**Report on the Deliberation Results**

May 28, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Verquvo Tablets 2.5 mg, Verquvo Tablets 5 mg, Verquvo Tablets 10 mg |
| **Non-proprietary Name** | Vericiguat (JAN*) |
| **Applicant** | Bayer Yakuhin, Ltd. |
| **Date of Application** | June 5, 2020 |

**Results of Deliberation**

In its meeting held on April 28, 2021, the First Committee on New Drugs concluded that the product may be approved after revising the risk management plan (draft) as shown below and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product is not classified as a poisonous drug or a powerful drug, and its drug substance is classified as a powerful drug.

Risk management plan (draft)

| New | Old |
|---|---|
| Important identified risks<br>· Hypotension<br>Important potential risks<br>· Concomitant use with nitrates or NO donors<br>· Concomitant use with PDE5 inhibitors<br>Important missing information<br>· Safety of vericiguat in patients with renal impairment<br>· Safety of vericiguat in patients with hepatic impairment<br>· Safety of vericiguat in patients with blood pressure <100 mmHg or symptomatic hypotension<br>· <u>Long-term safety (including the incidence of cardiovascular death)</u> | Important identified risks<br>· Hypotension<br>Important potential risks<br>· Concomitant use with nitrates or NO donors<br>· Concomitant use with PDE5 inhibitors<br>Important missing information<br>· Safety of vericiguat in patients with renal impairment<br>· Safety of vericiguat in patients with hepatic impairment<br>· Safety of vericiguat in patients with blood pressure <100 mmHg or symptomatic hypotension |
| Efficacy specification<br>· None | Efficacy specification<br>· None |
| Additional pharmacovigilance activities<br>· Early post-marketing phase vigilance<br>· <u>Comparative use-results survey</u><br>Additional risk minimization activities<br>· Disseminate data gathered during early post-marketing phase vigilance<br>· Prepare and distribute information materials to healthcare professionals (Guide for healthcare professionals prescribing Verquvo Tablets)<br>· Prepare and distribute information materials to patients (Guide for patients taking Verquvo Tablets) | Additional pharmacovigilance activities<br>· Early post-marketing phase vigilance<br>· <u>Specified use-results survey</u><br>Additional risk minimization activities<br>· Disseminate data gathered during early post-marketing phase vigilance<br>· Prepare and distribute information materials to healthcare professionals (Guide for healthcare professionals prescribing Verquvo Tablets)<br>· Prepare and distribute information materials to patients (Guide for patients taking Verquvo Tablets) |

(Underline denotes changes.)

**Approval Condition**

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

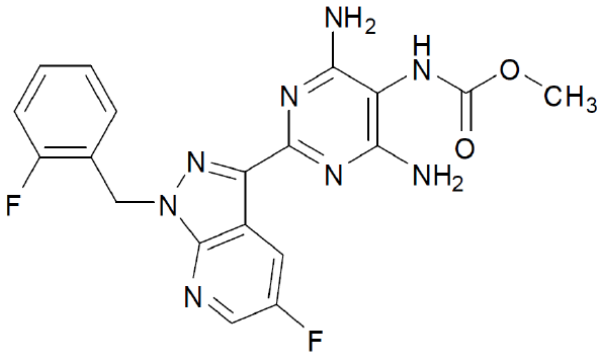
**Review Report**

February 3, 2021
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

| | |
|---|---|
| **Brand Name** | Verquvo Tablets 2.5 mg, Verquvo Tablets 5 mg, Verquvo Tablets 10 mg |
| **Non-proprietary Name** | Vericiguat |
| **Applicant** | Bayer Yakuhin, Ltd. |
| **Date of Application** | June 5, 2020 |
| **Dosage Form/Strength** | Tablets: Each tablet contains 2.5, 5, or 10 mg of vericiguat. |
| **Application Classification** | Prescription drug, (1) Drug with a new active ingredient |

**Chemical Structure**



Molecular formula: $C_{19}H_{16}F_2N_8O_2$
Molecular weight: 426.38
Chemical name:
Methyl (4,6-diamino-2-{5-fluoro-1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)carbamate

**Items Warranting Special Mention** None

**Reviewing Office** Office of New Drug II

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of chronic heart failure, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition. The incidence of hypotension etc. should be further investigated.

**Indication**

Chronic heart failure (only in patients who are receiving standard treatment for chronic heart failure)

**Dosage and Administration**

The usual adult starting dose is 2.5 mg of vericiguat administered orally once daily with food. The dose should be doubled every 2 weeks to 5 mg, and then to 10 mg. The dose should be decreased as appropriate according to the patient's condition such as blood pressure.

**Approval Condition**

The applicant is required to develop and appropriately implement a risk management plan.

**Attachment**

# Review Report (1)

December 11, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Verquvo Tablets 2.5 mg, Verquvo Tablets 5 mg, Verquvo Tablets 10 mg |
| **Non-proprietary Name** | Vericiguat |
| **Applicant** | Bayer Yakuhin, Ltd. |
| **Date of Application** | June 5, 2020 |
| **Dosage Form/Strength** | Tablets: Each tablet contains 2.5, 5, or 10 mg of vericiguat. |

**Proposed Indication**

Chronic heart failure (only in patients who are receiving standard treatment for chronic heart failure)

**Proposed Dosage and Administration**

The usual adult starting dose is 2.5 mg of vericiguat administered orally once daily with food. The dose should be doubled approximately every 2 weeks to 5 mg, and then to 10 mg once daily with food. The dose should be adjusted as appropriate according to the patient's condition.

**Table of Contents**



**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Vericiguat is a soluble guanylate cyclase (sGC) stimulator discovered by Bayer, which increases cyclic guanosine monophosphate (cGMP) production. This produces vasodilation, improved hemodynamics such as lowering of blood pressure, and reduced cardiac afterload, thus hypothetically slowing the pathologic processes of chronic heart failure.

Outside Japan, the clinical development of vericiguat began in 20[redacted]. In [redacted] 20[redacted], applications for the approval of vericiguat for the treatment of chronic heart failure with reduced left ventricular ejection fraction (LVEF) were submitted in the US and [redacted]. [redacted] as of [redacted] 20[redacted].

In Japan, the clinical development of vericiguat was initiated in 20[redacted]. The applicant has filed a marketing application for vericiguat for the indication of "chronic heart failure (only in patients who are receiving standard treatment for chronic heart failure)" based on the results from global studies in patients with chronic heart failure with reduced LVEF, etc.

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

### 2.1 Drug substance

#### 2.1.1 Characterization

The drug substance is a white to yellowish powder, and its appearance, ultraviolet/visible spectrum (UV/VIS), pH, dissociation constant, partition coefficient, hygroscopicity, density, and solubility have been determined. The drug substance exists in 5 polymorphic forms (Polymorphic Forms I to V), solvated forms ([redacted]/[redacted], [redacted], [redacted], [redacted], and [redacted]), and an amorphous substance. Polymorphic Form [redacted] is the most thermodynamically stable at room temperature. Polymorphic Form [redacted] only is consistently produced by the commercial manufacturing process.

Its chemical structure has been elucidated by infrared spectrophotometry (IR), Raman spectroscopy, UV/VIS, nuclear magnetic resonance spectrometry (NMR) ($^{1}$H- and $^{13}$C-NMR), mass spectrometry, and elemental analysis.

#### 2.1.2 Manufacturing process

The drug substance is synthesized by [redacted] reaction with a derivative formed by [redacted], using [redacted] as the starting material.

Quality by Design (QbD) approaches were used. A quality control strategy was established based on the following (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) and determination of the proven acceptable ranges for manufacturing process parameters through quality risk assessment etc.

Table 1. Overview of drug substance control strategy

| CQA | Method of control |
|---|---|
| Identity | Manufacturing process, Specification |
| Appearance | Specification |
| Related substances | Manufacturing process, Specification |
| Residual solvents | Manufacturing process, Specification |
| [redacted] | Manufacturing process, Specification |
| Water content | Manufacturing process, Specification |
| Particle size | Manufacturing process, Specification |
| Content | Manufacturing process, Specification |

[redacted] and [redacted] have been defined as critical steps. [redacted], [redacted], and [redacted] are controlled as critical intermediates.

### 2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identity (IR, high performance liquid chromatography [HPLC]), purity [[redacted] (inductively coupled plasma mass spectrometry), related substances (HPLC), residual solvents (gas chromatography [GC])], water content, particle size (laser diffraction), and assay (HPLC).

### 2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2. The stability results indicated that the drug substance is stable. Photostability data showed that the drug substance is photostable.

Table 2. Primary stability studies on drug substance

| Study | Primary batches | Temperature | Humidity | Storage package | Storage period |
|---|---|---|---|---|---|
| Long-term | 3 production-scale batches | 25°C | 60%RH | Polyethylene (PE) bag | 24 months |
| Accelerated | | 40°C | 75%RH | | 6 months |

Based on the above, a re-test period of 36 months was proposed for the drug substance packaged in a PE bag and stored at room temperature, in accordance with the ICH Q1E guideline.

## 2.2 Drug product

### 2.2.1 Description and composition of drug product and formulation development

The drug product is presented as film-coated tablets in 3 strengths. Each tablet contains 2.5, 5, or 10 mg of vericiguat and the following excipients: microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and lacquer white (2.5-mg tablets), lacquer red (5-mg tablets), or lacquer yellow (10-mg tablets).

### 2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of mixing, granulation, blending with [redacted], compression, coating, and packaging/labeling.

The quality control strategy has been formulated by doing the following using a quality by design (QbD) approach (Table 3):

- Identification of CQAs
- Identification of CPPs and determination of the proven acceptable ranges for manufacturing process parameters through failure mode effects analysis, design of experiments, etc.

Table 3. Overview of drug product control strategy

| CQA | Method of control |
|---|---|
| Description (Appearance) | Manufacturing process, Specification |
| Identity | Specification |
| Strength | Manufacturing process, Specification |
| Purity (Related substances) | Manufacturing process, Specification |
| Uniformity of dosage units | Manufacturing process, Specification |
| Dissolution | Manufacturing process, Specification |
| Microbial limits | Specification |

[redacted] has been defined as a critical step, and process control items and values have been established for [redacted] and [redacted].

### 2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identity (HPLC), purity [related substances (HPLC)], uniformity of dosage units (HPLC), microbial limits, dissolution (HPLC), and assay (HPLC).

### 2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 4. The stability results indicated that the drug product is stable. Photostability data showed that the drug product is photostable.

Table 4. Primary stability studies on drug product

| Study | Primary batches | Temperature | Humidity | Storage package | Storage period |
|---|---|---|---|---|---|
| Long-term | 3 pilot-scale batches | 25°C | 60%RH | Blister pack ([redacted] film/aluminum) | 24 months |
| Accelerated | | 40°C | 75%RH | | 6 months |

Based on the above, a shelf-life of 36 months was proposed for the drug product packaged in a blister pack ([redacted] film/aluminum) and stored at room temperature, in accordance with the ICH Q1E guideline. The long-term testing will be continued up to 60 months.

## 2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

### 3.1.1 *In vitro* studies

#### 3.1.1.1 Stimulation of sGC

##### 3.1.1.1.1 sGC (CTD 4.2.1.1.1 and 4.2.1.1.2)

Recombinant rat sGC was incubated with vericiguat (0.01-100 μmol/L) alone or in the presence of the nitric oxide (NO) donor, diethylamine/nitric oxide complex (DEA/NO) (1-100 nmol/L) or the sGC inhibitor, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) (100 μmol/L), with [$^{32}$P]-α-guanosine triphosphate (GTP), and the sGC activity was measured by the formation of [$^{32}$P]-cGMP. Vericiguat increased the sGC activity concentration-dependently, by 1.7-fold to 57.6-fold relative to no stimulation. In combination, vericiguat and DEA/NO increased the sGC activity concentration-dependently, and at the highest concentrations of vericiguat (100 μmol/L) and DEA/NO (100 nmol/L), the sGC activity was 341.6-fold above baseline. The stimulatory effect of vericiguat on sGC was inhibited by ODQ and reduced to 18-fold at 100 μmol/L of vericiguat.

Vericiguat (0.001-10 μmol/L) and the NO donor linsidomine (5 μmol/L) were added to recombinant rat sGC and incubated with GTP. The sGC activity over time was measured by the formation of pyrophosphoric acid (PPi). Vericiguat stimulated sGC in a concentration- and time-dependent manner.

##### 3.1.1.1.2 sGC-overexpressing cells (CTD 4.2.1.1.3, 4.2.1.1.4, 4.2.1.1.6, and 4.2.1.1.7)

Rat sGC overexpressed by a CHO cell line (a reporter cell line) expressing cyclic nucleotide-gated channel alfa 2 (CNGA2) and a calcium-sensitive photoprotein (aequorin) was incubated with vericiguat (0.0003-10 μmol/L) alone or in the presence of the NO donor, S-nitroso-N-acetyl-D,L-penicillamine (SNAP) (30 or 100 nmol/L), and the sGC activity was measured by aequorin luminescence induced by $Ca^{2+}$ influx through CNGA2 activated by intracellular cGMP. Pretreatment of the cell line with ODQ (10 μmol/L) was also conducted in the above experiment. Vericiguat increased the sGC activity concentration-dependently, with an $EC_{50}$ of 1005 ± 145 nmol/L. In the presence of SNAP (30 and 100 nmol/L), the $EC_{50}$ values shifted to 39.0 ± 5.1 and 10.6 ± 1.7 nmol/L, respectively. Pretreatment of the cell line with ODQ resulted in a reduced efficacy of vericiguat, and the effect of vericiguat was not enhanced in the presence of SNAP. A metabolite of vericiguat, M-1 (the *N*-glucuronide of vericiguat) (10 μmol/L) was tested in the same assay. M-1 did not increase the sGC activity.

The rat receptor guanylyl cyclase GC-A or the rat receptor guanylyl cyclase GC-B overexpressed by a reporter cell line was incubated with vericiguat (0.0003-30 μmol/L), and the GC activity was measured in the same manner. Vericiguat did not increase the GC activity.

##### 3.1.1.1.3 Vascular endothelial cells (CTD 4.2.1.1.5)

Endothelial cells isolated from porcine pulmonary artery were incubated with vericiguat (0.001-10 μmol/L) alone or in the presence of the NO donor DEA/NO (0.01-1 μmol/L) or the sGC inhibitor ODQ (10 μmol/L), and cGMP concentrations in the homogenate buffer were determined by a radioimmunoassay. DEA/NO (0.01-1 μmol/L) alone was also tested. Vericiguat alone increased the cGMP concentration concentration-dependently, by 1.3-fold to 110.8-fold relative to no stimulation. DEA/NO alone increased the cGMP concentration concentration-dependently, by 4.4-fold to 81.4-fold relative to no stimulation. In combination,

vericiguat and DEA/NO increased the cGMP concentration concentration-dependently, with a maximal effect at 10 μmol/L of vericiguat and 0.1 μmol/L of DEA/NO (the cGMP concentration was 604.7-fold above baseline). An increase in cGMP induced by vericiguat was inhibited by ODQ and reduced to 5-fold at 10 μmol/L of vericiguat.

#### 3.1.1.2 Effects on isolated vessels (CTD 4.2.1.1.8 and 4.2.1.1.11)

The effects of vericiguat (0.023-23 μmol/L) on phenylephrine-induced contractions of the rings of rabbit saphenous artery, rabbit aorta, and canine femoral vein were investigated. Phenylephrine-induced contractions were inhibited by vericiguat in a concentration-dependent manner with $IC_{50}$ values of 798, 692, and 3072 nmol/L, respectively. The effects of vericiguat (0.00023-23 μmol/L) on thromboxane $A_2$ ($TXA_2$) receptor agonist, U-46619-induced contractions of porcine coronary artery rings were investigated. Vericiguat inhibited the U-46619-induced contractions concentration-dependently, with an $IC_{50}$ of 956 nmol/L.

Isosorbide dinitrate (150-250 mg) was administered subcutaneously 3 times daily for 3 to 4 days to male rabbits (13-16/group), which led to the development of nitrate tolerance. The effect of vericiguat (0.00023-2.3 μmol/L) or nitroglycerin (0.00044-4.4 μmol/L) on phenylephrine-induced contractions of isolated saphenous artery rings taken from nitrate-tolerant male rabbits was examined. Isolated saphenous artery rings taken from normal male rabbits not treated with isosorbide dinitrate (14-17/group) were also tested. Vericiguat and nitroglycerin inhibited the phenylephrine-induced contractions of both nitrate-tolerant and normal saphenous artery rings of rabbits concentration-dependently. The $IC_{50}$ values of vericiguat were 5.8 and 5.6 nmol/L, respectively. The $IC_{50}$ values of nitroglycerin were 9.6 and 1.9 nmol/L, respectively.

#### 3.1.1.3 Effects on human platelets (CTD 4.2.1.1.10)

Human platelets (6/group) were prepared from venous blood collected from healthy volunteers and incubated with vericiguat (0.03-10 μmol/L), the NO donor sodium nitroprusside (SNP) (0.1-30 μmol/L), or the NO donor DEA/NO (0.001-0.3 μmol/L). Then, sGC-dependent vasodilator-stimulated phosphoprotein (VASP) phosphorylation (Ser239 and Ser157) was analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)-immunoblotting, and cGMP concentrations were determined by a radioimmunoassay. The sGC stimulatory effects of vericiguat (0.03 or 0.1 μmol/L) in combination with SNP (0.1-30 μmol/L) or vericiguat (0.1 μmol/L) in combination with DEA/NO (0.001-0.3 μmol/L) in human platelets (5-6/group) were also investigated. Vericiguat, SNP, or DEA/NO alone increased the cGMP concentration concentration-dependently, by up to 16-fold, 5.3-fold, or 9.3-fold, respectively, relative to no stimulation. Vericiguat in combination with SNP or DEA/NO induced a concentration-dependent increase in cGMP levels, with a maximal response at their highest concentrations, i.e., 18.4-fold or 35.5-fold increases, respectively. Each test article showed a concentration-dependent increase in VASP phosphorylation, and a similar trend was observed for Ser239 phosphorylation and Ser157 phosphorylation.

#### 3.1.1.4 Effects on isolated heart (CTD 4.2.1.1.9)

The hearts isolated from male rats (4-13/group) were perfused with Krebs-Henseleit solution and with vericiguat (0.001-10 μmol/L). Coronary perfusion pressure, heart rate, left ventricular developed pressure

(LVDP), and $+dP/dt_{max}$ as a marker of left ventricular contractility were measured. Vericiguat reduced the coronary perfusion pressure concentration-dependently with significant effects at ≥1 μmol/L, and there was a 31.8% reduction at 10 μmol/L. Heart rate, LVDP, or $+dP/dt_{max}$ was not significantly changed by the application of vericiguat up to the highest concentration tested.

### 3.1.2 *In vivo* studies

#### 3.1.2.1 Effects on hemodynamics in healthy animals (CTD 4.2.1.1.12, 4.2.1.1.13, 4.2.1.1.14, and 4.2.1.1.18)

Anesthetized male rats (7-8/group) were dosed with vericiguat (single oral dossing of 0.3, 1, 3, or 10 mg/kg, IV bolus dosing of 0.03, 0.1, 0.3 or 1 mg/kg) or vehicle (single oral dosing of Transcutol + Cremophor + water [10:20:70], IV bolus dosing of Transcutol + Cremophor + phosphate buffered saline [PBS] [10:10:80]), and hemodynamic parameters were measured (up to 120 minutes after single oral dosing, up to 60 minutes after IV bolus dosing). Single oral dosing of vericiguat resulted in a dose-dependent decrease in mean arterial pressure, and the maximum blood pressure lowering effect of vericiguat occurred by 50 to 60 minutes post-dose. The maximum changes from baseline were −12, −33, −45, and −45 mmHg at 0.3, 1, 3, and 10 mg/kg, respectively. A dose-dependent increase in heart rate was observed. IV bolus dosing of vericiguat resulted in a dose-dependent decrease in mean arterial pressure, and the maximum changes from baseline were −16, −26, −31, and −62 mmHg at 0.03, 0.1, 0.3, and 1 mg/kg, respectively. There was a trend towards an increase in heart rate at 10 mg/kg of vericiguat.

