.

Dose maintenance period

The dose determined during the dose titration period should be maintained. The maximum daily dose is 2.5 mg 3 times daily during the dose maintenance period as well. If the dose is not tolerated (e.g., occurrence of signs or symptoms of hypotension), the dose should be reduced. In the case that a dose is missed, the patient should continue with the next dose as scheduled.

After dose interruption

If the treatment is interrupted for 3 days or longer, the oral dose of riociguat should be resumed at 1.0 mg 3 times daily and the dose level should be continued for 2 weeks. Thereafter, the dose should be adjusted according to the procedure as described above.

[Precautions for Dosage and Administration]

- 1. It is desirable to administer riociguat at approximately 6- to 8-hour intervals. In case of a missed dose, the patients should continue with the next scheduled dose.
- 2. In case of a 3-day or longer interruption, the patients should resume the regimen at the daily oral dose of 1.0 mg 3 times daily for 2 weeks, after which the dose should be optimized according to the procedure as described above.

(Changes from the proposed dosage and administration: underlined words were added; struck-through words were deleted.)

4.(iii).B.(8) Post-marketing investigations

The applicant explained the post-marketing investigations of riociguat as follows:

Riociguat is expected to be used for a long-term period in patients with CTEPH. Since only a limited number of Japanese patients were investigated in the clinical studies, the applicant plans to conduct an all-case surveillance (standard observation period of 1 year, with a follow-up study period of up to 7 years, if possible, when riociguat is used continuously; target sample size, 400 patients in safety analysis population) with the purpose of evaluating the long-term safety and efficacy of riociguat in routine clinical use.

In this survey, information will be collected on the occurrences of hypotension and upper gastrointestinal motility disorder, on the safety in patients by their characteristics, including baseline SBP of <95 mmHg, hepatic impairment, renal impairment, and on the concomitant drugs. At the same time, efficacy parameters such as 6MWD, hemodynamic parameters, and time to clinical aggravation will be evaluated. In clinical studies, haemoptysis was observed as a serious TEAE, albeit at a low frequency. In addition, among patients with a diagnosis of pulmonary hypertension, those with pulmonary vein occlusion have a risk of serious pulmonary congestion and pulmonary oedema due to the vasodilating action of riociguat. Therefore, information on the occurrences of haemoptysis, pulmonary haemorrhage, pulmonary congestion, and pulmonary oedema will also be collected.

The target sample size was determined in consideration of feasibility because of the limited number of patients with CTEPH, a rare disease, in Japan. According to the number of patients issued with Certificate of a Recipient of Designated Disease Treatment from FY2009 through FY2011, there are 1590 patients with CTEPH in Japan as of 2011, and the number is increasing by approximately 150 every year, with the expected number in 2018 being around 2600. By taking into account the percentage of the target patients with inoperable or postoperative persistent or recurrent CTEPH among the patients with CTEPH, as well as other factors, it was decided that 400 cases should be collected by the all-case surveillance over 5 years starting from the market launch. Assuming the number of patients for safety analysis to be 400, at least 1 case of an adverse event with an incidence rate of 0.75% can be detected at the statistical power of 95%. Thus, it is possible to detect hypotension (9.2% [incidence in clinical studies]), upper gastrointestinal motility disorder (32.4%), and haemoptysis (2.3%), which are important risks of riociguat.

PMDA considers as follows:

Because of the limited number of Japanese patients investigated in clinical studies, a surveillance involving all patients treated with riociguat should be performed after the market launch, and information should be actively collected on (i) the long-term safety and efficacy, (ii) occurrences of hypotension, upper gastrointestinal motility disorder , haemoptysis, pulmonary haemorrhage, etc., (iii) safety in populations with limited clinical data (e.g., patients with hepatic impairment, renal impairment, hypotension), and (iv) effects of concomitant drugs (in particular, other PAH drugs expected to be concomitantly administered). Also the obtained information should be promptly made available. Details of the post-marketing surveillance will be finalized based on the "Risk Management Plan Guidance (PFSB/SD Notification No. 0411-1, PFSB/ELD Notification No. 0411-2, both dated April 11, 2012), including the appropriateness of safety specification and risk classification and the appropriateness of pharmacovigilance activities and risk minimization actions, taking account of comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1, 5.3.5.1.2). Results showed that, in some medical institutions, information influencing subjects' willingness was not provided to subjects at an appropriate timing to obtain revised consent for study continuation. Also, the sponsor did not notify information on unpredictable serious adverse reactions to the heads of the medical institutions at an appropriate timing after obtaining the relevant information. Thus, there were cases requiring improvements. However, since these subjects were handled appropriately, PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, PMDA considers that the efficacy of riociguat in treating inoperable or postoperative persistent or recurrent chronic thromboembolic pulmonary hypertension has been confirmed, and that its safety is acceptable in view of its observed benefits. At the current moment in Japan, there are no drugs approved with an indication for chronic thromboembolic pulmonary hypertension. Riociguat provides a new treatment option for inoperable or postoperative persistent or recurrent chronic thromboembolic pulmonary hypertension, and thus has a clinical significance. Further investigations are necessary on the dosage and administration, caution statements in the package insert, and post-marketing investigations.

PMDA considers that riociguat may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

I. Product Submitted for Registration

[Brand name] [Non-proprietary name] [Applicant] [Date of application] Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg Riociguat Bayer Yakuhin, Ltd. May 17, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Clinical positioning of Riociguat

Taking account of the fact that there are currently no drugs in Japan that are indicated for chronic thromboembolic pulmonary hypertension (CTEPH) and the design and results of studies conducted, PMDA concluded that Riociguat may be used as the first-line drug for patients with pulmonary endarterectomy (PEA)-ineligible or postoperative persistent or recurrent CTEPH. The conclusion of PMDA was supported by the expert advisors.

(2) Efficacy

In a global phase III study (Study 11348) including Japan, the efficacy of riociguat for CTEPH was demonstrated by the change in the 6-minute walking distance (6MWD) from baseline, the primary endpoint, and the change in pulmonary vascular resistance index (PVRI) from baseline, the additional endpoint. This conclusion of PMDA was supported by the expert advisors. The following comment was raised by expert advisors: The true endpoint is improvement of the prognosis, and 6MWD is considered to be a surrogate endpoint. Therefore, evaluation of the efficacy of riociguat in the post-marketing surveillance should be performed including the evaluation of the effect on the prognosis.

(3) Safety

1) Syncope

Although the results of clinical studies did not suggest any increased risk of syncope, caution should be raised against syncope, taking account of the mechanism of action of riociguat (vasodilating action) and the consequence of syncope in daily life. This conclusion of PMDA was supported by the expert advisors. Also, the following comment was raised by expert advisors: Since decreased blood pressure and/or syncope may occur during treatment with riociguat, patients receiving riociguat should be provided with precautions to be extremely careful while engaged in potentially hazardous machine operations including driving.

Based on the above, PMDA instructed the applicant to include precautions for operating potentially hazardous machines including driving in "Important Precautions," and the applicant followed these instructions appropriately.

2) Other adverse events of concern

Adverse events frequently observed after riociguat administration included headache, dyspepsia,

oedema peripheral, dizziness, diarrhoea, vomiting, and nasopharyngitis. These adverse events caused by the smooth muscle relaxant effect of riociguat including the vasodilating action are clinically acceptable risks. In patients with hypotension and patients with underlying diseases that may be aggravated by the vasodilating action of riociguat, the risks can be controlled by providing caution for careful administration. This conclusion of PMDA was supported by the expert advisors.

3) Administration in patients with renal impairment

In patients with renal impairment with creatinine clearance (CL_{CR}) of ≥ 15 and <80 mL/min, careful administration should be required, and consideration should be given to starting with a lower dose and to increase the dose while paying attention to possible hypotensive symptoms. This conclusion of PMDA was supported by the expert advisors. As regards patients with severe renal impairment with CL_{CR} of <15 mL/min and patients on dialysis, PMDA concluded that riociguat should be contraindicated in these patients for the following reasons: (i) blood riociguat concentration may increase, (ii) there is no clinical experience in this patient group, and (iii) hypotension-related risk may increase with the increase in exposure to riociguat. This conclusion of PMDA also was supported by the expert advisors.