Conscious female rats (4-5/group) were treated with a single oral dose of vericiguat (0.3, 1 or 3 mg/kg) or vehicle (Transcutol + Cremophor + water [10:20:70]), and hemodynamic parameters were measured using telemetry up to 24 hours post-dose. Single oral dosing of vericiguat resulted in a dose-dependent decrease in mean arterial pressure, and the vericiguat 1 and 3 mg/kg groups showed blood pressure lowering by approximately a maximum of 15% from baseline. Blood pressure reduction plateaued for 1 hour after dosing of 1 mg/kg and for 10 hours after dosing of 3 mg/kg and then slowly normalized to control levels. There was a dose-dependent increase in heart rate, with a maximum increase from baseline of 20%.

Anesthetized male dogs (5/group) were treated with IV bolus (cumulative doses from a low dose to a high dose) vericiguat (10, 30, 100, and 300 μg/kg), nitroglycerin (0.3, 1, and 3 μg/kg), or vehicle (Transcutol + saline [70:30]), and hemodynamic parameters were measured up to 50 minutes after each dose. IV bolus dosing of vericiguat resulted in a dose-dependent decrease in mean arterial pressure, and the maximum decreases from baseline were 2.1%, 3.4%, 8.6%, 17.0%, and 28.2% immediately after dosing of vehicle and vericiguat 10, 30, 100, and 300 μg/kg, respectively. Reductions in mean arterial pressure were accompanied by decreases in systolic left ventricular pressure, left ventricular end-diastolic pressure (LVEDP), central venous pressure, and systemic vascular resistance and increases in heart rate and first derivative of ventricular pressure (+dP/dt). Vericiguat 100 and 300 μg/kg showed a long-lasting decrease in pulmonary artery pressure. Dosing of vericiguat resulted in dose-dependent increases in cardiac output, coronary blood flow, and oxygen saturation in the coronary sinus ($SVO_2$).

#### 3.1.2.2 Effects in spontaneously hypertensive rats (CTD 4.2.1.1.15 and 4.2.1.1.16)

Conscious spontaneously hypertensive female rats (6/group) were treated with a single oral dose of vericiguat (0.03, 0.1, 0.3, 1, or 3 mg/kg) or vehicle (Transcutol + Cremophor + water [10:20:70]), and hemodynamic parameters were measured using telemetry up to 24 hours post-dose. Single oral dosing of vericiguat resulted in a dose-dependent decrease in mean arterial pressure. The maximum blood pressure lowering effect of vericiguat occurred within 2 hours post-dose in the 3 mg/kg group, which showed blood pressure lowering by approximately 30% from baseline. In the 0.3 and 1 mg/kg groups, the decrease in blood pressure lasted for 4 to 6 hours and then almost returned to baseline by 12 hours post-dose. Blood pressure reduction lasted for at least 24 hours in the vericiguat 3 mg/kg group. There was a dose-dependent increase in heart rate, with a maximum increase from baseline of approximately 30% in the vericiguat 3 mg/kg group, which returned to baseline by 24 hours post-dose.

Conscious spontaneously hypertensive female rats (6/group) were dosed with vericiguat (3 or 10 mg/kg) or vehicle (Transcutol + Cremophor + water [10:20:70]) orally once daily for 12 days, and hemodynamic parameters were measured using telemetry up to 2 days after the last dose. Vericiguat at both dose levels caused a decrease in mean arterial pressure and an increase in heart rate, and these effects disappeared at 1 day after the last dose.

#### 3.1.2.3 Effects in renin transgenic rats (CTD 4.2.1.1.17)

Renin transgenic rats carrying the mouse Ren2 gene (8 weeks of age, males) that spontaneously develop severe hypertension were treated with an NO synthase inhibitor that induces endothelial dysfunction and NO deficiency, NG-nitro-L-arginine methyl ester (L-NAME) (50 mg/L) in the drinking water, to create an animal model of further hypertension and heart hypertrophy-like symptoms. All of L-NAME-treated rats (15-20/group) were dosed with vericiguat (3 or 10 mg/kg) or vehicle (Transcutol + Cremophor + water [10:20:70]) orally once daily for 22 days. Blood pressure (before the start of treatment and on Days 7, 14, and 21) and body weight (on Days 1, 8, 15, and 22) were measured. The isolated hearts and kidneys were weighed, and plasma/urine parameters were determined on Day 22 (excluding animals that died during the study period). Five of 20 rats in the control group, 10 of 15 rats in the vericiguat 3 mg/kg group, and 14 of 15 rats in the vericiguat 10 mg/kg group survived through the end of the study. Systolic blood pressure (SBP) increased over time in all treatment groups. In rats treated with vericiguat, SBP was lower with no significant difference compared to the control group. While relative heart weight was significantly lower in the vericiguat 10 mg/kg group than in the control group, there were no differences in relative kidney weight between the treatment groups. Plasma atrial natriuretic peptide (ANP) levels were significantly lower in the vericiguat 10 mg/kg group than in the control group. Urea and creatinine in plasma, and urinary protein excretion were significantly decreased in the vericiguat 3 and 10 mg/kg groups compared to the control group.

#### 3.1.2.4 Effects in pulmonary hypertension model (CTD 4.2.1.1.19 to 4.2.1.1.21)

Anesthetized male dogs (3/group) were maintained under hypoxic conditions to induce acute pulmonary arterial hypertension. Then the animals received IV bolus dosing (cumulative doses from a low dose to a high dose) of vericiguat (10, 30, 100, and 300 μg/kg), nitroglycerin (0.3, 1, and 3 μg/kg), or vehicle (Transcutol +

saline [70:30]), and hemodynamic parameters were measured up to 50 minutes after each dose. The effect of reflex tachycardia was suppressed by the autonomic blockade induced by continuous intravenous infusion of atropine and propranolol. Dosing of vericiguat resulted in a dose-dependent decrease in mean arterial pressure, and the maximum decreases from baseline were 5.2%, 4.1%, 6.6%, 11.8%, and 21.6% immediately after dosing of vehicle and vericiguat 10, 30, 100, and 300 μg/kg, respectively. Reductions in mean arterial pressure were accompanied by decreases in systolic left ventricular pressure and LVEDP. Following dosing of vericiguat 100 and 300 μg/kg, a transient increase in heart rate associated with a transient increase in +dP/dt were observed. Dose-dependent decreases in pulmonary artery pressure and central venous pressure and a dose-dependent increase in cardiac output were observed with decreases in systemic vascular resistance and pulmonary vascular resistance and an increase in $SVO_2$.

Anesthetized female minipigs (3-5/group) received continuous intravenous infusion of $TXA_2$ receptor agonist, U-46619 to induce acute pulmonary arterial hypertension. Then, the animals received IV bolus dosing (cumulative doses from a low dose to a high dose) of vericiguat (3, 10, 30, 100, and 300 μg/kg) or vehicle (Transcutol + saline [70:30]), and hemodynamic parameters were measured up to 50 minutes after each dose. Dosing of vericiguat resulted in dose-dependent decreases in pulmonary artery pressure, central venous pressure, and blood pressure, and an increase in heart rate.

Three conscious male dogs implanted with steroid-eluting pacemaker electrode underwent right ventricular pacing at 220 beats/minute for 14 days. Then, vehicle (ethanol + polyethyleneglycol + water [10:40:50]) or vericiguat (0.3, 1, and 3 mg/kg) was administered orally (cumulative doses from a low dose to a high dose) at intervals of 2 to 3 days, and blood pressure was measured up to 4 hours after each dose. The pacer was turned off during the blood pressure measurement period, and then tachypacing was resumed for 2 to 3 days until the next measurement of blood pressure. Dosing of vericiguat resulted in a dose-dependent decrease of mean arterial pressure and pulmonary artery pressure, with a significant decrease with vericiguat 1 mg/kg compared to vehicle.

### 3.2 Secondary pharmacodynamics

#### 3.2.1 Inhibition of molecular targets (CTD 4.2.1.2.1 to 4.2.1.2.5)

Vericiguat (10 μmol/L) was assessed for its inhibitory activity against various receptors and transporters (n = 68), enzymes (n = 42), and cyclic phosphodiesterases (PDEs) 1 to 11. Vericiguat at 10 μmol/L did not cause ≥50% inhibition of any of the receptors, transporters, and enzymes, except for the human dopamine transporter. The $IC_{50}$ of vericiguat for inhibition of the human dopamine transporter was 2.9 μmol/L.

Likewise, vericiguat's metabolite, M-1 (10 μmol/L) was assessed for its inhibitory activity against various receptors, transporters, and enzymes (n = 77). M-1 did not show ≥50% inhibition of any of the receptors, transporters, and enzymes.

### 3.2.2 Effect on human platelet aggregation (CTD 4.2.1.2.6)

Using platelet-rich plasma and washed platelets collected from healthy volunteers, the effect of vericiguat (0.3-100 μmol/L) on platelet aggregation was assessed. Vericiguat inhibited platelet aggregation induced by adenosine diphosphate (ADP), thrombin receptor activator peptide 6 (TRAP-6), collagen, and thromboxane. The $IC_{50}$ was 18.9 to >100 μmol/L in platelet-rich plasma and 1.24 to 2.22 μmol/L in washed platelets.

## 3.3 Safety pharmacology

The results of safety pharmacology studies are shown in Table 5.

Table 5. An overview of safety pharmacology studies

| Organ systems evaluated | Test system | Endpoints/Method of assessment, etc. | Dose | Route of administration | Findings | CTD |
|---|---|---|---|---|---|---|
| CNS | Wistar rats (6 males/group) | General behavioral observation, body temperature | 0,[a] 1.5, 5, 15 mg/kg single dose | Oral | 5 mg/kg: splayed hind limbs<br>15 mg/kg: ptosis, splayed hind limbs, slow deliberate gait, hypoactivity, delayed righting reflex, decrease in body temperature | 4.2.1.3.2 |
| | Wistar rats (12 males/group) | Motor coordination (RotaRod test) | 0,[a] 1.5, 5, 15 mg/kg single dose | Oral | No alteration of motor coordination | 4.2.1.3.3 |
| | Wistar rats (7 males/group) | Effects on convulsive threshold dose of PTZ | 0,[a] 1.5, 5, 15 mg/kg single dose | Oral | 15 mg/kg: Vericiguat increased the threshold dose of PTZ. | 4.2.1.3.4 |
| Cardiovascular system | hERG-transfected HEK293 cells (n = 5/group) | hERG current | 0,[b] 0.1, 1, 10 μmol/L | *In vitro* | Vericiguat inhibited hERG current by 12.9% and 50.1% at 1 and 10 μmol/L, respectively. | 4.2.1.3.1 |
| | Beagle dogs (4/sex/group) | Blood pressure, heart rate, ECG (Telemetry) | 0,[c] 0.6, 2, 6 mg/kg single dose | Oral | ≥0.6 mg/kg: decrease in blood pressure, increase in heart rate, shortened PQ interval, shortened QT interval | 4.2.1.3.7 |
| Respiratory system | Wistar rats (8 males/group) | Respiration rate, tidal volume, minute volume (Plethysmography) | 0,[a] 1.5, 5, 15 mg/kg single dose | Oral | No effects | 4.2.1.3.5 |
| Gastrointestinal system | Wistar rats (6 males/group) | Gastric emptying, intestinal transit | 0,[d] 1.5, 5, 15 mg/kg single dose | Oral | ≥5 mg/kg: inhibition of intestinal transit | 4.2.1.3.6 |

a: Ethanol + polyethyleneglycol (15)-hydroxystearate + water (10:40:50)
b: Pre-drug controls
c: Ethanol + polyethyleneglycol 400 (10:90)
d: 0.5% hydroxyethyl cellulose solution

### 3.4 Pharmacodynamic drug interactions

#### 3.4.1 Interactions with nitroglycerin (CTD 4.2.1.4.1 and 4.2.1.4.3)

Anesthetized male rats (5-6/group) received continuous intravenous infusion of vericiguat (3 or 30 μg/kg/min) alone, continuous intravenous infusion of vehicle (Transcutol + Cremophor + PBS [10:10:80]) in combination with IV bolus nitroglycerin (10 μg/kg) (dosed at 10 minutes prior to and 10 and 20 minutes after the start of infusion of vehicle), or continuous intravenous infusion of vericiguat (3 or 30 μg/kg/min) in combination with IV bolus nitroglycerin (10 μg/kg) (dosed at 10 minutes prior to and 10 and 20 minutes after the start of infusion of vericiguat), and blood pressure was measured up to 30 minutes after the start of infusion of vericiguat or vehicle. The mean changes from baseline were −8 and −19 mmHg (at 10 and 20 minutes after the start of infusion, respectively) following infusion of vericiguat alone at 3 μg/kg/min, −19 and −42 mmHg, respectively, following infusion of vericiguat alone at 30 μg/kg/min, and −38 and −38 mmHg, respectively, following dosing of nitroglycerin alone. The mean changes with coadministration of vericiguat and nitroglycerin relative to nitroglycerin alone were −21 and −20 mmHg, respectively, at 3 μg/kg/min and −39 and −38 mmHg, respectively, at 30 μg/kg/min.

In a 6-treatment, 6-period crossover study, conscious male and female dogs (1/group) were dosed orally with (1) vericiguat 0.6 mg/kg alone, (2) vericiguat 2 mg/kg alone, (3) nitroglycerin 0.5 mg/kg alone (a total of 2 doses, at 1.5 and 6 hours after dosing of vehicle), (4) vericiguat 0.6 mg/kg in combination with nitroglycerin 0.5 mg/kg (a total of 2 doses, at 1.5 and 6 hours after dosing of vericiguat), (5) vericiguat 2 mg/kg in combination with nitroglycerin 0.5 mg/kg (a total of 2 doses, at 1.5 and 6 hours after dosing of vericiguat), or (6) vehicle (ethanol + polyethyleneglycol 400 [10:90] and 0.5% glucose solution), and hemodynamic parameters were measured using telemetry up to 24 hours after dosing of vericiguat or vehicle. A 6-day washout period was included between the treatment periods. Dosing of 0.6 and 2 mg/kg of vericiguat alone reduced SBP by up to 11% and 19%, respectively, compared with vehicle. Dosing of nitroglycerin alone reduced SBP by up to approximately 10%. Meanwhile, coadministration of vericiguat and nitroglycerin also reduced SBP by up to approximately 10%. Dosing of 0.6 and 2 mg/kg of vericiguat alone increased heart rate by up to 26% and 54%, respectively, compared with vehicle, whereas nitroglycerin alone had no effects on heart rate. Heart rate following coadministration of vericiguat and nitroglycerin was similar to that following dosing of vericiguat alone.

#### 3.4.2 Interactions with sacubitril/valsartan (CTD 4.2.1.4.2)

Conscious spontaneously hypertensive female rats (5-6/group) were treated with a single oral dose of vericiguat (0.1 or 0.3 mg/kg) alone, sacubitril (30 mg/kg)/valsartan (10 mg/kg), vericiguat (0.1 or 0.3 mg/kg) in combination with sacubitril (30 mg/kg)/valsartan (10 mg/kg), or vehicle (Transcutol + Cremophor + water [10:20:70]), and hemodynamic parameters were measured using telemetry up to 24 hours post-dose. The decrease in blood pressure produced by coadministration of vericiguat and sacubitril/valsartan was similar to the additive effects of vericiguat plus sacubitril/valsartan.

## 3.R Outline of the review conducted by PMDA

### 3.R.1 Primary pharmacodynamic studies

The applicant's explanation about the pharmacological effects of vericiguat:

The pathophysiology of heart failure includes endothelial cell dysfunction, which impairs NO production leading to decreased NO availability and reduced cGMP tissue levels. This reduced NO availability and insufficient stimulation of sGC result in coronary vasotone dysregulation etc., and organ damage and dysfunction driven by perfusion disturbances (*J Am Coll Cardiol*. 2012; 60: 1455-69, *Nitric Oxide*. 2018; 76: 105-12, etc.).

In *in vitro* studies using recombinant sGC or vascular endothelial cells, vericiguat selectively bound to sGC, leading to concentration-dependent cGMP production, regardless of the presence or absence of NO donor, showing that vericiguat stimulates sGC independently of NO. In combination, vericiguat and NO donor had a synergistic effect on cGMP production. sGC is a heterodimer composed of an α subunit and a heme-containing β subunit. While NO binds to the heme group of the β subunit, sGC stimulators bind to the α subunit (*Nature*. 2001; 410: 212-5, *Circ Res*. 2017; 120: 1174-82). Vericiguat is considered to enhance cGMP production efficiently even at a low NO concentration by stabilizing NO binding to the heme group of the β subunit of sGC (*Nat Rev Drug Discov*. 2006; 5: 755-68). In *in vivo* studies, oral or intravenous dosing of vericiguat in healthy and spontaneously hypertensive rats resulted in a decrease in blood pressure and a reflex increase in heart rate. In healthy dogs, intravenous dosing of vericiguat resulted in decreases in central venous pressure, systemic vascular resistance, and pulmonary artery pressure, and a positive shift in the myocardial oxygen balance was also indicated. Renin transgenic rats develop severe hypertension, and as the disease progresses, heart and kidney dysfunction such as heart hypertrophy, increased myocardial fibrosis, left ventricular contractile and diastolic dysfunction, and an increase in intraglomerular pressure occurs (*Regul Pept*. 1998; 77: 3-8, *Am J Hypertens*. 2002; 15: 644-52, etc.). Administration of L-NAME induces endothelial dysfunction, leading to a further increase in blood pressure and a decrease in renal blood flow, decreasing the survival rate (*Br J Pharmacol*. 2002; 135: 344-55, *Kidney Blood Press Res*. 2005; 28: 117-26, etc.). In a study in L-NAME-treated renin transgenic rats, survival was increased in rats treated with vericiguat, and a decrease in relative heart weight, decreases in plasma ANP, urea, and creatinine, and a decrease in urinary protein excretion were observed in surviving animals compared with the placebo group. Thus, these effects may have contributed to the improved survival. In the animal model of pulmonary hypertension, oral or intravenous dosing of vericiguat resulted in an increase in cardiac output and decreases in systemic vascular resistance and pulmonary vascular resistance, suggesting that vericiguat decreases cardiac afterload by lowering systemic blood pressure and pulmonary artery pressure. In renin transgenic rats and dogs with tachypacing-induced pulmonary hypertension, hemodynamic effects such as blood pressure lowering were observed at doses that are presumed to be not substantially different (approximately 1- to 7-fold) from the steady-state vericiguat (unbound) exposure ($C_{max}$, 7.6 μg/L; $AUC_{0\text{-}24h}$, 145.6 μg·h/L) at the recommended clinical dose (10 mg/day).

Based on the above, in the pathophysiology of heart failure with endothelial cell dysfunction and decreased NO availability, vericiguat selectively stimulates sGC, independently of and synergistically with NO, to increase cGMP production, resulting in vasodilation and improved hemodynamics such as blood pressure

lowering as well as decreased pulmonary artery pressure and reduced cardiac afterload. Vericiguat is considered to exert its efficacy in the treatment of chronic heart failure by reducing cardiac hypertrophy and counteracting the deterioration of cardiac function.

PMDA's view:
The results of *in vitro* studies showed that vericiguat stimulates sGC, independently of and synergistically with NO, to increase cGMP production. In *in vivo* studies in healthy animals and the animal model of pulmonary hypertension, a decrease in blood pressure, decreases in systemic vascular resistance and pulmonary vascular resistance, and a decrease in pulmonary artery pressure were observed, and an increase in left ventricular contractility was also suggested. In an *in vivo* study that investigated the effects of vericiguat in renin transgenic rats, though survival was increased, the causes of deaths were not identified, and it cannot necessarily be concluded that vericiguat reduced mortality due to heart failure. However, decreases in relative heart weight and plasma ANP levels were observed in surviving animals, and vericiguat may have helped improve the outcome by reducing cardiac load via improved hemodynamics. Given the above findings and reports on the pathophysiology of chronic heart failure (*J Am Coll Cardiol*. 2012; 60: 1455-69, *Nitric Oxide*. 2018; 76: 105-12, etc.), PMDA concludes from the submitted non-clinical pharmacology data that in chronic heart failure in which endothelial cell dysfunction leads to decreased NO production and availability, vericiguat is expected to improve chronic heart failure by acting on the NO-sGC pathway and reducing cardiac load such as blood pressure lowering, etc.

### 3.R.2 Safety pharmacology studies

The applicant's explanation about the findings observed in safety pharmacology studies of vericiguat:
With respect to the effects of vericiguat on the central nervous system, decreased body temperature noted in rats is considered secondary to peripheral and skin vasodilation by vericiguat, and hypoactivity and gait/posture abnormalities are considered attributed to decreased body temperature. Given that the distribution of vericiguat into the brain was limited [see Section "4.2.1 Tissue distribution"], and that vericiguat (unbound) exposure ($C_{max}$, 283.2 μg/L) at which the findings were observed was approximately 37-fold the human exposure at the maximum clinical dose ($C_{max}$, 7.6 μg/L), these findings are unlikely to become a clinically relevant problem. As to the effects of vericiguat on the cardiovascular system, though vericiguat significantly inhibited the hERG current at ≥1 μmol/L, the $IC_{20}$ for the hERG current (1.9 μmol/L) was approximately 106-fold the vericiguat (unbound) exposure at the maximum clinical dose ($C_{max}$, 17.9 nmol/L). Though the PQ and QT intervals were shortened in dogs at approximately ≥4-fold the human exposure at the maximum clinical dose, vericiguat had no significant effect on the heart rate-corrected QT (QTc) interval even at a dose resulting in exposure ($C_{max}$, 198.8 μg/L) approximately 26-fold the vericiguat (unbound) exposure at the maximum clinical dose, etc. Thus, these findings are unlikely to become a clinically relevant problem. As to the effects of vericiguat on the gastrointestinal system, though vericiguat exposure at which inhibited intestinal transit was noted in rats was approximately 6-fold the human exposure at the maximum clinical dose, this effect is considered related to smooth muscle relaxation based on the mode of action of vericiguat. Based on the above, the principal findings observed in the safety pharmacology studies are related to the mode of action of vericiguat, and are unlikely to become a clinically relevant problem, given vericiguat exposure levels in humans.

PMDA's view:

The applicant's explanation about the observed CNS and cardiovascular effects of vericiguat is appropriate, and these findings are unlikely to become a clinically relevant problem. The gastrointestinal effect of vericiguat is related to the pharmacological effects of vericiguat, and safety in humans will be assessed in Section "7.R.3.3 Other adverse events."

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Plasma concentrations of vericiguat were determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), and the lower limits of quantification (LLOQ) were 1 to 5, 1 to 10, 1, and 1 μg/L in mouse, rat, rabbit, and dog plasma, respectively. Radioactivity concentrations following administration of $^{14}$C-vericiguat were determined using liquid scintillation counter or quantitative whole-body autoradiography.

Unless otherwise specified, PK parameters are expressed as the mean.

### 4.1 Absorption

#### 4.1.1 Single-dose studies (CTD 4.2.2.2.1 to 4.2.2.2.3)

Table 6 shows PK parameters of vericiguat following a single intravenous or oral dose of vericiguat or $^{14}$C-vericiguat in male rats.

Table 6. PK parameters of vericiguat following a single intravenous or oral dose of vericiguat or $^{14}$C-vericiguat

| Route of administration | Dose (mg/kg) | $C_{max}$ (μg/L) | $t_{max}$ (h) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) | BA[a] (%) |
|---|---|---|---|---|---|---|
| IV | 0.3 | — | — | 1300 | 2.45 | — |
| | 1[b] | — | — | 5220 | 3.09 | — |
| Oral | 0.3 | 104 | 1.50 | 606 | 3.43 | 38.8 |
| | 1 | 305 | 3.00 | 2250 | 3.45 | 43.1 |
| | 3[b] | 1140 | 1.50 | 7410 | 2.57 | 47.3 |
| | 10 | 6980 | 1.00 | 52100 | 8.36 | 99.9 |

N = 3/time point, Geometric mean, —: Not calculated

a: Calculated relative to $AUC_{0-\infty, norm}$ at 1 mg/kg IV

b: $^{14}$C-vericiguat was administered.

Table 7 shows PK parameters of vericiguat following a single intravenous infusion over 1 hour or a single oral dose of vericiguat in female dogs.

Table 7. PK parameters of vericiguat following a single intravenous or oral dose of vericiguat or $^{14}$C-vericiguat

| Route of administration | Dose (mg/kg) | Number of animals | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) | BA[b] (%) |
|---|---|---|---|---|---|---|---|
| IV | 0.03 | 3 | 27.6 ± 1.02[c] | 1.00 | 197 ± 1.20 | 5.39 ± 1.03 | — |
| Oral | 0.03 | 3 | 16.1 ± 1.12 | 1.50 | 141 ± 1.24 | 5.67 ± 1.22 | 71.6 ± 1.09 |
| | 0.3 | 3 | 167 ± 1.15 | 2.00 | 1472 ± 1.12 | 6.95 ± 1.51 | 74.7 ± 1.19 |
| | 0.6[d] | 4 | 262 ± 1.21 | 0.500 | 1950 ± 1.11 | 4.94 ± 1.13 | — |

Geometric mean ± geometric standard deviation, —: Not calculated

a: Median

b: Calculated relative to $AUC_{0-\infty, norm}$ at 0.03 mg/kg IV

c: At the end of infusion

d: $^{14}$C-vericiguat was administered.

### 4.1.2 Repeated-dose studies (CTD 4.2.3.2.2, 4.2.3.2.6, and 4.2.3.2.10)

Table 8 shows PK parameters of vericiguat following once daily oral administration of vericiguat in male and female mice or rats.

Table 8. PK parameters of vericiguat following repeated oral administration of vericiguat

| Animal species | Dose (mg/kg/day) | Time point (Day) | $C_{max}$ (μg/L) | | $AUC_{0-24h}$ (μg·h/L) | |
|---|---|---|---|---|---|---|
| | | | M | F | M | F |
| Mouse | 5 | 2 | 620 | 415 | 14600 | 8360 |
| | | 76 | 559 | 370 | 10800 | 7340 |
| | 15 | 2 | 1980 | 1290 | 43400 | 28900 |
| | | 76 | 1820 | 941 | 36100 | 19500 |
| | 50 | 2 | 7060 | 3820 | 147000 | 86900 |
| | | 76 | 6710 | 4430 | 128000 | 89400 |
| Rat | 3 | 1 | 791 | 1100 | 8390 | 13200 |
| | | 149 | 1360 | 1530 | 13800 | 16800 |
| | 10 | 1 | 2670 | 3330 | 29000 | 44500 |
| | | 149 | 4700 | 6000 | 45000 | 62600 |
| | 30 | 1 | 6080 | 7310 | 95500 | 130000 |
| | | 149 | 12500 | 18400 | 150000 | 167000 |

N = 3/time point

Table 9 shows PK parameters of vericiguat following once daily oral administration of vericiguat in male and female dogs.

Table 9. PK parameters of vericiguat following repeated oral administration of vericiguat

| Dose (mg/kg/day) | Number of animals (M/F) | Time point (Day) | $C_{max}$ (μg/L) | | $AUC_{0-24h}$ (μg·h/L) | |
|---|---|---|---|---|---|---|
| | | | M | F | M | F |
| 0.5 | 4/4 | 1 | 348 ± 1.14 | 343 ± 1.13 | 2010 ± 1.17 | 2090 ± 1.17 |
| | | 91 | 267 ± 1.15 | 261 ± 1.21 | 1810 ± 1.25 | 1830 ± 1.25 |
| | | 273 | 341 ± 1.05 | 314 ± 1.19 | 2610 ± 1.19 | 2170 ± 1.19 |
| 1.5 | 4/4 | 1 | 890 ± 1.07 | 889 ± 1.08 | 5960 ± 1.07 | 5920 ± 1.09 |
| | | 91 | 847 ± 1.22 | 876 ± 1.20 | 5400 ± 1.13 | 6670 ± 1.16 |
| | | 273 | 867 ± 1.35 | 1010 ± 1.14 | 6280 ± 1.41 | 8260 ± 1.16 |
| 5 | 4/4 | 1 | 2130 ± 1.23 | 2190 ± 1.17 | 16500 ± 1.51 | 15500 ± 1.37 |
| | | 91 | 2300 ± 1.27 | 2040 ± 1.85 | 19300 ± 1.48 | 13300 ± 1.59 |
| | | 273 | 1250 ± 2.23 | 1780 ± 1.53 | 10500 ± 2.73 | 13800 ± 1.59 |

Geometric mean ± geometric standard deviation

## 4.2 Distribution

### 4.2.1 Tissue distribution (CTD 4.2.2.3.1 and 4.2.2.3.2)

Following a single oral administration of $^{14}$C-vericiguat 3 mg/kg in male and female albino rats, radioactivity concentrations in different tissues were determined at 1, 2, 4, 8, 24, 72, and 168 hours post-dose in male rats and at 2 and 24 hours post-dose in female rats (N = 1/time point). In male rats, maximum concentrations of radioactivity were reached in most tissues at 2 to 4 hours post-dose, and the rank order of radioactivity was the kidney cortex (5780 µg eq/L), kidney medulla (5130 µg eq/L in the outer medulla, 2200 µg eq/L in the inner medulla), adrenal cortex (4880 µg eq/L), liver (3060 µg eq/L), and Harderian gland (2730 µg eq/L). The maximum radioactivity concentrations in the blood and brain were 1020 and 24.5 µg eq/L, respectively. At 72 hours post-dose, radioactivity was below the LLOQ in all tissues examined, except for the kidney cortex, outer medulla, and liver. Tissue distribution of radioactivity in female rats was similar to that in male rats.

Following a single oral administration of $^{14}$C-vericiguat 3 mg/kg in male pigmented rats, radioactivity concentrations in different tissues were determined at 1, 2, 4, 8, 24, 72, 168, and 336 hours post-dose (N = 1 at all time points except for 24 hours post-dose, N = 2 at 24 hours post-dose). Tissue distribution of radioactivity in pigmented rats was generally similar to that in albino rats, except for melanin-containing tissues. Among melanin-containing tissues, the tissue to blood ratio of radioactivity $AUC_{0-\infty}$ was >100 for the eyewall, and there was a trend towards higher exposure compared with albino rats (the tissue to blood ratio of $AUC_{0-\infty}$ <1). While the radioactivity concentration in less pigmented skin was below the LLOQ at 72 hours post-dose, radioactivity was detected in highly pigmented skin and eyewall even at 336 hours post-dose. The whole-body autoradiography showed the distribution of radioactivity also in the meninges and choroid plexus, i.e., melanin-containing tissues.

### 4.2.2 Plasma protein binding (CTD 4.2.2.3.4 and 4.2.2.3.6)

When $^{14}$C-vericiguat 100 to 10000 µg/L was added to the plasma from mouse, rat, rabbit, dog, and monkey, the plasma protein binding of vericiguat was 90.50% to 92.81%, 94.13% to 96.20%, 95.08% to 96.96%, 88.6% to 90.50%, and 92.67% to 95.35%, respectively.

When M-1 100 to 10000 µg/L was added to the plasma from mouse, rat, rabbit, and dog, the plasma protein binding of M-1 was 83.6% to 85.8%, 96.78% to 96.96%, 94.53% to 96.18%, and 83.3% to 85.7%, respectively.

### 4.2.3 Distribution in blood cells (CTD 4.2.2.3.4)

When $^{14}$C-vericiguat 100 to 10000 µg/L was added to the blood from male rat and female dog, the blood to plasma ratio of vericiguat was 0.689 to 0.940 and 0.838 to 0.904, respectively.

### 4.2.4 Placental transfer (CTD 4.2.2.3.3)

Following a single oral dose of $^{14}$C-vericiguat 3 mg/kg in rats on gestation day 19, radioactivity concentrations in tissues were determined at 1, 2, 4, 8, 24, and 48 hours post-dose (N = 1/time point). Fetal transfer of radioactivity was observed, and based on the $AUC_{0-48h}$ of blood radioactivity, the fetal to maternal ratio was 0.67.

## 4.3 Metabolism

### 4.3.1 *In vitro* metabolism (CTD 4.2.2.4.5)

When $^{14}$C-vericiguat 5 μmol/L was added to mouse, rat, rabbit, dog, and monkey liver microsomes and incubated at 37°C for 90 minutes, M-9 (a structural isomer of vericiguat) was detected as a major metabolite in all species.

When $^{14}$C-vericiguat 2.5 μmol/L was added to rat and dog primary hepatocytes and incubated at 37°C for 4 hours, M-1 was detected as a major metabolite in both species.

### 4.3.2 *In vivo* metabolism

#### 4.3.2.1 Metabolites in plasma (CTD 4.2.2.4.1 to 4.2.2.4.3)

Following single oral doses of $^{14}$C-vericiguat 1, 3, and 0.6 mg/kg in male mice (N = 3/time point), male rats (N = 3/time point), and female dogs (N = 4), respectively, unchanged vericiguat was the main component in the plasma of all species (>90% of plasma radioactivity $AUC_{0-\infty}$ [mouse and rat] or $AUC_{0-4h}$ [dog]), and M-1 was a minor component (<2% of total plasma radioactivity $AUC_{0-\infty}$ [mouse and rat] or $AUC_{0-4h}$ [dog]).

#### 4.3.2.2 Metabolites in urine, feces, and bile (CTD 4.2.2.4.2 and 4.2.2.4.3)

Following a single oral dose of $^{14}$C-vericiguat 3 mg/kg in male rats (N = 5), unchanged vericiguat (9.23% of the administered radioactivity), M-3 (hydroxylated metabolite) (0.535%), M-1 (0.524%), and M-2 (*N*-dealkylated metabolite) (0.380%) were mainly detected in the urine collected up to 168 hours post-dose. Unchanged vericiguat (69.9%), M-1/M-4 (hydroxylated metabolites)[1)] (5.12%), and M-3/M-5 (hydroxylated metabolites)[1)] (4.40%) were detected in the feces collected up to 168 hours post-dose.

Following a single intravenous dose of $^{14}$C-vericiguat 1 mg/kg in bile duct cannulated male rats (N = 3), unchanged vericiguat (10.6%), M-1 (1.19%), and M-3 (1.23%) were mainly detected in the urine collected up to 24 hours post-dose. Unchanged vericiguat (29.6%) was the main component in the feces collected up to 24 hours post-dose. In the bile collected up to 24 hours post-dose, M-1 (13.6%), unchanged vericiguat (8.25%), M-12 (sulfate conjugate of M-4 or M-5) (4.37%), M-10 (glucuronide conjugate of M-3) (2.71%), and M-16 (glutathione conjugate of hydroxylated metabolite) (2.29%) were mainly detected.

Following a single oral dose of $^{14}$C-vericiguat 3 mg/kg in bile duct cannulated male rats (n = 3), unchanged vericiguat (4.07%), M-1 (1.66%), and M-3 (1.27%) were mainly detected in the urine collected up to 24 hours post-dose. Unchanged vericiguat (35.3%) was the main component in the feces collected up to 24 hours post-dose. In the bile collected up to 24 hours post-dose, M-1 (11.2%), unchanged vericiguat (5.16%), M-12 (3.61%), and M-5 (2.46%) were mainly detected.

1) Co-eluted.

Following a single oral dose of $^{14}$C-vericiguat 0.6 mg/kg in female dogs (N = 4), unchanged vericiguat (2.35%) was the main component in the urine collected up to 168 hours post-dose. In the feces collected up to 168 hours post-dose, M-1 (50.9%), unchanged vericiguat (19.3%), and M-3 (7.86%) were mainly detected.

## 4.4 Excretion

### 4.4.1 Urinary, fecal, and biliary excretion (CTD 4.2.2.5.1 and 4.2.2.2.3)

Following a single oral dose of $^{14}$C-vericiguat 3 mg/kg in male rats (N = 5), 11.4% and 81.2% of the administered radioactivity were recovered in the urine and feces over 168 hours, respectively.

Following a single intravenous dose of $^{14}$C-vericiguat 1 mg/kg in bile duct cannulated male rats (N = 3), 14.8%, 30.0%, and 43.3% of the administered radioactivity were recovered in the urine, feces, and bile over 24 hours, respectively.

Following a single oral dose of $^{14}$C-vericiguat 3 mg/kg in bile duct cannulated male rats (N = 3), 9.88%, 36.4%, and 34.7% of the administered radioactivity were recovered in the urine, feces, and bile over 24 hours, respectively.

Following a single oral dose of $^{14}$C-vericiguat 0.6 mg/kg in female dogs (N = 4), 4.41% and 89.2% of the administered radioactivity were recovered in the urine and feces over 168 hours, respectively.

### 4.4.2 Excretion in milk (CTD 4.2.2.5.2)

Following a single intravenous dose of $^{14}$C-vericiguat 1 mg/kg in rats on lactation day 8 (N = 3/time point), 10.4% to 15.1% and 9.65% to 12.8% of the administered radioactivity were excreted in milk over 8 and 24 hours, respectively.

## 4.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the non-clinical pharmacokinetics of vericiguat were adequately evaluated.

### 4.R.1 Tissue distribution

Tissue distribution studies showed high concentrations of radioactivity in the kidneys/adrenal glands, liver, and melanin-containing tissues (eyewall, pigmented skin, meninges, choroid plexus, etc.) [see Section "4.2.1 Tissue distribution"]. PMDA asked the applicant to explain the possibility that safety issues in humans may arise from the distribution of vericiguat or its metabolites in these tissues.

The applicant's explanation:

Although repeated-dose toxicity studies in rats and dogs [see Section "5.2 Repeated-dose toxicity"] or a carcinogenicity study in rats [see Section "5.4 Carcinogenicity"] showed histopathological changes in the liver, kidneys, and adrenal glands in some animals treated with vericiguat, these changes were not associated with degeneration or necrosis and were reversible upon drug withdrawal. Thus, the findings in the liver were

considered an adaptive response to the induction of liver metabolizing enzymes, and the findings in the kidneys/adrenal glands were considered attributable to compensatory activation of the renin-angiotensin-aldosterone system (RAAS) and the adrenergic system due to decreases in systemic vascular resistance/blood pressure. All those findings were not considered adverse. Vericiguat (unbound) exposure ($AUC_{0\text{-}24h}$) at which those findings were observed was ≥4 times the human exposure at the maximum clinical dose. As to the melanin affinity of vericiguat or its metabolites, a mechanistic study in pigmented rats [see Section "5.7.3 Mechanistic study in pigmented rats"] showed no histopathological changes in the pigmented tissues of the brain, eyes, and inner ear at vericiguat (unbound) exposures ($AUC_{0\text{-}\infty}$) of up to approximately 40 times the human exposure at the maximum clinical dose. M-1 is a major metabolite of vericiguat in humans and is a minor component in the plasma of rat and dog [see Section "4.3 Metabolism"], but it was concluded that there are no toxicological concerns about M-1, a glucuronide conjugate of vericiguat [see Section "5.7.4 Metabolite safety evaluation"].

Based on the above, safety issues in humans are unlikely to arise from the distribution of vericiguat or its metabolites in the liver, kidneys, adrenal glands, and melanin-containing tissues.

Given the applicant's explanation, PMDA concludes that the results of non-clinical studies do not suggest that any safety issue in humans arises from the distribution of vericiguat or its metabolites in the tissues that exhibited high concentrations of radioactivity in tissue distribution studies.

## 5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from toxicity studies of vericiguat: repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other studies (juvenile animal studies, a phototoxicity study, mechanistic studies in pigmented rats, etc.).

### 5.1 Single-dose toxicity

No single-dose toxicity study of vericiguat was conducted. The acute toxicity of vericiguat was assessed based on the findings after the first dose in repeated-dose toxicity studies in rats and dogs (Table 10).