Based on the above, PMDA instructed the applicant to provide a caution statement in "Careful Administration" to give consideration to starting the treatment in patients with renal impairment at a lower dose than 1.0 mg 3 timesdaily. The applicant followed the instructions appropriately.

4) Administration in patients with hepatic impairment

In patients with mild to moderate hepatic impairment (Child-Pugh class A or B), careful administration should be required because of the following reasons: increase in blood riociguat concentration is of concern; clinical experience in these patients are limited. This conclusion of PMDA was supported by the expert advisors. In patients with severe hepatic impairment (Child-Pugh class C), riociguat should be contraindicated for the following reasons: (i) it is difficult to predict the extent of increase in blood riociguat concentration, (ii) there is no information on the pharmacokinetics, efficacy, or safety of riociguat, and (iii) hypotension-related risk may be enhanced with the increase in exposure to riociguat. This conclusion of PMDA also was supported by the expert advisors.

5) **Drug-drug interaction studies**

Concomitant use with clarithromycin caused a 1.3 to 1.5 times increase in AUC of riociguat. The increase in plasma riociguat concentration induced by concomitant drugs may possibly enhance the effects of riociguat such as hypotention. Therefore, potent CYP3A inhibitors should be specified as drugs requiring precautions for concomitant use in the package insert to advise physicians to administer riociguat carefully with these drugs. This conclusion of PMDA was supported by the expert advisors.

Based on the above, PMDA instructed the applicant to specify potent CYP3A inhibitors as drugs requiring precautions for concomitant use in the package insert, and the applicant followed the instructions appropriately.

(4) Consistency of data between the entire population and the Japanese population

Consistency in data between the entire population and the Japanese population in Study 11348 was discussed at the Expert Discussion. The following comments were raised by expert advisors: (i) There were no sufficient number of Japanese patients to allow the evaluation of efficacy; however, results of individual Japanese patients showed improvements in both 6MWD and PVRI in 7 of 11 patients in the riociguat group, whereas, in the placebo group, no patients showed improvement in either 6MWD or PVRI; thus, the data demonstrate a certain level of efficacy in the Japanese population as well; (ii) There is a divergence between the mean and median change

in 6MWD from baseline in the Japanese patients, with the mean change suggesting a tendency different from that in the entire population; this raises skepticism concerning the consistency in data between the entire population and the Japanese population. To the latter comment, PMDA explained that, among a small number of patients in the Japanese population, there was 1 patient who did not make the visit at study discontinuation due to clinical aggravation and whose missing data was imputed by the worst value (0 m) and that the divergence between the mean and median change of 6MWD in the Japanese population was likely to be caused by this factor. When the median changes in 6MWD were compared in consideration of such a background, there was no discrepancy in data between the entire population and the Japanese population. Also, PVRI, another objective parameter, showed a tendency of improvement in the riociguat group compared with the placebo group in the Japanese population as well. Thus, upon comprehensive evaluation of data, including the efficacy results in individual Japanese patients, PMDA concluded that riociguat is expected to be effective in Japanese patients as well.

On the basis of the above discussion, the expert advisors supported the PMDA's conclusion that the efficacy demonstrated in the entire population is expected in the Japanese population as well.

(5) Indication

Discussion was made at the Expert Discussion on the PMDA's conclusion that it is acceptable to indicate riociguat for inoperable or postoperative persistent or recurrent chronic thromboembolic pulmonary hypertension. The following comments were raised by expert advisors: (i) In order to identify the study population in the clinical studies of riociguat more clearly, the term inoperable or postoperative persistent or recurrent should be changed to pulmonary endarterectomy-ineligible, or postoperative persistent or recurrent; (ii) At the current moment, there are no problems in clearly indicating pulmonary endarterectomy (PEA); however, since surgical treatments other than PEA may become widely used in future, including percutaneous transluminal pulmonary artery dilatation (balloon pulmonary angioplasty) using catheters, which is being performed in an increasing frequency in Japan, it is more appropriate to describe surgical treatment-ineligible, or postoperative persistent or recurrent; (iii) A caution statement should be provided to indicate that the surgical treatment is the treatment recommended in the guideline for CTEPH treatment.

Discussion was also made on the PMDA's conclusion that riociguat should be indicated for CTEPH regardless of WHO functional class. The following comments were raised by expert advisors: (i) Since patients with WHO functional class I were assigned only to the riociguat group in Study 11348, efficacy of riociguat relative to placebo cannot be evaluated; therefore, appropriateness of including class I patients in the indication should be carefully determined; (ii) Patients for whom riociguat is indicated, namely those with surgical treatment-ineligible CTEPH or those with postoperative persistent or recurrent CTEPH, are obviously in considerably aggravated conditions; therefore, it is unlikely that riociguat is administered to class I patients for whom consideration of the feasibility of surgical operation is unnecessary; thus, for riociguat treatment, it is unnecessary to clearly indicate patients' eligibility according to WHO functional class. As a result of the discussion, the expert advisors agreed that it is not necessary to limit the indication of riociguat by WHO functional class.

Based on the above discussion, PMDA has concluded that indication and precautions for indication should be set as shown below.

[Indication]

Inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or postoperative persistent or recurrent CTEPH

[Precautions for indication]

Appropriateness of riociguat administration should be determined by referring to the current guideline for the treatment of chronic thromboembolic pulmonary hypertension.

(6) **Dosage and administration**

Dosage and administration and Precautions for dosage and administration which PMDA presented in "4.(iii).B.(7). Dosage and administration" of the Review Report (1) were supported by the expert advisors. The following comment was raised by expert advisors: safety has not been investigated in patients with systolic blood pressure of <95 mmHg treated with riociguat at the starting dose of 1.0 mg 3 times daily; therefore, to ensure safety, it should be cautioned that a lower starting dose needs to be considered in such patients.

PMDA concluded that it is necessary to raise caution to consider a lower starting dose, depending on the condition of each patient, for the following reasons: (i) exposure to riociguat is likely to increase in patients with renal impairment, hepatic impairment, and in patients receiving concomitant other drugs; and (ii) safety has not been investigated in patients with systolic blood pressure of <95 mmHg. Based on the above discussion, PMDA has concluded that "Dosage and administration" and "Precautions for dosage and administration" should be set as shown below.

[Dosage and administration]

Dose titration period

The usual initial dosage for adults is 1.0 mg of Riociguat administered orally 3 times daily. If the systolic blood pressure remains at \geq 95 mmHg for 2 weeks and the patient shows no signs or symptoms of hypotension, the dose should be increased by 0.5 mg at 2-week intervals up to the maximum daily dose of 2.5 mg 3 times daily. If the systolic blood pressure is <95 mmHg but the patient shows no signs or symptoms of hypotension, the current dose should be maintained. If the patient shows any signs or symptoms of hypotension, the dose should be reduced by 0.5 mg 3 times daily.

Dose maintenance period

The dose determined during the dose titration period should be maintained. The maximum daily dose is 2.5 mg 3 times daily during the dose maintenance period as well. If not tolerated (e.g., occurrence of signs or symptoms of hypotension), the dose should be reduced by 0.5 mg 3 times daily.

[Precautions for dosage and administration]

- 1. Consideration should be given to starting the treatment at a lower daily dose than 1.0 mg 3 times daily depending on the condition of each patient (see "Careful Administration" and "Interactions").
- 2. It is desirable to administer riociguat at approximately 6- to 8-hour intervals. In case of a missed dose, the patients should continue with the next scheduled dose.
- 3. If the treatment is interrupted for 3 days or longer, the patients should resume the regimen by referring to the starting dose, after which the dose should be adjusted according to the procedure as described in the "Dosage and administration".

(7) Risk management plan (draft)

Based on the results of the review in "4.(iii).B.(8) Post-marketing investigations" of the Review Report (1) and on the comments raised by expert advisors at the Expert Discussion, PMDA considers that the following should be added to the post-marketing surveillance.