Table 10. Single-dose toxicity studies

| Test system | Route of administration | Dose (mg/kg) | Principal findings | Approximate lethal dose (mg/kg) | Attached document CTD |
|---|---|---|---|---|---|
| Male and female rats (Wistar) | Oral | 0,[a] 10, 30, 100 | Acute toxicity was assessed in a 2-week repeated-dose toxicity study.<br><br>No acute toxicity | >100 | 4.2.3.2.3 |
| Male and female dogs (Beagle) | Oral | 0,[b] 2.5, 7.5, 25 | Acute toxicity was assessed in a 4-week repeated-dose toxicity study.<br><br>No acute toxicity | >25 | 4.2.3.2.8 |

a: Ethanol + polyethyleneglycol (15)-hydroxystearate + water (10:40:50)
b: Polyethyleneglycol 400

## 5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in mice (13 weeks), rats (4, 13, and 26 weeks), and dogs (4, 13, and 39 weeks) (Table 11). Vericiguat-related changes secondary to the pharmacological action of vericiguat, i.e., vasodilation or blood pressure lowering, and smooth muscle relaxation in the gastrointestinal tract (increased water consumption, changes in electrolytes in urine/blood, changes in hematological parameters, decreased total protein, abnormal gait, changes in feces, salivation, changes in the intestine, etc.) were observed, and the applicant discussed that vascular medial thickening in the heart, plexiform change in the mesenteric veins, and adrenal effects were adaptive changes [see Section "5.R.1 Effects on cardiovascular system" and Section "5.R.3 Carcinogenicity"]. Vericiguat (unbound) exposure ($AUC_{0\text{-}24h}$) at the no observed adverse effect level (NOAELs) in rat (26 weeks) and dog (39 weeks) repeated-dose toxicity studies (30 mg/kg/day in rats, 5 mg/kg/day in dogs) were 6825 to 7599 μg·h/L and 1244 μg·h/L, respectively, which were approximately 47- to 52-fold and approximately 8-fold the human exposure at the maximum clinical dose ($AUC_{0\text{-}24h}$), respectively.

Table 11. Repeated-dose toxicity studies

| Test system | Route of administration | Duration of dosing | Doses (mg/kg/day) | Principal findings | NOAEL (mg/kg/day) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male and female mice (CD-1) | Oral, diet | 13 weeks | 0, 5, 15, 50 | ≥5: increased water consumption, decreased creatinine<br>50: decreased urea | 50 | 4.2.3.2.2 |
| Male and female rats (Wistar) | Oral | 4 weeks (once daily) + 2-week recovery period | 0,[a] 15, 30, 60 | ≥15: gastrointestinal symptoms, abnormal gait, increased water consumption, decreases in hematological parameters, decreases in urine specific gravity/creatinine, changes in liver metabolizing enzyme activity, crystal-like structures in the urinary sediment, hypertrophy of the adrenal zona glomerulosa/fasciculata, thickened growth plate in the femur, bone remodeling<br>≥30: agitated behavior, increased urinary volume, decrease in urine protein (male), vascular medial thickening in the heart, periportal fat deposits<br>60: decreased body weight, decreased body weight gain, decreased food consumption, adverse clinical signs, decreased weights/atrophy of the prostate gland/seminal vesicle, increases in adrenal/liver weights (female), hepatocellular hypertrophy in the liver (male)<br><br>These findings were reversible. | <15 | 4.2.3.2.4 |
| Male and female rats (Wistar) | Oral | 13 weeks (once daily) | 0,[a] 3, 10, 30 | ≥3: crystal-like structures in the urinary sediment, increased spleen weight, hypertrophy of the adrenal zona glomerulosa<br>≥10: increased water consumption, decreased creatinine, decreased phosphate (female), increased adrenal weight (male), vacuolation of the adrenal zona fasciculata (male), elongation/dilation of the intestine/changes in intestinal content consistency (male), Paneth cell hypertrophy in the jejunum/ileum, inflammatory cell infiltration in the cecum mucosa<br>30: decreased food consumption, increased urinary volume (male), decreases in triglycerides/total protein, increased extramedullary hematopoiesis in the spleen, vascular medial thickening in the heart, bone remodeling | 10 | 4.2.3.2.5 |
| Male and female rats (Wistar) | Oral | 26 weeks (once daily) | 0,[a] 3, 10, 30 | ≥3: increased water consumption, increased urinary volume, plexiform change in the mesenteric veins, hypertrophy/hyperplasia of the adrenal zona glomerulosa, activation of chromaffin cells in the adrenal medulla<br>≥10: increased Na (male), decreased creatinine, decreased Cl (male), crystal-like structures in the urinary sediment, dilated cecum, changes in small/large intestinal content consistency (male), hepatocellular hypertrophy in the liver (female)<br>30: decreased cholesterol (male), elongated small intestine/large intestine (male), vascular medial thickening in the heart (male), prominent bile ducts (female) | 30 | 4.2.3.2.6 |
| Male and female dogs (Beagle) | Oral | 4 weeks (once daily) | 0,[b] 2.5, 7.5, 25/15[c] | Mortality: 25 (1 of 3 males), rectal prolapses<br>≥2.5: cardiovascular effects (decreased SBP, reflex tachycardia, stronger pulse beats), hypertrophy of myocardial arteries<br>7.5: myocardial fibrosis (female)<br>≥7.5: decreased body weight gain, vomiting (female), salivation, rectal prolapses, rectal inflammation, hypertrophy of the juxtaglomerular apparatus of the kidney<br>25/15: decreased food consumption (female), tremor (female), focal inflammatory infiltrates in the heart (female), basophilic tubules (female), increased width of the adrenal zona glomerulosa | 2.5 | 4.2.3.2.8 |
| Male and female dogs (Beagle) | Oral | 13 weeks (once daily) | 0,[b] 1.25, 2.5, 5 | ≥1.25: decreased body weight gain, salivation<br>5: decreased food consumption, decreased blood pressure, increased heart rate (female), arterial hypertrophy in papillary muscle in the heart | 5 | 4.2.3.2.9 |
| Male and female dogs (Beagle) | Oral | 39 weeks (once daily) | 0,[b] 0.5, 1.5, 5 | ≥0.5: salivation<br>1.5: vomiting (male) | 5 | 4.2.3.2.10 |

a: Ethanol + polyethyleneglycol (15)-hydroxystearate + water (10:40:50)
b: Polyethyleneglycol 400
c: Due to severe gastrointestinal disorder (rectal prolapses), the dose was reduced to 15 mg/kg/day on Day 15. The doses before and after dose reduction are referred to as 25 mg/kg/day and 25/15 mg/kg/day, respectively.

## 5.3 Genotoxicity

Vericiguat was not genotoxic in the *in vitro* bacterial reverse mutation assay, the *in vitro* chromosomal aberration assay in cultured mammalian cells, and the *in vivo* micronucleus assays in mice and rats (Table 12).

Table 12. Genotoxicity studies

| Type of study | | Test system | Metabolic activation (Treatment) | Concentrations (μg/plate or μg/mL) or doses (mg/kg/day) | Test result | Attached document CTD |
|---|---|---|---|---|---|---|
| *In vitro* | Bacterial reverse mutation assay (Ames test) | *Salmonella typhimurium*: TA98, TA100, TA102, TA1535, TA1537 | S9 −/+ | 0,[a] 100, 250, 500, 1000, 2500, 5000 | Negative | 4.2.3.3.1.1 |
| | Chromosomal aberration assay in cultured mammalian cells | Mouse lymphoma L5178Y | S9 −/+<br>(−: 3 and 24 hours;<br>+: 3 hours) | 0,[a] 10, 25, 50, 100,[d] 200[d,e] | Negative | 4.2.3.3.1.2 |
| *In vivo* | Mouse micronucleus assay | Male mice (NMRI) bone marrow | | 0,[b] 31.25, 62.5, 125 | Negative | 4.2.3.3.2.1 |
| | Rat micronucleus assay | Male and female rats (Wistar) bone marrow | | 0,[c] 3, 10, 30 | Negative | 4.2.3.2.6 |

a: DMSO

b: 0.5% Tylose solution

c: Ethanol + polyethyleneglycol (15)-hydroxystearate + water (10:40:50)

d: Precipitates

e: Only treatment for 3 hours with or without metabolic activation

## 5.4 Carcinogenicity

Long-term carcinogenicity studies in mice and rats were conducted (Table 13). In rats, increases in pheochromocytoma and Leydig cell adenoma were not statistically significant [see Section "5.R.3 Carcinogenicity"].

Table 13. Carcinogenicity studies

| Test system | Route of administrati | Duration of dosing | Major lesions | Dose F/M | (mg/kg/day) | | | | | NOEL for carcinogenicity (mg/kg/day) | Attached document CTD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | [a]/0 | 6/5 | 20/15 | 60/50 | 250/150 | | |
| | | | | N | 60/sex | 60/sex | 60/sex | 60/sex | 60/sex | | |
| Male and female mice (CD-1) | Oral, diet | 2 years | Neoplastic lesions | | None | | | | | 250/150 | 4.2.3.4.1.1 |
| | | | Non-neoplastic lesions | | increased water consumption, degeneration/inflammation in the Harderian gland, increased liver weight, centrilobular hepatocellular hypertrophy in the liver, dilation/increased secretion of the mammary gland, gallstones/hyalinosis in the gallbladder, increased incidence of plasma cells in the mesenteric lymph nodes | | | | | | |
| Male and female rats (Wistar) | Oral | 2 years | Major lesions | Dose | (mg/kg/day) | | | | | 6 | 4.2.3.4.1.2 |
| | | | | | [b] | [c] | 2 | 6 | 20 | | |
| | | | | N | 60/sex | 60/sex | 60/sex | 60/sex | 60/sex | | |
| | | | Neoplastic lesions | | | | | | | | |
| | | | Pheochromocytoma | F | 0 | 2 | 1 | 1 | 0 | | |
| | | | | M | 4 | 2 | 4 | 6 | 10 | | |
| | | | Leydig cell adenoma | F | – | – | – | – | – | | |
| | | | | M | 2 | 0 | 1 | 0 | 6 | | |
| | | | Non-neoplastic lesions | | increased water consumption, increased urine volume, distention of the cecum, adrenal medullary hyperplasia, Leydig cell hyperplasia | | | | | | |

a: As 75% of females in the control group died at Week 93/94 during the study period, all female groups were sacrificed early at Week 93/94. The causes of deaths in all treatment groups including the control group were all consistent with the common causes of death in CD-1 mice, and the applicant concluded that these deaths were not treatment-related.
b: Ethanol + polyethyleneglycol (15)-hydroxystearate + water (10:40:50)
c: Water

## 5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in male and female rats, embryo-fetal development studies in rats and rabbits, and a rat study for effects on pre- and postnatal development, including maternal function, were conducted (Table 14). In all studies, parent animals exhibited adverse clinical signs related to the pharmacological action of vericiguat. As fetal toxicities secondary to serious maternal toxicities, abortion and total resorption of litter in the rabbit embryo-fetal development study, and decreased pup survival in the rat study for effects on pre- and postnatal development, including maternal function, were observed. The applicant concluded that as these findings may be relevant to humans, it is necessary to appropriately provide the information using the package insert.

Table 14. Reproductive and developmental toxicity studies

| Type of study | Test system | Route of administration | Duration of dosing | Doses (mg/kg/day) | Principal findings | NOAEL (mg/kg/day) | Attached document CTD |
|---|---|---|---|---|---|---|---|
| Fertility and early embryonic development to implantation | Male and female rats (Wistar) | Oral | Males: 28 days prior to mating, during mating, and up to the day before necropsy (once daily)<br><br>Females: 14 days prior to mating, during mating, and through gestation day 7 (once daily) | 0,[a] 5, 15, 50 | Parent animals:<br>Mortality: 50 (1 of 24 males, 3 of 24 females)<br>50: changes in body weight gain/food consumption, increased water consumption, increased urination, piloerection (female)<br><br>Fertility, early embryonic development:<br>None | Parent animals (General toxicity): 15<br>(Fertility, early embryonic development): 50 | 4.2.3.5.1.1 |
| Embryo-fetal development | Female rats (Wistar) | Oral | Gestation day 6 through 17<br>(once daily) | 0,[a] 5, 15, 50 | Dams:<br>≥15: decreased body weight gain, decreased food consumption<br>50: increased water consumption, increased urination, light-colored feces<br><br>Fetuses:<br>50: extended thymus[c] | Maternal toxicity: 5<br><br>Embryo-fetal development: 50 | 4.2.3.5.2.1 |
| | Female rabbits (NZW) | Oral | Gestation day 6 through 20<br>(once daily) | 0,[b] 0.75, 2.5, 7.5 | Dams:<br>≥2.5: abortion, body weight loss, decreased food consumption, reduced amount of feces, discoloration of urine, reddish excretion, light-colored feces<br>7.5: soft feces, total resorption, whitish punctiform areas of the placenta<br><br>Fetuses:<br>≥2.5: truncus arteriosus communis with ventricular septal defect [d]<br>7.5: decreased viable fetuses, increased postimplantation loss | Maternal toxicity: 0.75<br><br>Embryo-fetal development: 0.75 | 4.2.3.5.2.2 |
| Pre- and postnatal development, including maternal function | Female rats (Wistar) | Oral | Gestation day 6 through lactation day 21<br>(once daily) | 0,[a] 7.5, 15, 30 | Dams:<br>≥15: decreased body weight gain, deceased food consumption, piloerection<br><br>Pups:<br>≥7.5: body weight loss, delayed development (delay in pinna unfolding/ incisor eruption, decrease in surface righting),[e] delayed sexual maturation (delayed vaginal opening)[e]<br>≥15: delayed development (delayed eye opening)<br>30: total litter death, increased stillbirths/pup mortality, decreased pup survival, increased pups with no milk in the stomach,[f] increased locomotor activity, delayed sexual maturation (delayed balanopreputial separation) | Maternal animals (General toxicity) 7.5<br>(Reproductive toxicity) 15<br><br>Pup development: 7.5 | 4.2.3.5.3.2 |

a: Ethanol + polyethyleneglycol (15)-hydroxystearate + water (10:40:50)

b: 0.5% Tylose solution

c: The thymus was localized more cranially, without any effect on size or shape. The applicant concluded that the finding was of little toxicological significance.

d: As the incidence fell within the historical control range, the applicant concluded that the finding was unrelated to vericiguat.

e: Since the findings were minimal effects secondary to body weight loss, and decreased body weight gain was reversible, the applicant concluded that the findings in the 7.5 mg/kg group were of little toxicological significance.

f: The applicant discussed that the finding correlated to the increased incidence of stillbirth/increased pup mortality and attributable to the death of many pups before suckling, and concluded that the finding was of little toxicological significance.

## 5.6 Local tolerance

Local tolerance in the stomach and intestine was assessed as part of repeated-dose toxicity studies in rats and dogs [see Section "5.2 Repeated-dose toxicity studies"], and the applicant concluded that vericiguat does not induce local irritation.

## 5.7 Other studies

### 5.7.1 Juvenile animal studies

Repeated-dose toxicity studies (4 and 13 weeks) were conducted in juvenile rats (Table 15). Vericiguat (unbound) exposure ($AUC_{0\text{-}24h}$) at the NOAEL in the repeated-dose toxicity study in juvenile rats (13 weeks) was 4670 to 4930 μg·h/L.

Table 15. Juvenile animal studies

| Test system | Route of administration | Duration of dosing | Doses (mg/kg/day) | Principal findings | NOAEL (mg/kg/day) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male and female juvenile rats (Wistar) | Oral | 4 weeks,<br>Postnatal days 10-37 (once daily)<br>+<br>4-week recovery period | 0,[a] 1, 3, 10 | ≥3: changes in small intestinal content consistency<br>10: cecal dilatation | 3 | 4.2.3.5.4.2 |
| | | 13 weeks,<br>Postnatal days 10-100 (once daily)<br>+<br>8-week recovery period | | Mortality: 10 (7 of 12 females, 4 of 12 males), adverse clinical signs, necrotizing enteritis<br><br>10: salivation, piloerection, breathing sounds, emaciation, hypothermia, abnormal gait | | |

a: 0.5% Tylose solution

### 5.7.2 Phototoxicity

An *in vitro* phototoxicity study was conducted, and the applicant concluded that vericiguat is not phototoxic (Table 16).

Table 16. Phototoxicity study

| Type of study | Test system | Test method | Findings | Attached document CTD |
|---|---|---|---|---|
| Phototoxicity | Mouse fibroblasts Balb/c 3T3 | Balb/c 3T3 cells were treated with vericiguat 0-60 μg/mL for 1 hour in the presence or absence of UV-A, and cell viability was determined. | Not phototoxic | 4.2.3.7.7.1 |

### 5.7.3 Mechanistic studies in pigmented rats

Since vericiguat is distributed in melanin-containing tissues [see Section "4.2.1 Tissue distribution"], repeated-dose toxicity studies in pigmented rats were conducted. There were no vericiguat-related effects on the pigmented tissues (Table 17).

Table 17. Mechanistic study in pigmented rats

| Test system | Route of administration | Duration of dosing | Doses (mg/kg/day) | Principal findings | NOAEL (mg/kg/day) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male rats (Long Evans) | Oral | 13 weeks | 0,[a] 10, 30 | No effects on pigmented tissues (pigmented epithelium in the eye, substantia nigra in the brain, stria vascularis in the inner ear) | 30 | 4.2.3.7.3.2 |

a: Ethanol + polyethyleneglycol (15)-hydroxystearate + water (10:40:50)

### 5.7.4 Metabolite safety evaluation

A glucuronide conjugate of vericiguat, M-1 is a major metabolite in humans. M-1 is not an acyl-glucuronide. The applicant concluded that M-1 is of no toxicological concern (Questions and Answers [Q&A] on "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," Administrative Notice dated August 16, 2012).

## 5.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there is no problem with the clinical use of vericiguat from a non-clinical toxicological perspective.

### 5.R.1 Effects on cardiovascular system

PMDA asked the applicant to explain the significance of cardiovascular effects observed in repeated-dose toxicity studies.

The applicant's explanation:

Changes called plexiform vasculopathy characterized by vascular medial/adventitial thickening and vascular proliferation have been reported in rats following treatment with a hypotensive agent that increases local blood flow, such as a PDE inhibitor (Boorman's Pathology of the Rat 2nd edition, Academic Press; 2017. p616). Vascular medial thickening in the heart and plexiform change in the mesenteric veins observed in multiple repeated-dose toxicity studies in rats seemed to result from smooth muscle hypertrophy in the vascular media as an adaptive response to the stress imposed on the vessel wall due to increased blood flow via vasodilation, i.e., the pharmacological action of vericiguat. Taking also into account that the finding was not associated with vascular degeneration or necrosis and was reversible in a 4-week repeated-dose toxicity study, the finding is unlikely to become a clinically relevant problem.

PMDA considers that the applicant's explanation about the mechanism of the cardiovascular effects of vericiguat and its potential clinical relevance is appropriate.

### 5.R.2 Bone effects

The applicant's explanation about bone effects observed in repeated-dose toxicity studies:

In 4- and 13-week repeated-dose toxicity studies in rats, bone effects such as thickened growth plates, hyperostosis, and remodeling of metaphyseal/diaphyseal bone were observed. Similar findings have been

reported also with the currently approved sGC stimulator, riociguat (see "Review Report on Adempas tablets 0.5 mg/1.0 mg/2.5 mg as of November 19, 2013"). The bone effects are attributable to increased intracellular cGMP levels related to the mode of action of vericiguat, namely, vericiguat stimulated osteoblast via the NO-sGC-cGMP pathway (*Wimalawansa SJ Ann N Y Acad Sc*. 2010;1192: 391-403) and inhibited osteoclast proliferation and differentiation. Since no histopathological changes in the bone or changes in blood parameters related to bone metabolism were observed in a 26-week repeated-dose toxicity study in rats or repeated-dose toxicity studies in dogs, these findings are changes specific to growing rodent bones, and will not raise a concern when administering vericiguat to adults in a clinical setting.

PMDA considers that the applicant's explanation that the bone effects of vericiguat are unlikely to become a clinically relevant problem is appropriate.

**5.R.3 Carcinogenicity**

The applicant's explanation about benign pheochromocytomas and Leydig cell adenomas noted in a carcinogenicity study in rats:

Vericiguat lowers blood pressure via vasodilation. The adrenal medulla is known to release catecholamines in response to hypotension via compensatory activation of the RAAS and stimulation of chromaffin cells by angiotensin II (*J Physiol*. 1986; 373: 343-52), and it seems that continuous stimulation of chromaffin cells induced benign pheochromocytomas. Catecholamines have been suggested to stimulate Leydig cells, increasing the synthesis and release of testosterone (*The Leydig cell in health and disease*. 2007; 291-304), and it seems that continuous stimulation induced Leydig cell adenomas. Multiple hypotensive agents have been shown to induce pheochromocytomas or Leydig cell tumors in rats (*Lab Invest*. 1988; 58: 733-5, *Crit Rev in Toxicol*. 1999; 29: 169-261, etc.), which also indicates that both pheochromocytomas and Leydig cell adenomas were secondary to decreases in blood pressure related to the pharmacological action of vericiguat.