• Safety in patients with baseline systolic blood pressure of <95 mmHg, patients with renal impairment, and patients with hepatic impairment

Safety of concomitant use with CYP3A inhibitors, CYP1A1 inhibitors, and inhibitors of Pglycoprotein (P-gp)/breast cancer-resistant protein (BCRP)

PMDA instructed the applicant to investigate the above issues in the post-marketing surveillance, to which the applicant responded by submitting an appropriate post-marketing surveillance plan (draft) (Table 31).

Based on the above discussion, PMDA concluded, regarding the risk management plan of riociguat at the current moment, that safety- and efficacy-related investigation should be conducted as shown in Table 29, and that additional pharmacovigilance activities and risk minimization actions should be conducted as shown in Table 30. The applicant responded by submitting the risk management plan (draft) based on Tables 29 and 30.

 Table 29. Safety and Efficacy Specification in the risk management plan

Safety Specification		
Important identified risks	Important potential risks	Important missing information
 Hypotension Motility disorder of upper gastrointestinal tract Patients with pulmonary vein occlusive disease (PVOD) 	 Severe haemoptysis/pulmonary haemorrhage Drug-drug interactions (CYP1A1 inhibitors) Smoking 	 Long term administration Patients with baseline systolic blood pressure of <95 mmHg Patients with renal impairment Patients with hepatic impairment Concomitant use (CYP3A inhibitors, CYP1A1 inhibitors, P- gp/BCRP inhibitors)
Efficacy Specification		
Long-term efficacy in routine	clinical use	

Table 30. Additional pharmacovigilance activities and risk minimization actions in the risk management plan

Additional pharmacovigilance activities	Additional risk minimization actions
 Early Post-marketing phase vigilance Use-results survey (all-case surveillance) Post-marketing clinical study^{a)} 	 Information provision based on early post- marketing phase vigilance Preparation and distribution of materials for patients for proper use (information leaflets for patients)

a) After approval of riociguat, Study 11349 (ongoing) is to be continued under the name of a postmarketing clinical study until riociguat becomes widely available for use in medical institutions.

Objective	To investigate the long-term safety and efficacy in routine clinical use
Method	All-case surveillance
Patients	Patients with inoperable CTEPH or those with postoperative persistent or recurrent CTEPH
Observation period	One year standard observation period, with a follow-up study period of up to 7 years whenever possible if riociguat is used continuously
Target sample size	420 patients (400 patients to be included in safety analysis population)
Priority investigation items	Hypotension, upper gastrointestinal motility disorder, haemoptysis/pulmonary haemorrhage, pulmonary congestion/pulmonary oedema

Table 31. Outline of use-results survey (proposed)

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administrations shown below, with the following conditions. The re-examination period of the product is 10 years, the drug substance and the drug product are both

classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]	Inoperable chronic thromboembolic pulmonary hypertension (CTEPH)
	or postoperative persistent or recurrent CTEPH

[Dosage and administration]

Dose titration period

The usual initial dosage for adults is 1.0 mg of Riociguat administered orally 3 times daily. If the systolic blood pressure remains at \geq 95 mmHg for 2 weeks and the patient shows no signs or symptoms of hypotension, the dose should be increased by 0.5 mg at 2-week intervals up to the maximum daily dose of 2.5 mg 3 times daily. If the systolic blood pressure is <95 mmHg but the patient shows no signs or symptoms of hypotension, the current dose should be maintained. If the patient shows any signs or symptoms of hypotension, the dose should be reduced by 0.5 mg 3 times daily.

Dose maintenance period

The dose determined during the dose titration period should be maintained. The maximum daily dose is 2.5 mg 3 times daily during the dose maintenance period as well. If not tolerated (e.g., occurrence of signs or symptoms of hypotension), the dose should be reduced by 0.5 mg 3 times daily.

[Conditions for approval]

The applicant is required to conduct a drug use-results survey involving all treated patients after the market launch until data from a certain number of patients have been accumulated in order to grasp the characteristics of patients treated with this product, since the product has been studied only in a limited number of patients in Japan; and at the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.