Benign pheochromocytoma and Leydig cell tumors are common in aged male rats. These tumors observed in the rat carcinogenicity study should be findings specific to rats, which resulted from spontaneous tumors in rats enhanced by the pharmacological action of vericiguat. On the other hand, these spontaneous tumors are known to be very rare in humans, and there is no report that drugs inducing these tumors in rats also induce corresponding tumors in humans (*Crit Rev in Toxicol*. 2009; 39: 695-718, *Crit Rev in Toxicol*. 1999; 29: 169-261). Thus, these tumors are expected to be of little relevance to humans.

PMDA considers that the applicant's explanation that pheochromocytomas and Leydig cell adenomas associated with vericiguat noted in the rat carcinogenicity study are of little relevance to humans is appropriate.

**5.R.4 Teratogenicity**

Fetal ventricular septal defect was observed in embryo-fetal development studies in rabbits and rats. A similar finding has been reported also with the currently approved sGC stimulator, riociguat, in an embryo-fetal development study in rats (see "Review Report on Adempas tablets 0.5 mg/1.0 mg/2.5 mg as of November 19,

2013"). PMDA asked the applicant to explain the relationship between the pharmacological action of vericiguat and this finding.

The applicant's explanation:
Although fetal ventricular septal defect was observed in the mid- and high-dose groups in an embryo-fetal development study with vericiguat in rabbits, there was no dose-response relationship, and the number of affected fetuses was similar to that in the control group. Thus, the finding was unlikely to be related to vericiguat. In an embryo-fetal development study with vericiguat in rats, fetal ventricular septal defect was observed in the high-dose group (vericiguat 50 mg), but the incidence fell within the historical control range. On the other hand, there was a significant increase in the incidence of fetal ventricular septal defects in the high-dose group (riociguat 25 mg) compared with the control group in an embryo-fetal development study with riociguat in rats, which showed a different trend from the results with vericiguat. The high-doses of both compounds are assumed to be sufficient to exert their pharmacological effects, even as compared with the doses used in primary pharmacodynamic studies in rats. Since there was no increased incidence of fetal ventricular septal defect with vericiguat in rats at doses needed to exert pharmacological effects, fetal ventricular septal defect observed in the embryo-fetal development study with riociguat is not attributable to a class effect of sGC stimulators.

PMDA considers that the applicant's explanation that fetal ventricular septal defect noted in the embryo-fetal development studies in rabbits and rats is unlikely to be related to vericiguat is appropriate.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Unless otherwise specified, PK parameters are expressed as the mean or the mean ± SD.

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma concentrations of vericiguat and M-1 were determined by LC-MS/MS, and the LLOQs for vericiguat and M-1 were 0.2 to 1 and 1 to 5 μg/L, respectively.

The to-be-marketed formulation is the 2.5-, 5-, and 10-mg tablets. Dissolution testing demonstrated the bioequivalence (BE) between the 2.5-mg tablet proposed for marketing and the 2.5-mg tablet used in a phase III study and between the 5- and 10-mg tablets proposed for marketing and the 5- and 10-mg tablets used in the phase III study and a food effect study (Studies 15356 and 18580), in accordance with the BE Guideline for Formulation Changes. Dissolution testing demonstrated the BE among the different strengths of the to-be-marketed formulation, in accordance with the BE guideline for different dosage form strengths.

#### 6.1.1 Absolute bioavailability (BA) study (Study 17114, CTD 5.3.1.1.1 [Reference data], October 20[redacted])

Ten non-Japanese healthy adult male subjects received a single oral dose of vericiguat 10 mg with food followed 4 hours later by intravenous infusion of $^{14}$C-vericiguat 20 μg over 30 minutes. The absolute BA

(calculated based on the geometric least-square mean ratio of the dose-normalized $AUC_{0-\infty}$ [oral/intravenous]) [90% confidence interval (CI)] was 0.9303 [0.8986, 0.9631]. Following intravenous infusion of $^{14}$C-vericiguat 20 µg over 30 minutes, the CL, $V_{ss}$, and $CL_R$ of vericiguat were 1.62 L/h, 43.7 L, and 0.132 L/h, respectively.

### 6.1.2 Food effect studies

#### 6.1.2.1 Food effect study (a) (Study 15356, CTD 5.3.1.2.1 [Reference data], December 20[redacted] to March 20[redacted])

A 4-treatment, 4-period crossover study was conducted in 16 non-Japanese healthy adult male subjects (a washout period of ≥5 days). A single oral dose of vericiguat 1.25 (tablet) or 5 mg (tablet and oral solution) was administered under fasting conditions, or a single oral dose of vericiguat 5 mg (tablet) was administered with food. Table 18 shows the PK parameters of vericiguat following a single oral dose of vericiguat.

Table 18. PK parameters of vericiguat following a single oral dose of vericiguat

| Dosing condition | Dose (mg) | $C_{max}$ (µg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (µg·h/L) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| Fasted | 1.25 | 41.0 (29.7) | 1.00 | 754 (21.7) | 18.8 (12.4) |
| | 5[b] | 106 (44.9) | 1.50 | 2300 (33.0) | 20.4 (22.7) |
| | 5[c] | 176 (17.5) | 1.00 | 3260 (21.9) | 21.4 (19.6) |
| Fed | 5 | 115 (16.9) | 4.00 | 2730 (14.6) | 18.9 (17.2) |

Geometric mean (Geometric coefficient of variation %)
a: Median
b: Tablet
c: Oral solution

The geometric least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ (fed vs. fasted) [90% CI] were 1.0923 [0.9238, 1.2915] and 1.1876 [1.0787, 1.3074], respectively.

#### 6.1.2.2 Food effect study (b) (Study 18580, CTD 5.3.1.2.3 [Reference data], June to October 20[redacted])

A 4-treatment, 4-period crossover study was conducted in non-Japanese healthy adult male subjects (a washout period of ≥5 days). A single oral dose of vericiguat 2.5, 5, or 10 mg was administered with food, or a single oral dose of vericiguat 10 mg was administered under fasting conditions. Table 19 shows the PK parameters of vericiguat following a single oral dose of vericiguat with food.

Table 19. PK parameters of vericiguat following a single oral dose of vericiguat with food

| Dose (mg) | N | $C_{max}$ (µg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (µg·h/L) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| 2.5 | 27 | 72.0 (17.3) | 4.00 | 1360 (20.1) | 18.5 (17.6) |
| 5 | 27 | 129 (22.8) | 4.02 | 2520 (22.9) | 18.1 (16.4) |
| 10 | 27 | 279 (12.5) | 4.47 | 5480 (18.0) | 17.6 (15.5) |

Geometric mean (Geometric coefficient of variation %)
a: Median

Table 20 shows the PK parameters of vericiguat following a single oral dose of vericiguat 10 mg under fasting or fed conditions. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ (fed vs. fasted) [90% CI] were 1.4067 [1.1883, 1.6652] and 1.4379 [1.2708, 1.6269], respectively.

Table 20. PK parameters of vericiguat following a single oral dose of vericiguat 10 mg under fasting or fed conditions

| Dosing condition | N | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| Fasted | 29 | 195 (60.4) | 1.98 | 3890 (41.4) | 18.9 (23.5) |
| Fed | 29 | 274 (15.5) | 4.47 | 5600 (19.3) | 18.0 (18.3) |

Geometric mean (Geometric coefficient of variation %)
a: Median

## 6.2 Clinical pharmacology

### 6.2.1 *In vitro* studies using human biomaterials

#### 6.2.1.1 Plasma protein binding (CTD 4.2.2.3.4 and 4.2.2.3.6)

When $^{14}$C-vericiguat or M-1 100 to 10000 μg/L was added to human plasma, the extent of plasma protein binding was 95.95% to 98.00% and 98.21% to 98.60%, respectively. When vericiguat 1000 μg/L was added to human serum albumin, α1-acid glycoprotein, α-globulin, and γ-globulin, the binding of vericiguat to these proteins was 94.97%, 33.1%, 66.4%, and 47.0%, respectively.

#### 6.2.1.2 Distribution in blood cells (CTD 4.2.2.3.4)

When $^{14}$C-vericiguat 100 to 10000 μg/L was added to human blood, the blood to plasma ratio was 0.645 to 0.672.

#### 6.2.1.3 *In vitro* metabolism

##### 6.2.1.3.1 Metabolism of vericiguat (CTD 4.2.2.4.5)

When $^{14}$C-vericiguat 5 μmol/L was added to human liver microsomes and incubated at 37°C for 90 minutes, M-9 (4.1% of the total radioactivity) and M-4 (0.4%) were detected as major metabolites.

When $^{14}$C-vericiguat 2.5 μmol/L was added to human primary hepatocytes and incubated at 37°C for 4 hours, M-1 (1.2%) and M-2 (0.3%) were detected as major metabolites.

##### 6.2.1.3.2 Identification of CYP isoforms involved in metabolism of vericiguat (CTD 4.2.2.6.2)

$^{14}$C-vericiguat 1 μmol/L was added to microsomes expressing human CYP isoforms (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP3A7, CYP4A11, CYP4F2, CYP4F3A, CYP4F3B, CYP4F12, CYP19A1) and incubated at 37°C for 30 minutes. The metabolites of vericiguat were detected in microsomes expressing CYP1A1, CYP1A2, CYP2J2, CYP3A4, and CYP3A5.

##### 6.2.1.3.3 Identification of UGT isoforms involved in glucuronidation of vericiguat (CTD 4.2.2.6.1 and 4.2.2.6.3)

$^{14}$C-vericiguat 1 to 10 μmol/L was added to human liver, kidney, or intestinal microsomes and incubated at 37°C for 60 minutes. M-1 was detected in all microsomes.

$^{14}$C-vericiguat 1 to 10 μmol/L was added to microsomes expressing human uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15, UGT2B17) and incubated at 37°C for 60 minutes. The high level of M-1 was formed in the microsomes expressing UGT1A1 and UGT1A9.

$^{14}$C-vericiguat 1 μmol/L was added to human liver microsomes and incubated at 37°C, in the presence of the inhibitors of human UGT isoforms. Mefenamic acid (an UGT1A9 inhibitor) and niflumic acid (an UGT1A9 inhibitor) inhibited the metabolism of vericiguat to M-1, with $IC_{50}$ values of 26.1 and 4.7 μmol/L, respectively. Atazanavir (an UGT1A1 inhibitor) and probenecid (a non-selective UGT inhibitor) did not inhibit the metabolism of vericiguat to M-1, with $IC_{50}$ values of >100 μmol/L and >2000 μmol/L, respectively. When tested also in human kidney or intestinal microsomes, mefenamic acid and niflumic acid inhibited the metabolism of vericiguat to M-1 also in the kidney microsomes.

#### 6.2.1.4 Enzyme inhibition

##### 6.2.1.4.1 Inhibition of CYP isoforms (CTD 4.2.2.6.4 to 4.2.2.6.6)

Using human liver microsomes and substrates for different CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4), the potential of vericiguat 1.6 to 50 μmol/L to inhibit the metabolism of the substrates for different CYP isoforms was evaluated. Vericiguat inhibited CYP1A1 with an $IC_{50}$ of 2.9 μmol/L. Vericiguat caused little inhibition of other CYP isoforms ($IC_{50}$ >50 μmol/L).

Using human liver microsomes and substrates for different CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4), the potential of M-1 3.1 to 100 μmol/L to inhibit the metabolism of the substrates for different CYP isoforms was evaluated. M-1 inhibited CYP1A1 and CYP2C19 with $IC_{50}$ values of 9.9 and 87 μmol/L, respectively. M-1 caused little inhibition of other CYP isoforms ($IC_{50}$ >100 μmol/L).

Vericiguat or M-1 did not cause time-dependent inhibition of any of the CYP isoforms tested.

##### 6.2.1.4.2 Inhibition of UGT isoforms (CTD 4.2.2.6.7 and 4.2.2.6.8)

Using human liver microsomes and substrates for different UGT isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7), the potential of vericiguat 1 to 50 μmol/L to inhibit the metabolism of the substrates for different UGT isoforms was evaluated. Vericiguat inhibited UGT1A9, with an $IC_{50}$ of 10.6 μmol/L. Vericiguat caused little inhibition of other UGT isoforms ($IC_{50}$ >50 μmol/L).

Using human liver microsomes and substrates for different UGT isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7), the potential of M-1 1.6 to 50 μmol/L to inhibit the metabolism of the substrates for different UGT isoforms was evaluated. M-1 caused little inhibition of all UGT isoforms tested ($IC_{50}$ >50 μmol/L).

#### 6.2.1.5 Enzyme induction (CTD 4.2.2.6.9)

Vericiguat 0.0117 to 23.5 μmol/L or M-1 0.0680 to 149 μmol/L was added to human primary hepatocytes and incubated at 37°C for 72 hours. Either vericiguat or M-1 did not increase the mRNA expression level of CYP1A2, CYP2B6, or CYP3A4, and did not affect CYP1A2 (*O*-dealkylation of phenacetin), CYP2B6 (*N*-demethylation of (*S*)-mephenytoin), or CYP3A4 (6β-hydroxylation of testosterone) activity.

#### 6.2.1.6 Studies on transporters (CTD 4.2.2.6.10 to 4.2.2.6.21)

When vericiguat 2 μmol/L was added to Caco-2 cells, the apparent permeability coefficient ($P_{app}$) in the apical to basolateral direction ($P_{app}$ A→B) was 111 nm/s, and the $P_{app}$ in the basolateral to apical direction ($P_{app}$ B→A) was 464 nm/s. The efflux ratio ($P_{app}$ B→A/$P_{app}$ A→B) of vericiguat was 4.21.

When M-1 2 to 20 μmol/L was added to Caco-2 cells, the $P_{app}$ A→B of M-1 was 1.1 to 1.3 nm/s, and the $P_{app}$ B→A was 1.0 to 1.3 nm/s. The efflux ratio of M-1 was 0.92 to 0.98.

When vericiguat 0.1 to 100 μmol/L was added to LLC-PK1 (Lewis lung carcinoma pork kidney cell line) cells expressing P-gp and its control cells, the efflux ratios were 1.4 to 6.9 and 0.8 to 5.5, respectively. When vericiguat 1 μmol/L was added in the presence or absence of ivermectin (a P-gp inhibitor), the efflux ratios were 1.3 and 6.9, respectively, in the P-gp-expressing cells and 1.0 and 2.2, respectively, in the control cells. When vericiguat 0.2 to 20 μmol/L was added to Madin Darby canine kidney II (MDCKII) cells expressing breast cancer resistance protein (BCRP) and its control cells, the efflux ratios were 6.6 to 13.1 and 2.1 to 2.7, respectively. When vericiguat 2 μmol/L was added in the presence or absence of Ko143 (a BCRP inhibitor), the efflux ratios were 0.7 and 10.8, respectively, in the BCRP-expressing cells and 2.5 and 2.1, respectively, in the control cells.

When M-1 1 to 50 μmol/L was added to LLC-PK1 cells expressing P-gp and its control cells, the efflux ratios were 1.4 to 1.9 and 0.9 to 1.1, respectively. When M-1 1 to 50 μmol/L was added to MDCKII cells expressing BCRP and its control cells, the efflux ratios were 1.6 to 2.2 and 2.3 to 3.5, respectively.

When $^{14}$C-vericiguat 0.5 to 5 μmol/L was added to human embryonic kidney 293 (HEK293) cells expressing organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, or organic cation transporter 1 (OCT1), the cellular uptake of vericiguat was similar to that of the control cells.

When $^{3}$H-M-1 0.2 to 2 μmol/L was added to HEK293 cells expressing OATP1B1 or OATP1B3, the cellular uptake of M-1 was similar to that of the control cells.

Using LLC-PK1 cells expressing P-gp, MDCK Ⅱ cells expressing BCRP, HEK293 cells expressing multidrug and toxic compound 1 (MATE1) or MATE2-K, and sandwich-cultured human hepatocytes (SCHH) expressing bile salt export pump (BSEP), the potential of vericiguat and M-1 to inhibit the transport of the substrates of these transporters was evaluated. Vericiguat inhibited BCRP, with an $IC_{50}$ of 20 to 26 μmol/L. Vericiguat showed little inhibition of other transporters ($IC_{50}$ >100 μmol/L for P-gp and BSEP; $IC_{50}$ >10 μmol/L for

MATE1 and MATE2-K). M-1 showed little inhibition of all transporters ($IC_{50}$ >200 μmol/L for P-gp and BCRP; $IC_{50}$ >10 μmol/L for MATE1 and MATE2-K; $IC_{50}$ >100 μmol/L for BSEP).

Using HEK293 cells expressing OATP1B1, OATP1B3, organic anion transporter 1 (OAT1), OAT3, OCT1, or OCT2, the potential of vericiguat and M-1 to inhibit the transport of the substrates of these transporters was evaluated. Vericiguat inhibited OATP1B1 and OATP1B3, with $IC_{50}$ values of 16 and 30 μmol/L, respectively. Vericiguat showed little inhibition of other transporters ($IC_{50}$ >5 μmol/L for OAT1, OAT3, and OCT2; $IC_{50}$ >50 μmol/L for OCT1). M-1 inhibited OATP1B1 and OATP1B3, with $IC_{50}$ values of 25.6 and 16.6 μmol/L, respectively. M-1 showed little inhibition of other transporters ($IC_{50}$ >5 μmol/L for OAT1, OAT3, and OCT2; $IC_{50}$ >50 μmol/L for OCT1).

### 6.2.2 Studies in healthy adult subjects

#### 6.2.2.1 Single- and multiple-dose study in Japanese healthy adult subjects (Study 15836, CTD 5.3.3.1.4, November 20[redacted] to May 20[redacted])

Table 21 shows the PK parameters of vericiguat following a single oral dose of vericiguat 1.25, 5, 7.5, or 10 mg in Japanese healthy adult male subjects under fasting conditions. There was a 3-day washout period between single and multiple dosing. Table 22 shows the PK parameters of vericiguat following once daily oral administration of vericiguat 1.25, 5, 7.5, or 10 mg for 7 days (under fed conditions on the first day only and under fasting conditions for the subsequent 6 days).

Table 21. PK parameters of vericiguat following a single oral dose of vericiguat under fasting conditions

| Dose (mg) | N | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-24h}$ (μg·h/L) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 1.25 | 9 | 61.8 (28.5) | 1.00 | 703 (16.6) | 1190 (17.5) | 22.3 (18.2) |
| 5 | 9 | 236 (28.9) | 1.00 | 2540 (20.6) | 4140 (21.1) | 21.1 (31.0) |
| 7.5 | 9 | 324 (39.6) | 1.00 | 3230 (30.7) | 5140 (38.6) | 17.9 (17.9) |
| 10 | 9 | 365 (37.1) | 2.50 | 4410 (29.9) | 7410 (30.5) | 18.3 (20.1) |

Geometric mean (Geometric coefficient of variation %)
a: Median

Table 22. PK parameters of vericiguat following multiple oral doses of vericiguat

| Dose (mg) | N | Time point (Day) | $C_{max,ss}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-24h}$ (μg·h/L) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 1.25 | 9 | 1 | 46.4 (17.1) | 4.00 | 666 (11.0) | － |
| | | 7 | 89.2 (18.6) | 1.00 | 1170 (14.5) | 27.0 (23.6) |
| 5 | 8 | 1 | 161 (18.1) | 4.00 | 2370 (13.0) | － |
| | | 7 | 289 (25.1) | 1.75 | 3670 (23.4) | 23.5 (30.6) |
| 7.5 | 9 | 1 | 242 (13.5) | 4.00 | 3300 (18.6) | － |
| | | 7 | 407 (24.2) | 2.50 | 4810 (27.6) | 22.1 (15.9) |
| 10 | 9 | 1 | 285 (18.1) | 4.00 | 4340 (13.9) | － |
| | | 7 | 472 (30.6) | 2.50 | 6170 (29.9) | 20.7 (25.2) |

Geometric mean (Geometric coefficient of variation %), －: Not calculated
a: Median

### 6.2.2.2 Single- and multiple-dose studies in non-Japanese healthy adult subjects

#### 6.2.2.2.1 Single-dose study (Study 15355, CTD 5.3.3.1.1 [Reference data], July 20[redacted] to January 20[redacted])

Table 23 shows the PK parameters of vericiguat following a single oral dose of vericiguat 0.5, 1, 2.5, 5, 7.5, 10, or 15 mg in non-Japanese healthy adult male subjects who were non-smokers under fasting conditions and following a single oral dose of vericiguat 5 mg in non-Japanese healthy adult male subjects who were smokers under fasting conditions.

Table 23. PK parameters of vericiguat following a single oral dose of vericiguat under fasting conditions

| Dose (mg) | Smoker/Non-smoker | N | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 0.5 | Non-smoker | 7 | 17.2 (20.8) | 1.00 | 273 (26.9) | 17.2 (19.8) |
| 1 | Non-smoker | 8 | 39.3 (23.2) | 0.750 | 618 (20.1) | 19.4 (13.9) |
| 2.5 | Non-smoker | 8 | 82.7 (23.3) | 0.867 | 1450 (14.0) | 19.4 (16.9) |
| 5 | Non-smoker | 7 | 158 (12.8) | 1.00 | 2900 (24.1) | 19.8 (24.4) |
| | Smoker | 6 | 194 (15.1) | 0.733 | 2500 (16.3) | 14.5 (25.9) |
| 7.5 | Non-smoker | 8 | 259 (20.5) | 1.00 | 4460 (21.9) | 19.8 (15.9) |
| 10 | Non-smoker | 8 | 285 (8.9) | 1.25 | 4940 (20.0) | 20.7 (43.9) |
| 15 | Non-smoker | 4 | 430 (9.3) | 1.75 | 7900 (16.2) | 17.2 (27.8) |

Geometric mean (Geometric coefficient of variation %)
a: Median

#### 6.2.2.2.2 Multiple-dose study (Study 15357, CTD 5.3.3.1.2 [Reference data], May to November 20[redacted])

Non-Japanese healthy adult male subjects received vericiguat 1.25, 5, or 10 mg orally once daily under fasting conditions for 7 days or vericiguat 5 mg orally twice daily under fasting conditions for 7 days. PK parameters of vericiguat are shown in Table 24.

Table 24. PK parameters of vericiguat following multiple oral doses of vericiguat under fasting conditions

| Treatment group | N | Time point (Day) | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{\tau}$ (μg·h/L) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 1.25 mg once daily | 9 | 1 | 38.5 (21.8) | 1.00 | 423 (12.6) | － |
| | | 7 | 51.4 (21.1) | 1.98 | 656 (18.7) | 25.7 (18.0) |
| 5 mg once daily | 8 | 1 | 114 (28.2) | 1.00 | 1370 (20.0) | － |
| | | 7 | 185 (30.6) | 1.48 | 2230 (28.8) | 24.7 (26.3) |
| 10 mg once daily | 8 | 1 | 200 (61.6) | 1.00 | 2240 (45.1) | － |
| | | 7 | 310 (25.6) | 1.00 | 3840 (25.2) | 19.9 (11.3) |
| 5 mg twice daily | 7 | 1 | 136 (33.0) | 1.00 | 951 (26.8) | － |
| | | 7 | 312 (38.5) | 0.983 | 2600 (33.8) | 20.7 (23.2) |

Geometric mean (Geometric coefficient of variation %), －: Not calculated
a: Median

### 6.2.2.3 Mass balance study (Study 15817, CTD 4.2.2.4.4, 5.3.3.1.5 [Reference data], April to June 20[redacted])

Following a single oral dose of $^{14}$C-vericiguat 5 mg in 6 non-Japanese healthy adult male subjects under fasting conditions, 53.1% and 45.2% of the administered radioactivity were recovered in the urine and feces over 336 hours, respectively. Unchanged vericiguat and M-1 were mainly excreted in the urine (9.00% and 40.8% of the administered radioactivity, respectively), and unchanged vericiguat was mainly excreted in the feces (42.6% of the administered radioactivity).

### 6.2.3 Intrinsic factors

#### 6.2.3.1 Effects of age and gender on PK (Study 15816, CTD 5.3.3.3.1 [Reference data], August to September 20[redacted])

Following a single oral dose of vericiguat 5 mg in 42 non-Japanese healthy adult male and female subjects (non-elderly [18-45 years] subjects [9 each], elderly [≥65 years] subjects [12 each]) under fed conditions, the least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of vericiguat for elderly vs. non-elderly [90% CI] were 0.995 [0.822, 1.204] and 1.046 [0.859, 1.274], respectively, in male subjects, and 1.010 [0.835, 1.223] and 1.149 [0.944, 1.400], respectively, in female subjects. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ for female vs. male [90% CI] were 1.321 [1.160, 1.505] and 1.373 [1.197, 1.575], respectively.

#### 6.2.3.2 Clinical pharmacology study in subjects with renal impairment (Study 15813, CTD 5.3.3.3.2 [Reference data], June 2014 to January 2015)

Non-Japanese subjects with mild renal impairment (eGFR, ≥60 mL/min/1.73 $m^2$ and <90 mL/min/1.73 $m^2$), moderate renal impairment (eGFR, ≥30 mL/min/1.73 $m^2$ and <60 mL/min/1.73 $m^2$), or severe renal impairment (eGFR <30 mL/min/1.73 $m^2$), and subjects with normal renal function matched for age, body weight, and sex with subjects with renal impairment received a single oral dose of vericiguat 2.5 mg under fed conditions. PK parameters of vericiguat and M-1 are shown in Table 25 and Table 26, respectively.[2)] Table 27 shows vericiguat (unbound) exposure ratio for renal impairment vs. normal renal function.

Table 25. PK parameters of vericiguat following a single oral dose of vericiguat

| | N | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|---|
| Total concentration | | | | | | | |
| Normal renal function | 8 | 83.1 (16.9) | 3.50 | 1330 (25.9) | 20.7 (36.7) | 1.88 (25.9) | 56.1 (35.2) |
| Mild renal impairment | 9 | 76.2 (26.1) | 3.00 | 1390 (30.3) | 17.1 (24.8) | 1.80 (30.3) | 44.6 (22.8) |
| Moderate renal impairment | 14 | 92.7 (33.7) | 4.00 | 2200 (30.4) | 32.1 (23.0) | 1.14 (30.4) | 52.7 (40.2) |
| Severe renal impairment | 8 | 91.4 (20.8) | 4.00 | 2940 (19.5) | 36.9 (20.6) | 0.85 (19.5) | 45.3 (18.9) |
| Unbound | | | | | | | |
| Normal renal function | 8 | 1.77 (16.0) | — | 28.3 (25.5) | — | 88.2 (25.5) | 2630 (38.1) |
| Mild renal impairment | 9 | 1.54 (27.9) | — | 28.0 (38.3) | — | 89.2 (38.3) | 2210 (23.8) |
| Moderate renal impairment | 14 | 2.11 (26.6) | — | 49.9 (45.2) | — | 50.1 (45.2) | 2320 (52.2) |
| Severe renal impairment | 8 | 2.01 (19.9) | — | 64.5 (25.1) | — | 38.8 (25.1) | 2060 (26.4) |

Geometric mean (Geometric coefficient of variation %), —: Not calculated
a: Median

[2)] Renal impairment was classified according to eGFR at screening, but reclassified according to CLcr calculated from 24-hour urine collection on the day before administration of vericiguat (CLcr [mL/min], normal >80; mild ≥50 and ≤80; moderate ≥30 and <50; severe <30). In this section, the results based on eGFR at screening are presented. Five of 9 patients with mild renal impairment based on eGFR had CLcr >80, 5 of 14 patients with moderate renal impairment based on eGFR had CLcr ≥50 and ≤80, 1 of 14 patients with moderate renal impairment based on eGFR had CLcr <30, and 1 of 8 patients with severe renal impairment based on eGFR had CLcr ≥30 and <50.

Table 26. PK parameters of M-1 following a single oral dose of vericiguat

| | N | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|---|
| Total concentration | | | | | | | |
| Normal renal function | 8 | 91.8 (27.3) | 24.0 | 10800 (48.2) | 67.5 (42.5) | 0.326 (48.2) | 31.8 (29.0) |
| Mild renal impairment | 9 | 110 (36.3) | 24.1 | 17000 (44.7)[b] | 91.2 (57.6)[b] | 0.208 (44.7)[b] | 27.3 (23.8)[b] |
| Moderate renal impairment | 14 | 122 (27.4) | 36.0 | 17300 (43.0)[c] | 73.6 (57.5)[c] | 0.204 (43.0)[c] | 21.6 (28.6)[c] |
| Severe renal impairment | 8 | 123 (26.5) | 42.0 | 21300 (29.7)[b] | 99.0 (25.2)[b] | 0.166 (29.7)[b] | 23.7 (37.3)[b] |
| Unbound | | | | | | | |
| Normal renal function | 8 | 1.17 (28.8) | － | 138 (49.4) | － | 25.7 (49.4) | 2500 (31.0) |
| Mild renal impairment | 9 | 1.06 (31.4) | － | 182 (54.3)[b] | － | 19.4 (54.3)[b] | 2550 (17.0)[b] |
| Moderate renal impairment | 14 | 1.50 (24.1) | － | 199 (38.6)[c] | － | 17.7 (38.6)[c] | 1882 (27.9)[c] |
| Severe renal impairment | 8 | 1.66 (29.8) | － | 273 (34.7)[b] | － | 12.9 (34.7)[b] | 1846 (41.4)[b] |

Geometric mean (Geometric coefficient of variation %), －: Not calculated
a: Median
b: N = 5
c: N = 8

Table 27. Vericiguat (unbound) exposure ratio for renal impairment vs. normal renal function

| | N | $C_{max}$ | $AUC_{0-\infty}$ |
|---|---|---|---|
| Mild renal impairment/Normal renal function | 9/8 | 0.869 [0.716, 1.054] | 0.989 [0.740, 1.322] |
| Moderate renal impairment/Normal renal function | 14/8 | 1.189 [0.997, 1.418] | 1.762 [1.352, 2.296] |
| Severe renal impairment/Normal renal function | 8/8 | 1.134 [0.929, 1.383] | 2.275 [1.688, 3.067] |

Geometric least-square mean ratio [90% CI]

### 6.2.3.3 Clinical pharmacology study in subjects with hepatic impairment (Study 15840, CTD 5.3.3.3.3 [Reference data], July 2014 to January 2015)

Non-Japanese subjects with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B), and subjects with normal hepatic function matched for age, body weight, and sex with subjects with hepatic impairment received a single oral dose of vericiguat 2.5 mg under fed conditions. PK parameters of vericiguat and M-1 are shown in Table 28 and Table 29, respectively. Table 30 shows vericiguat (unbound) exposure ratio for hepatic impairment vs. normal hepatic function.

Table 28. PK parameters of vericiguat following a single oral dose of vericiguat

| | N | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|---|
| Total concentration | | | | | | | |
| Normal hepatic function | 9 | 68.7 (29.2) | 4.00 | 1250 (34.5) | 20.2 (26.4) | 2.00 (34.5) | 58.3 (14.4) |
| Mild hepatic impairment | 9 | 66.6 (27.2) | 4.00 | 1550 (23.4) | 19.8 (16.9) | 1.61 (23.4) | 46.1 (15.7) |
| Moderate hepatic impairment | 9 | 69.5 (34.4) | 4.00 | 1780 (34.6) | 23.7 (39.5) | 1.41 (34.6) | 48.1 (23.6) |
| Unbound | | | | | | | |
| Normal hepatic function | 9 | 1.66 (21.3) | － | 30.3 (33.3) | － | － | － |
| Mild hepatic impairment | 9 | 1.40 (25.9) | － | 32.7 (17.9) | － | － | － |
| Moderate hepatic impairment | 9 | 1.67 (30.3) | － | 42.7 (41.2) | － | － | － |

Geometric mean (Geometric coefficient of variation %), －: Not calculated
a: Median

Table 29. PK parameters of M-1 following a single oral dose of vericiguat

| | N | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0-\infty}$ (μg·h/L) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| Total concentration | | | | | |
| Normal hepatic function | 9 | 84.8 (32.6) | 24.0 | 8460 (63.6) | 49.2 (65.5) |
| Mild hepatic impairment | 9 | 107 (36.0) | 36.0 | 18300 (46.0)[b] | 95.2 (35.2)[b] |
| Moderate hepatic impairment | 9 | 93.0 (50.3) | 60.0 | 26800 (61.9)[c] | 152 (54.9)[c] |
| Unbound | | | | | |
| Normal hepatic function | 9 | 0.935 (28.2) | — | 93.4 (59.4) | — |
| Mild hepatic impairment | 9 | 1.32 (35.5) | — | 228 (49.8)[b] | — |
| Moderate hepatic impairment | 9 | 1.37 (54.4) | — | 403 (76.2)[c] | — |

Geometric mean (Geometric coefficient of variation %), —: Not calculated
a: Median
b: N = 8
c: N = 6

Table 30. Vericiguat (unbound) exposure ratio for hepatic impairment vs. normal hepatic function

| | N | $C_{max}$ | $AUC_{0-\infty}$ |
|---|---|---|---|
| Mild hepatic impairment/Normal hepatic function | 9/9 | 0.8454 [0.6875, 1.0396] | 1.0804 [0.8396, 1.3902] |
| Moderate hepatic impairment/Normal hepatic function | 9/9 | 1.0057 [0.8178, 1.2367] | 1.4110 [1.0966, 1.8157] |

Geometric least-square mean ratio [90% CI]

### 6.2.4 Drug interaction studies

The results of drug interaction studies of vericiguat are shown below. Drug interaction studies other than the following studies were also conducted. Coadministration with ketoconazole, mefenamic acid, or digoxin did not affect vericiguat plasma concentrations, and vericiguat did not affect digoxin plasma concentrations.

#### 6.2.4.1 Drug interaction study with omeprazole or antacid (Study 15811, CTD 5.3.3.4.1 [Reference data], July to December 20[redacted])

A 3-treatment, 3-period crossover study was conducted in 12 non-Japanese healthy adult male subjects (a washout period of ≥5 days). (1) A single oral dose of vericiguat 5 mg was administered, (2) omeprazole 40 mg was administered orally once daily for 4 days, and a single oral dose of omeprazole 40 mg was followed 2 hours later by a single oral dose of vericiguat 5 mg on Day 5, or (3) a single oral dose of antiacid (aluminum oxide 900 mg and magnesium hydroxide 600 mg) was immediately followed by a single oral dose of vericiguat 5 mg. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of vericiguat for vericiguat + omeprazole (2) vs. vericiguat alone (1) [90% CI] were 0.5037 [0.4262, 0.5952] and 0.6780 [0.6078, 0.7563], respectively. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of vericiguat for vericiguat + antiacid (3) vs. vericiguat alone (1) [90% CI] were 0.5430 [0.4595, 0.6417] and 0.7291 [0.6536, 0.8133], respectively.

#### 6.2.4.2 Drug interaction study with rifampicin (Study 17746, CTD 5.3.3.4.10 [Reference data], September to November 20[redacted])

A study was conducted in 16 non-Japanese healthy adult male subjects (a washout period of 6 ± 1 days). In the vericiguat alone phase, a single oral dose of vericiguat 10 mg was administered. In the coadministration phase, rifampicin 600 mg was administered orally once daily for 7 days, with a single oral dose of vericiguat 10 mg coadministered on Day 7. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of unchanged vericiguat for vericiguat + rifampicin vs. vericiguat alone [90% CI] were 0.9142 [0.7963, 1.0496] and 0.7134 [0.6376,

0.7982], respectively. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of M-1 were 0.9131 [0.8256, 1.0099] and 0.6127 [0.5283, 0.7107], respectively.

#### 6.2.4.3 Drug interaction study with midazolam (Study 15815, CTD 5.3.3.4.5 [Reference data], February to May 20[redacted])

A 2-treatment, 2-period crossover study was conducted in 32 non-Japanese healthy adult male subjects (a washout period of ≥10 days). A single oral dose of midazolam 7.5 mg was administered, or vericiguat 10 mg was administered orally once daily for 4 days, with a single oral dose of midazolam 7.5 mg coadministered on Day 4. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of midazolam for midazolam + vericiguat vs. midazolam alone [90% CI] were 0.7685 [0.6830, 0.8645] and 0.8221 [0.7762, 0.8708], respectively. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of 1'-hydroxy midazolam were 0.8387 [0.7283, 0.9658] and 0.8803 [0.8380, 0.9246], respectively.

#### 6.2.4.4 Drug interaction study with aspirin (Study 15838, CTD 5.3.3.4.3 [Reference data], June to September 20[redacted])

A 3-treatment, 3-period crossover study was conducted in 14 non-Japanese healthy adult male subjects (a washout period of ≥14 days). (1) A single oral dose of vericiguat 15 mg was administered, (2) aspirin 500 mg was administered orally once daily for 2 days, or (3) a single oral dose of aspirin 500 mg was administered on Day 1, and a single oral dose of vericiguat 15 mg was coadministered with aspirin 500 mg on Day 2. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of vericiguat for vericiguat + aspirin (3) vs. vericiguat alone (1) [90% CI] were 0.9325 [0.8107, 1.0726] and 0.9492 [0.8473, 1.0633], respectively. There was no significant increase in bleeding time following coadministration of vericiguat with aspirin (3) compared with aspirin alone (2).

#### 6.2.4.5 Drug interaction study with warfarin (Study 15839, CTD 5.3.3.4.6 [Reference data], March to September 20[redacted])

A 2-treatment, 2-period crossover study was conducted in 23 non-Japanese healthy adult male subjects to investigate the effect of vericiguat on the PK and pharmacodynamics of warfarin. In the warfarin alone phase, placebo was administered orally once daily for 9 days, with a single oral dose of warfarin 25 mg coadministered on Day 6. In the coadministration phase, vericiguat 10 mg was administered orally once daily for 9 days, with a single oral dose of warfarin 25 mg coadministered on Day 6. A washout period of ≥17 days was included between the treatment phases. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of *R*-warfarin for warfarin + vericiguat vs. warfarin alone [90% CI] were 0.9944 [0.9595, 1.0305] and 0.9849 [0.9673, 1.0029], respectively. The least-square mean ratios of $C_{max}$ and $AUC_{0-\infty}$ of *S*-warfarin were 0.9833 [0.9467, 1.0212] and 0.9775 [0.9568, 0.9987], respectively. Multiple doses of vericiguat once daily given together with a single dose of warfarin did not have an effect on prothrombin time in comparison to warfarin alone.

#### 6.2.4.6 Drug interaction studies with nitroglycerin

##### 6.2.4.6.1 Study in healthy adult subjects (Study 17115, CTD 5.3.4.1.1 [Reference data], August 20[redacted] to April 20[redacted])

A 4-treatment, 4-period crossover study was conducted in 38 non-Japanese healthy adult male subjects (17 in cohort 1, 21 in cohort 2) to investigate the effect of vericiguat on the pharmacodynamics of nitroglycerin (a washout period of ≥5 days). In cohort 1, a single oral dose of vericiguat 5 mg or placebo was followed 6 or 12 hours later by a single sublingual dose of nitroglycerin 0.2 mg. In cohort 2, a single oral dose of vericiguat 5 mg or placebo was followed 4 or 8 hours later by a single sublingual dose of nitroglycerin 0.2 mg. When a single oral dose of vericiguat 5 mg was followed 4 hours later by a single sublingual dose of nitroglycerin 0.2 mg, the mean maximum change from baseline in SBP was −11.34 mmHg, which was not substantially different from −11.72 mmHg in the placebo group.

##### 6.2.4.6.2 Study in patients with stable coronary artery disease (Study 17849, CTD 5.3.4.2.1 [Reference data], November 2015 to May 2016)

A drug interaction study was conducted in 36 patients with stable coronary artery disease (24 in the vericiguat group, 12 in the placebo group) to investigate the effect of vericiguat on the pharmacodynamics of nitroglycerin. In the vericiguat group, vericiguat was up-titrated from 2.5 to 5 and then to 10 mg, and each was administered orally once daily for approximately 14 days. At steady state at each dose level, a single sublingual dose of nitroglycerin 0.4 mg was administered at the trough (at 2.5 hours before treatment on the day before the last day) and peak (at 4 hours after treatment on the last day) plasma concentrations of vericiguat. In the placebo group, placebo instead of vericiguat was orally administered. At steady state following multiple oral doses of vericiguat 10 mg, the mean changes in SBP from baseline to 5 minutes after a single sublingual dose of nitroglycerin 0.4 mg were −6.3 mmHg (trough) and −6.3 mmHg (peak), which were not substantially different from −7.2 mmHg (trough) and −8.9 mmHg (peak) in the placebo group.

#### 6.2.4.7 Drug interaction study with isosorbide mononitrate (Study 18582, CTD 5.3.4.2.2 [Reference data], August 2017 to February 2018)

A drug interaction study was conducted in 41 patients with stable coronary artery disease (28 in the vericiguat group, 13 in the placebo group) to investigate the effect of vericiguat on the pharmacodynamics of isosorbide mononitrate. In the run-in phase, the isosorbide mononitrate extended-release formulation was up-titrated from 30 to 60 mg, and each was administered orally once daily for approximately 7 days. In the coadministration phase, the isosorbide mononitrate extended-release formulation 60 mg was administered before meal, and vericiguat or placebo was administered orally once daily with food. Vericiguat was up-titrated from 2.5 to 5 and then to 10 mg, and each was administered orally for approximately 14 days. When vericiguat was given 1 hour after administration of isosorbide mononitrate on the first and last days of each dose step of vericiguat, the mean maximum changes from baseline (before administration of isosorbide mononitrate) in SBP were −32.2 to −25.7 mmHg, and vericiguat at all dose levels had an additive blood pressure lowering effect compared with placebo (−30.2 to −21.0 mmHg) (the treatment difference [the least-square mean] was −5.08 to −1.41 mmHg).

#### 6.2.4.8 Drug interaction study with sildenafil (Study 17743, CTD 5.3.3.4.8 [Reference data], February to June 20[redacted])

A study was conducted in 32 non-Japanese healthy adult male subjects (16 in the vericiguat group, 16 in the placebo group). Vericiguat 10 mg or placebo was administered orally once daily for 16 days, with single oral doses of 25, 50, and 100 mg of sildenafil coadministered on Days 13, 14, and 15, respectively. At steady state following multiple oral doses of vericiguat 10 mg, the mean maximum change in SBP from baseline to after a single dose of sildenafil was −15.8 to −9.5 mmHg, showing a further decrease compared with −11.0 to −10.2 mmHg in the placebo group.

#### 6.2.4.9 Drug interaction study with sacubitril/valsartan (Study 17745, CTD 5.3.3.4.9 [Reference data], April to July 20[redacted])

A drug interaction study was conducted in 32 non-Japanese healthy adult male subjects (16 in the vericiguat group, 16 in the placebo group) to investigate the effect of vericiguat on the PK and pharmacodynamics of sacubitril/valsartan. In the run-in phase (Days 0-26), sacubitril/valsartan 100 mg was administered orally twice daily for 14 days, and then sacubitril/valsartan 200 mg was administered orally twice daily for 13 days. Only on the first day of treatment (Day 0), vericiguat 2.5 mg or placebo was administered in combination with sacubitril/valsartan. In the coadministration phase (Days 27-40), vericiguat 2.5 mg or placebo once daily together with sacubitril/valsartan 200 mg twice daily were administered orally for 14 days. The least-square mean ratios of $C_{max}$ and $AUC_{0\text{-}12h}$ of sacubitril for sacubitril/valsartan + vericiguat vs. sacubitril/valsartan alone [90% CI] were 1.1822 [0.8907, 1.5692] and 1.0802 [0.9917, 1.1765], respectively. The least-square mean ratios of $C_{max}$ and $AUC_{0\text{-}12h}$ of LBQ657, an active metabolite of sacubitril, were 1.0158 [0.9708, 1.0629] and 1.0127 [0.9716, 1.0555], respectively. The least-square mean ratios of $C_{max}$ and $AUC_{0\text{-}12h}$ of valsartan were 1.1267 [0.9757, 1.3011] and 1.1168 [0.9529, 1.3088], respectively. Vericiguat had no clear effect on the maximum change in SBP compared with placebo.

### 6.2.5 QT evaluation study (Study 18979, CTD 5.3.4.2.3, May to November 2018)

The effect of vericiguat on QT interval was investigated in 74 patients with stable coronary artery disease. Vericiguat 2.5, 5, or 10 mg or placebo was administered orally once daily under fed conditions for 14 days, or a single oral dose of moxifloxacin 400 mg was administered.

Following multiple oral administration of vericiguat 2.5, 5, and 10 mg, the median $t_{max}$ values of vericiguat on Day 14 were all 4.5 hours, and the $C_{max}$ values (geometric mean [geometric coefficient of variation %]) were 96.6 (22.6), 180 (27.7), and 322 (32.0) µg/L, respectively.

Across all time points, the upper bound of the 90% confidence interval for the mean difference (vericiguat 10 mg minus placebo) in Fridericia-corrected QT interval (QTcF) change from baseline (ΔΔQTcF) was <10 msec. Across all time points, the lower bound of the 90% confidence interval for ΔΔQTcF for moxifloxacin was above 5 msec.

### 6.2.6 PPK analyses (Analysis 20964, CTD 5.3.3.5.10 [Reference data])

Using 3375 vericiguat plasma concentrations from 362 patients in a global phase II study (Study 15371) and 4717 vericiguat plasma concentrations from 1959 patients in a global phase III study (Study 16493), population pharmacokinetic (PPK) analyses were performed. The PK of vericiguat were described by a 1-compartment model with first-order absorption and first-order elimination. The distribution of the major demographic and clinical characteristics of patients included in the PPK analyses was as follows: sex (1786 men, 535 women), race (1609 White patients, 416 Asian patients, 156 multiracial patients, 111 Black patients, 29 patients [others]), ethnicity (356 Hispanic/Latino patients, 1920 patients [others], 27 patients [not reported], 18 patients [unknown]), New York Heart Association (NYHA) class (11 patients [class I], 1402 patients [class II], 880 patients [class III], 27 patients [class IV], 1 patient [unknown]), history of atrial fibrillation (1008 patients [Yes], 1313 patients [No]), use of any drugs affecting gastric pH (1362 patients [Yes], 959 patients [No]), age (69 [24-96] years [median (min.-max.)]), albumin (4.20 [2.6-5.4] g/dL), bilirubin (0.59 [0.2-6.4] mg/dL), left ventricular ejection fraction (LVEF) (30.00 [6.0-53.1] %), N-terminal pro-B type natriuretic peptide (NT-proBNP) (2659.50 [10.0-175000.0] pg/mL), body weight (77.58 [32.5-164.0] kg), and estimated glomerular filtration rate (eGFR) (57.82 [11.0-221.2] mL/min/1.73 $m^2$). In the final model, body weight was selected as a significant covariate on CL/F and V/F.[3)]

The estimated population mean parameters from the final model were as follows: CL/F was 1.09 L/h, and V/F was 46.8 L. Interindividual variability (coefficient of variation %) and residual error were 33.9% and 5.00%, respectively, for CL/F and 35.5% and 21.3%, respectively, for V/F. The steady-state vericiguat exposures were simulated using empirical Bayesian parameter estimates from the final model and Studies 15371 and 16493. Table 31 shows the steady-state PK parameters of vericiguat following once daily oral administration of vericiguat 2.5, 5, or 10 mg in chronic heart failure patients with reduced LVEF. Patients were categorized according to body weight (<60 kg, ≥60 kg and ≤90 kg, >90 kg), and the PK parameters of vericiguat estimated using the above method were compared among these groups. Compared to patients with body weight ≥60 kg and ≤90 kg, the $C_{max}$ and $AUC_{0\text{-}24h}$ were 27% and 27% higher, respectively, in patients with body weight <60 kg, and the $C_{max}$ and $AUC_{0\text{-}24h}$ were 19.4% and 19.6% lower, respectively, in patients with body weight >90 kg.

Table 31. Steady-state PK parameters of vericiguat (Estimates based on simulation)

| Dose (mg) | N | $C_{max}$ (μg/L) | $t_{max}$[a] (h) | $AUC_{0\text{-}24h}$ (μg·h/L) | $t_{1/2}$ (h) | $C_{trough}$ (μg/L) |
|---|---|---|---|---|---|---|
| 2.5 | 2321 | 120 (29.0) | 2.13 | 2300 (33.9) | 29.5 (31.5) | 71.2 (42.7) |
| 5 | 2321 | 201 (29.0) | 2.13 | 3850 (33.9) | 29.5 (31.5) | 119 (42.7) |
| 10 | 2321 | 350 (29.0) | 2.13 | 6680 (33.9) | 29.5 (31.5) | 207 (42.7) |

Geometric mean (Geometric coefficient of variation %)
a: Median

[3)] Body weight, bilirubin, eGFR, albumin, sex, race, ethnicity, age, LVEF, NYHA class, NT-proBNP, and history of atrial fibrillation were evaluated as potential covariates on CL/F. Body weight, albumin, sex, race, ethnicity, age, LVEF, NYHA class, and NT-proBNP were evaluated as potential covariates on V/F. Body weight, albumin, use of any drugs affecting gastric pH, and dose were evaluated as potential covariates on $k_a$. Use of any drugs affecting gastric pH and dose were evaluated as potential covariates on BA.

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Food effect

The applicant's explanation about the timing of dosing relative to meals in the DOSAGE AND ADMINISTRATION section of the package insert:

Since Study 15356 that investigated the effect of food with vericiguat 5 mg showed that food increases vericiguat exposure and suggested that vericiguat shows lower interindividual variability when taken with food [see Section "6.1.2.1 Food effect study (a)"], vericiguat was to be taken with food in a global phase II study (Study 15371) and a global phase III study (Study 16493). Study 18580 was conducted later to investigate the effect of food with vericiguat 10 mg, which also showed that food increases vericiguat exposure [see Section "6.1.2.2 Food effect study (b)"], and Study 16493 in which vericiguat was to be taken with food demonstrated the efficacy and safety of vericiguat in patients with chronic heart failure with reduced LVEF. Given these findings, vericiguat is recommended to be taken with food.

Given the applicant's explanation, PMDA considers that intake of vericiguat with food is appropriate.

### 6.R.2 PK differences between Japanese and non-Japanese populations

The applicant's explanation about differences in the PK of vericiguat between Japanese and non-Japanese populations:

PK parameters and PK parameters normalized to dose per kg body weight following single and multiple doses of vericiguat in Japanese and foreign phase I studies are shown in Table 32 and Table 33, respectively. Following both single and multiple doses of vericiguat, the $C_{max}$ and $AUC_{0-\infty}$ of vericiguat were higher in Japanese healthy adult subjects than in non-Japanese healthy adult subjects. As covariate exploration in the PPK analysis (Analysis 20964) identified body weight as a significant covariate on the PK parameters of vericiguat [see Section "6.2.6 PPK analyses"], the $C_{max}$ and AUC of vericiguat normalized to dose per kg body weight were compared. The $C_{max,norm}$ and $AUC_{0-\infty,norm}$ of vericiguat following a single oral dose in Japanese healthy adult subjects were 0.97- to 1.53-fold and 1.14- to 1.24-fold those in non-Japanese healthy adult subjects, respectively, and the $C_{max,norm}$ and $AUC_{0-\infty,norm}$ of vericiguat following multiple doses in Japanese healthy adult subjects were 1.00- to 1.09-fold and 1.06- to 1.16-fold those in non-Japanese healthy adult subjects, respectively. There were little differences in vericiguat exposure normalized to dose per kg body weight between Japanese and non-Japanese populations. Covariate exploration in Analysis 20964 did not identify race or ethnicity as a significant covariate on the PK parameters of vericiguat. The steady-state vericiguat exposures were simulated using empirical Bayesian parameter estimates from the final model and Study 16493. Following once daily administration of vericiguat at modal doses used between Day 57 and Day 168 (2.5-10 mg), the estimated steady-state $C_{max}$ and $AUC_{0-24h}$ of vericiguat were 348 µg/L and 6730 µg·h/L, respectively, in Japanese patients with chronic heart failure, 340 µg/L and 6540 µg·h/L, respectively, in non-Japanese Asian patients, and 298 µg/L and 5750 µg·h/L, respectively, in non-Asian patients, and there were no major differences in vericiguat exposure among these groups.

Based on the above, there are no clinically relevant differences in the PK of vericiguat between Japanese and non-Japanese patients with chronic heart failure with reduced LVEF.

Table 32. PK parameters following a single oral dose of vericiguat under fasting conditions

| Population | Dose (mg) | N | $C_{max}$ (μg/L) | $AUC_{0-\infty}$ (μg·h/L) | $C_{max,norm}$ (kg/L) | $AUC_{0-\infty,norm}$ (kg·h/L) |
|---|---|---|---|---|---|---|
| Japanese | 5[a] | 9 | 236 (28.9) | 4140 (21.1) | 2.69 (19.0) | 47.2 (19.0) |
| | 10[a] | 9 | 365 (37.1) | 7410 (30.5) | 2.34 (36.2) | 47.6 (29.9) |
| Non-Japanese | 5[b] | 15 | 106 (44.9) | 2300 (33.0) | 1.76 (40.7) | 38.1 (30.3) |
| | 5[c] | 10 | 142 (45.8) | 2492 (23.4) | 2.31 (46.5) | 40.6 (22.7) |
| | 10[d] | 8 | 285 (8.9) | 4940 (20.0) | 2.41 (11.1) | 41.8 (19.6) |

Geometric mean (Geometric coefficient of variation %)
a: See the results of Study 15836.
b: See the results of Study 15356.
c: See the results of Study 15811.
d: See the results of Study 15355.

Table 33. PK parameters following multiple oral doses of vericiguat under fasting conditions

| Population | Dose (mg) | N | $C_{max}$ (μg/L) | $AUC_{0-\infty}$ (μg·h/L) | $C_{max,norm}$ (kg/L) | $AUC_{0-\infty,norm}$ (kg·h/L) |
|---|---|---|---|---|---|---|
| Japanese | 5[a] | 8 | 289 (25.1) | 3670 (23.4) | 3.19 (20.0) | 40.5 (19.8) |
| | 10[a] | 8 | 472 (30.6) | 6170 (29.9) | 3.02 (27.5) | 39.6 (28.2) |
| Non-Japanese | 5[b] | 9 | 185 (30.6) | 2230 (28.8) | 3.18 (21.9) | 38.2 (18.8) |
| | 10[b] | 8 | 310 (25.6) | 3840 (25.2) | 2.76 (26.4) | 34.1 (26.7) |

Geometric mean (Geometric coefficient of variation %)
a: See the results of Study 15836.
b: See the results of Study 15357.

PMDA's view:

Comparison of vericiguat exposures normalized to body weight presented by the applicant showed no clear differences between Japanese and non-Japanese populations. However, body weight has been shown to be a factor influencing the PK parameters of vericiguat, and when not corrected for body weight, vericiguat exposure was 1.5- to 1.8-fold higher in Japanese subjects than in non-Japanese subjects (Table 32 and Table 33), and also in Analysis 20964, the mean body weights in Japanese, non-Japanese Asian, and non-Asian patients with chronic heart failure were different, i.e. 61.5, 69.6, and 82.4 kg, respectively. Given these findings, it cannot be concluded that there are no differences in the PK of vericiguat following administration of the same dose of vericiguat between Japanese and non-Japanese patients with chronic heart failure with reduced LVEF.

The appropriateness of selecting the same dosing regimen for Japanese and non-Japanese patients in a global phase II study (Study 15371) and a global phase III study (Study 16493) needs to be determined, taking account of the efficacy and safety results from Studies 15371 and 16493 [see Section "7.R.5 Dosage and administration"].

### 6.R.3 Use in patients with renal impairment

The applicant's explanation about the use of vericiguat in patients with renal impairment:

In a clinical pharmacology study in subjects with renal impairment (Study 15813), subjects with mild, moderate, and severe renal impairment had 7.6%, 72.6%, and 143% higher $AUC_{0-\infty,norm}$ of vericiguat (unbound), respectively, compared to subjects with normal renal function [see Section "6.2.3.2 Clinical

pharmacology study in subjects with renal impairment"]. On the other hand, the results of Analysis 20964 showed that vericiguat exposure ($AUC_{0\text{-}24h}$) was increased in chronic heart failure patients with mild, moderate, and severe renal impairment by 5%, 13%, and 20%, respectively, compared to chronic heart failure patients with normal renal function. These differences were considered attributable to differences in body weight among these groups, and renal impairment did not have an impact on vericiguat exposure.

A mass balance study showed that urinary recovery of unchanged vericiguat is low [see Section "6.2.2.3 Mass balance study"]. Generally, renal function is considered to have a small effect on the PK of a drug with low urinary excretion. The results of *in vitro* studies suggested that in the clearance process of vericiguat, the kidneys are involved in the metabolism of unchanged vericiguat to M-1 via UGT1A9 [see Section "6.2.1.3.3 Identification of UGT isoforms involved in glucuronidation of vericiguat"] and the excretion of unchanged vericiguat and M-1 via tubular secretion [see Section "6.2.1.6 Studies on transporters"] as well as glomerular filtration. Thus, vericiguat (unchanged) exposure increased with increasing severity of renal impairment in Study 15813, which was possibly due to a decreased capacity of glomerular filtration, a decreased capacity of the kidneys to metabolize vericiguat, and a decreased capacity of tubular secretion in patients with renal impairment in this study. The possible causes of differences in the impact of renal function on unchanged vericiguat exposure between Study 15813 and the PPK analysis (Analysis 20964) are as follows: Other renal functions (the metabolism of vericiguat to M-1, tubular secretion of vericiguat and M-1) were not reduced so much as glomerular filtration decreased in patients with renal impairment enrolled in Studies 15371 and 16493; patients with chronic heart failure had decreased capacities of the liver to metabolize and excrete vericiguat into the bile due to congestive hepatopathy resulting from heart failure, which made it difficult to detect the impact of decreased renal function on the PK of vericiguat; and differences in the study design such as food. The definitive cause is unknown.

Although the reason for differences in the conclusion between the clinical pharmacology study and the PPK analysis is not clear, the results of Analysis 20964 based on Studies 15371 and 16493 in patients with chronic heart failure are considered to represent PK in a setting closer to clinical practice, compared to the results of Study 15813. Thus, the need for a precautionary statement regarding use in patients with moderate or severe renal impairment in the package insert should be determined based on the results of Analysis 20964. Study 16493 in chronic heart failure patients with eGFR ≥15 mL/min/1.73 $m^2$ showed no clinically relevant differences in the incidence of adverse events in the vericiguat and placebo groups according to the degree of renal impairment [see Section "7.R.3.4 Use in patients with renal impairment"]. Based on the above, no dose adjustment of vericiguat is required in chronic heart failure patients with eGFR ≥15 mL/min/1.73 $m^2$.

No clinical studies of vericiguat were conducted in chronic heart failure patients with eGFR <15 mL/min/1.73 $m^2$ or on dialysis. Given the following points, vericiguat should not be contraindicated in these patients. The package insert should advise that a decision to use vericiguat in these patients should be made carefully, and that vericiguat should be used with caution, closely monitoring the patient's condition such as blood pressure.

- The results of Analysis 20964 are considered to reflect PK in a setting closer to clinical practice, which showed no trend towards markedly increasing vericiguat exposure with decreasing eGFR in patients with heart failure.
- Four patients with baseline eGFR <15 mL/min/1.73 $m^2$ were enrolled in Study 16493, of whom 3 had PK data available. The steady-state $AUC_{0\text{-}24h}$ values of vericiguat (estimates from the PPK model) in these 3 patients were 5210, 11700, and 6300 μg·h/L, respectively, which were all within the vericiguat exposure range of patients with chronic heart failure in Analysis 20964.
- The dosing regimen of vericiguat with a starting dose of 2.5 mg (a low dose) allows dose titration and treatment discontinuation/dose interruption according to the patient's condition.

PMDA's view:
Both the clinical pharmacology study (Study 15813) and the PPK analysis including chronic heart failure patients with renal impairment (Analysis 20964) showed a trend towards increasing vericiguat exposure with decreasing eGFR, and the increase in vericiguat exposure observed in Study 15813 was greater than the effect from Analysis 20964.

Since the applicant did not give a scientific rational explanation about the reason for differences in the impact of eGFR on vericiguat exposure between Study 15813 and Analysis 20964, the possibility that in chronic heart failure patients with renal impairment with eGFR ≥15 mL/min/1.73 $m^2$, vericiguat exposure is increased to an extent similar to that observed in Study 15813, cannot be ruled out. Although no marked increase in vericiguat exposure was observed in 3 patients with baseline eGFR <15 mL/min/1.73 $m^2$ in Study 16493, there are also limitations to predicting changes in vericiguat exposure in chronic heart failure patients with eGFR <15 mL/min/1.73 $m^2$ or on dialysis, based on the currently available data.

Based on the above, the package insert should advise that vericiguat exposure may be increased in patients with renal impairment. The need for dose adjustment of vericiguat in chronic heart failure patients with renal impairment and a relevant precautionary statement in the package insert should be determined, taking also account of the safety results etc. in patients with renal impairment from Study 16493 in patients with chronic heart failure, and will be discussed in Section "7.R.3.4 Use in patients with renal impairment." The above conclusion by PMDA will be finalized, taking account of comments from the Expert Discussion.

### 6.R.4 Use in patients with hepatic impairment

The applicant's explanation about the use of vericiguat in patients with hepatic impairment:
In a clinical pharmacology study in subjects with hepatic impairment (Study 15840), subjects with mild and moderate hepatic impairment had 20.9% and 47.1% higher $AUC_{0\text{-}\infty,norm}$ of vericiguat (unbound), respectively, compared to subjects with normal hepatic function [see Section "6.2.3.3 Clinical pharmacology study in subjects with hepatic impairment"]. On the other hand, covariate exploration in the PPK analysis performed based on the data from Studies 15371 and 16493 (Analysis 20964) suggested that indicators of hepatic function, albumin (2.6-5.4 g/dL) and bilirubin (0.2-6.4 mg/dL) have no effect on the PK of vericiguat within the scope investigated. Study 15371 excluded patients with Child-Pugh B or C, and Study 16493 excluded patients with

severe hepatic insufficiency such as hepatic encephalopathy. As information on Child-Pugh class was not collected in these studies, the effect of hepatic function based on Child-Pugh classification on the PK of vericiguat could not be evaluated in the PPK analysis. Since the results of Analysis 20964 based on Studies 15371 and 16493 in patients with chronic heart failure are considered to represent PK in a setting closer to clinical practice, compared to the results of Study 15840, it is appropriate to determine the need for a precautionary statement regarding use in patients with mild or moderate hepatic impairment in the package insert, based on the results of Analysis 20964. Safety by hepatic function in Study 16493 was evaluated using albumin-bilirubin (ALBI) score,[4)] which is for assessing the severity of liver dysfunction, and 3889 patients, 1056 patients, and 4 patients were categorized as ALBI grade[5)] I, II, and III, respectively. The incidences of all adverse events in the placebo and vericiguat groups were 80.7% (1554 of 1926 subjects) and 80.3% (1577 of 1963 subjects), respectively, for ALBI grade I, and 82.2% (454 of 552 subjects) and 81.5% (411 of 504 subjects), respectively, for ALBI grade II. The incidences of hypotension-related adverse events were 14.4% (278 of 1926 subjects) and 15.8% (311 of 1963 subjects), respectively, for ALBI grade I, and 16.7% (92 of 552 subjects) and 18.1% (91 of 504 subjects), respectively, for ALBI grade II. There should be no clear safety concerns with increasing ALBI grade.

Based on the above, no dose adjustment of vericiguat is required in chronic heart failure patients with hepatic impairment. No vericiguat PK data from patients with severe hepatic impairment are available. However, as the major metabolizing enzymes for vericiguat are UGT1A1 and UGT1A9, and UGT1A9 is expressed not only in the liver, but also in the kidneys, decreased hepatic function may be compensated by metabolism in the kidneys. The dosing regimen of vericiguat with a starting dose of 2.5 mg (a low dose) allows dose titration and treatment discontinuation/dose interruption according to the patient's condition. Given these points etc., there is no need to contraindicate vericiguat in patients with severe hepatic impairment. However, as no clinical studies in patients with severe hepatic impairment have been conducted, the package insert will advise that a decision to use vericiguat in these patients should be made carefully, and that vericiguat should be used with caution, closely monitoring the patient's condition such as blood pressure.

PMDA's view:
Given the extent of increase in vericiguat exposure in subjects with mild or moderate (Child-Pugh A or B) hepatic impairment in Study 15840, and no clear safety concerns with decreasing hepatic function in Study 16493, the applicant's explanation that no dose adjustment is required in chronic heart failure patients with mild or moderate hepatic impairment is appropriate. Although no clinical studies in chronic heart failure patients with severe (Child-Pugh C) hepatic impairment have been conducted, vericiguat is cleared via multiple routes such as metabolism in the liver, glomerular filtration and metabolism in the kidneys, and biliary excretion. The tolerability of vericiguat 10 mg once daily (a starting dose of 10 mg) in Japanese healthy adult subjects has been demonstrated [see Section "7.1.1 Japanese phase I study"]. Vericiguat is started at a low dose, and up-titration and dose modification occur, monitoring the patient's condition. Given these points, these

[4)] ALBI score is used for assessing hepatic functional reserve, and calculated using the following formula.
ALBI score = log[10] (total bilirubin concentration [μmol/L]) × 0.66 + albumin concentration (g/L) × −0.085
[5)] Categorized by ALBI score (ALBI grade I, ≤−2.60; ALBI grade II, >−2.60 and ≤−1.39; ALBI grade III, >−1.39).

patients should not be excluded from treatment with vericiguat, and if its therapeutic benefits are considered to outweigh the possible risks, vericiguat may be used in these patients. The above conclusion by PMDA will be finalized, taking account of comments from the Expert Discussion.

### 6.R.5 Pharmacokinetic interactions with proton pump inhibitors or antacids

The applicant's explanation about pharmacokinetic interactions between vericiguat and proton pump inhibitors or antacids:

In a drug interaction study (Study 15811), omeprazole and antiacid decreased the $C_{max}$ and $AUC_{0-\infty}$ of vericiguat by 45.7% to 49.6% and 27.1% to 32.2%, respectively. Vericiguat is highly soluble at acidic pH and less soluble at neutral pH. Following administration of vericiguat with these drugs, decreased exposure was considered attributable to a decrease in the solubility of vericiguat at higher pH. On the other hand, an absolute BA study (Study 17114) showed that the BA of vericiguat increased when taken with food [see Section "6.1.1 Absolute BA study"]. These findings indicate that the extent of increase in the solubility of vericiguat due to improved affinity for bile acids and water in food when taken with food is greater than the extent of decrease in solubility due to changes in the gastrointestinal environment (increasing pH) when taken with food. In Studies 15371 and 16493 in which vericiguat was to be taken with food, the concomitant use of proton pump inhibitors or antacids was not prohibited. In Analysis 20964, the distribution of steady-state vericiguat exposures estimated from the model was similar, regardless of administration of vericiguat with or without proton pump inhibitors or antacids ([with concomitant medications], 1140 patients; [without concomitant medications], 785 patients), and use of these drugs had no effect on vericiguat exposure.

Based on the above, a precautionary statement about concomitant use of vericiguat with proton pump inhibitors or antacids in the package insert is unnecessary.

PMDA's view:

Study 15811 showed that omeprazole or antiacid decreased vericiguat exposure due to a decrease in the solubility of vericiguat under fasting conditions. However, Study 17114 suggested that the solubility or absorption of vericiguat is not decreased even in the gastrointestinal environment after a meal, i.e., at higher pH, and vericiguat is recommended to be taken with food. Taking account of these points, the applicant's explanation that a precautionary statement about concomitant use of vericiguat with proton pump inhibitors or antacids in the package insert is unnecessary is appropriate.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the main efficacy and safety evaluation data, in the form of the results from 3 studies presented in Table 34. The applicant also submitted the results from a global phase II study in patients with chronic heart failure with preserved LVEF as reference data.

Table 34. Overview of main efficacy and safety clinical studies

| Data category | Geographical location | Study Number | Phase | Study population | No. of subjects enrolled | Dosing regimen | Main endpoints |
|---|---|---|---|---|---|---|---|
| Evaluation data | Japan | 15836 | I | Healthy adult subjects | 48 | Single-dose: Placebo or vericiguat 1.25, 5, 7.5, or 10 mg orally under fasting conditions<br>Multiple-dose: Placebo or vericiguat 1.25, 5, 7.5, or 10 mg orally once daily for 7 days under fasting conditions (under fed conditions on Day 5 only) | Safety<br>PK |
| | Global | 15371 | II | Patients with chronic heart failure with reduced LVEF | 456 | Placebo or vericiguat orally once daily with food. Dose doublings every 2 weeks.<br>Doses:<br>(1) Vericiguat 1.25 mg<br>(2) Vericiguat 2.5 mg<br>(3) Vericiguat 2.5 mg→5 mg<br>(4) Vericiguat 2.5 mg→5 mg→10 mg | Efficacy<br>Safety<br>PK |
| | Global | 16493 | III | Patients with chronic heart failure with reduced LVEF | 5050 | Placebo or vericiguat orally once daily with food. Dose doublings every 2 weeks.<br>Doses:<br>Vericiguat 2.5 mg→5 mg→10 mg | Efficacy<br>Safety |
| Reference data | Global | 19334 | II | Patients with chronic heart failure with preserved LVEF | 789 | Placebo or vericiguat orally once daily with food. Dose doublings every 2 weeks.<br>Doses:<br>(1) Vericiguat 2.5 mg→5 mg→10 mg<br>(2) Vericiguat 2.5 mg→5 mg→10 mg→15 mg | Efficacy<br>Safety |

## 7.1 Phase I study

### 7.1.1 Japanese phase I study (Study 15836, CTD 5.3.3.1.4, November 20[redacted] to May 20[redacted])

A placebo-controlled, randomized, single-blind, parallel-group study was conducted at 1 site in Japan to evaluate the safety and PK of vericiguat in Japanese healthy adult male subjects (target sample size, 48 subjects). A single oral dose of placebo or vericiguat 1.25, 5, 7.5, or 10 mg was administered under fasting conditions on Day 1, followed by multiple oral doses once daily for 7 days on Days 5 to 11 (under fed conditions on Day 5 only, under fasting conditions on Day 6 onwards).

Twelve subjects were randomized to each dose level (3 in the placebo group, 9 in the vericiguat group), and all of 48 subjects who received study drug were included in the safety population.

Adverse events occurred in 6 of 12 subjects in the placebo group, 3 of 9 subjects in the vericiguat 1.25 mg group, 6 of 9 subjects in the vericiguat 5 mg group, 3 of 9 subjects in the vericiguat 7.5 mg group, and 4 of 9 subjects in the vericiguat 10 mg group, of which the events reported by 4 of 12 subjects in the placebo group (abdominal pain, diarrhoea, and cough; blood triglycerides increased; headache; and orthostatic hypotension [1 subject each]), the events reported by 3 of 9 subjects in the vericiguat 1.25 mg group (creatinine renal clearance decreased [2 subjects]; and protein urine present [1 subject]), the events reported by 3 of 9 subjects in the vericiguat 5 mg group (abdominal pain and diarrhoea; ALT increased; and blood triglycerides increased [1 subject each]), the events reported by 3 of 9 subjects in the vericiguat 7.5 mg group (ALT increased [2 subjects]; and protein urine present [1 subject]), and the events reported by 3 of 9 subjects in the vericiguat 10 mg group (erythema; headache; and orthostatic hypotension [1 subject each]) were considered related to study drug.

There were no adverse events leading to death or serious adverse events.

## 7.2 Phase II studies

### 7.2.1 Global phase II study (Study 15371, CTD 5.3.5.1.3, November 2013 to June 2015)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 144 sites in Japan and foreign countries including the US and Europe to evaluate the efficacy and safety of vericiguat in patients with chronic heart failure with reduced LVEF on standard heart failure (HF) therapy (target sample size, 410 randomized subjects).

Table 35 shows key inclusion and exclusion criteria.

Table 35. Key inclusion and exclusion criteria for Study 15371

| Inclusion criteria | Exclusion criteria |
|---|---|
| · Adult patients with chronic heart failure requiring hospitalization or IV diuretic treatment for HF without hospitalization<br>· NYHA class Ⅱ to Ⅳ<br>· LVEF <45%<br>· Worsening HF [a] at hospitalization or at the time of IV diuretic treatment for HF without hospitalization<br>· No IV vasodilator for >24 hours and no IV diuretic for >12 hours before randomization, and SBP ≥110 and <160 mmHg and resting heart rate ≥50 and <100 bpm at randomization | · IV inotropes at any time between hospitalization and randomization<br>· Concurrent or anticipated nitrate use (all routes, including pro re nata [prn]) for the treatment of ischemic heart disease or HF<br>· eGFR <30 mL/min/1.73 $m^2$<br>· Hepatic insufficiency classified as Child-Pugh B or C<br>· Concomitant treatment with a PDE5 inhibitor or sGC stimulator |

a: (1) NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL (≥192 pg/mL in Japan) in sinus rhythm, or NT-proBNP ≥1600 pg/mL or BNP ≥500 pg/mL (≥319 pg/mL in Japan) in atrial fibrillation, and (2) symptoms and signs of congestion (clinical or radiographic signs in routine chest X-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly)

Vericiguat or matching placebo was to be administered orally once daily after breakfast for 12 weeks. (1) Vericiguat 1.25 mg was to be administered orally once daily (vericiguat 1.25 mg group), (2) vericiguat 2.5 mg was to be administered orally once daily (vericiguat 2.5 mg group), (3) vericiguat was to be started at 2.5 mg and up-titrated to 5 mg once daily after 2 weeks, in accordance with the dose modification guidance presented in Table 36 (vericiguat 5 mg group), and (4) vericiguat was to be started at 2.5 mg and up-titrated to 5 mg once daily after 2 weeks and to 10 mg once daily after 4 weeks, in accordance with the dose modification guidance presented in Table 36 (vericiguat 10 mg group).

Table 36. Dose modification guidance in Study 15371

| Blood pressure assessment | Dose modification |
|---|---|
| SBP [a] ≥100 mmHg | Double the dose |
| SBP[a] between 90 mmHg and <100 mmHg | Maintain the dose |
| SBP[a] <90 mmHg without symptoms of hypotension | Halve the dose [b] |

a: Mean SBP (3 measurements, 2 minutes apart) before intake of the dose
b: Dose halving was possible at any time if the investigator (sub-investigator) felt this was justified for safety reasons. If a second dose halving was required, this was to result in discontinuation of study drug treatment, and down-titration attempts from a dose of 1.25 mg was to result in discontinuation.

Among 456 randomized subjects, 455 subjects (92 [5 Japanese subjects) in the placebo group, 91 [8 Japanese subjects] in the vericiguat 1.25 mg group, 90 (5 Japanese subjects) in the vericiguat 2.5 mg group, 91 [4

Japanese subjects] in the vericiguat 5 mg group, 91 [8 Japanese subjects] in the vericiguat 10 mg group) after excluding 1 subject who did not receive study drug (vericiguat 2.5 mg group) were included in the safety population. Among the 456 randomized subjects, 351 subjects who had a valid measurement of NT-proBNP at baseline and Week 12 and no major protocol deviations (69 [4 Japanese subjects] in the placebo group, 69 [8 Japanese subjects] in the vericiguat 1.25 mg group, 73 [5 Japanese subjects] in the vericiguat 2.5 mg group, 67 [2 Japanese subjects] in the vericiguat 5 mg group, 73 [8 Japanese subjects] in the vericiguat 10 mg group) were included in the per protocol set (PPS), which was used as the primary efficacy analysis population. There were 94 withdrawals from the study (19 [1 Japanese subject] in the placebo group, 21 in the vericiguat 1.25 mg group, 15 in the vericiguat 2.5 mg group, 22 [2 Japanese subjects] in the vericiguat 5 mg group, 17 in the vericiguat 10 mg group). The main reasons for withdrawals were adverse events (42 subjects) (7 subjects, 10 subjects, 9 subjects, 8 subjects [1 Japanese subject], 8 subjects), consent withdrawal (18 subjects) (5 subjects, 2 subjects, 1 subject, 7 subjects, 3 subjects), death (10 subjects) (3 subjects, 2 subjects, 2 subjects, 1 subject, 2 subjects), the withdrawal criteria met (8 subjects) (0 subjects, 5 subjects, 0 subjects, 2 subjects [1 Japanese subject], 1 subject), protocol deviations (8 subjects) (2 subjects [1 Japanese subject], 0 subjects, 1 subject, 3 subjects, 2 subjects), and poor compliance (5 subjects) (1 subject, 2 subjects, 2 subjects, 0 subjects, 0 subjects). The final doses of vericiguat at Week 12 in subjects treated with study drug were 1.25 mg in the vericiguat 1.25 mg group (70 of 70 subjects) (8 of 8 Japanese subjects), 1.25 mg (1 of 75 subjects) and 2.5 mg (74 of 75 subjects) (5 of 5 Japanese subjects) in the vericiguat 2.5 mg group, 2.5 mg (9 of 69 subjects) and 5 mg (60 of 69 subjects) (2 of 2 Japanese subjects) in the vericiguat 5 mg group, and 1.25 mg (3 of 74 subjects) (1 of 8 Japanese subjects), 2.5 mg (7 of 74 subjects) (1 of 8 Japanese subjects), 5 mg (11 of 74 subjects) (1 of 8 Japanese subjects), and 10 mg (53 of 74 subjects) (5 of 8 Japanese subjects) in the vericiguat 10 mg group.

The primary efficacy endpoint of the change from baseline to Week 12 in log-transformed NT-proBNP is shown in Table 37. In the primary analysis, i.e., pooled comparison of the 3 highest-dose vericiguat groups with placebo, the change in log-transformed NT-proBNP from baseline to Week 12 was not statistically significantly different between the pooled vericiguat group and the placebo group. Table 38 shows the results of exploratory endpoints of cardiovascular (CV) death or HF hospitalization (the first event) and its components and all-cause mortality up to Week 12.

Table 37. Change from baseline to Week 12 in NT-proBNP (Study 15371, PPS)

| NT-proBNP (pg/mL) | Baseline | Change from baseline to Week 12 | Change from baseline to Week 12 (Log transformed value) | Difference of means vs. placebo (Log transformed value) | *P*-value[b] |
|---|---|---|---|---|---|
| Overall population | | | | | |
| Placebo (N = 69) | 6189.499 ± 6256.048 | −1480.941 ± 4716.245 | −0.280 ± 0.8197 | −0.1220 [−0.32, 0.07] | 0.1506 |
| Pooled vericiguat group[a] (N = 213) | 4789.407 ± 6649.006 | −1008.481 ± 5298.565 | −0.402 ± 0.8603 | | |
| 1.25 mg (N = 69) | 5212.968 ± 5695.436 | −731.329 ± 3362.653 | −0.265 ± 0.7658 | 0.0151 [−0.21, 0.24] | — |
| 2.5 mg (N = 73) | 4908.649 ± 5378.969 | −1286.767 ± 4445.398 | −0.320 ± 0.7799 | −0.0396 [−0.26, 0.18] | — |
| 5 mg (N = 67) | 3047.533 ± 2221.021 | −248.249 ± 2138.386 | −0.353 ± 0.8404 | −0.0731 [−0.31, 0.16] | — |
| 10 mg (N = 73) | 6268.870 ± 9573.900 | −1427.942 ± 7610.304 | −0.529 ± 0.9475 | −0.2494 [−0.50, −0.00] | — |
| Japanese subgroup | | | | | |
| Placebo (N = 4)) | 2809.475 ± 1710.632 | −1258.350 ± 1197.267 | −0.857 ± 0.6887 | 0.1032 [−0.59, 0.79] | — |
| Pooled vericiguat group[a] (N = 15) | 6665.820 ± 8321.190 | −3594.127 ± 7550.579 | −0.754 ± 0.7065 | | |
| 1.25 mg (N = 8) | 4278.725 ± 5740.808 | −1241.488 ± 3697.455 | 0.121 ± 0.7614 | 0.9794 [0.16, 1.80] | — |
| 2.5 mg (N = 5) | 12197.060 ± 13025.988 | −7787.840 ± 12606.736 | −0.929 ± 0.8100 | −0.0717 [−1.04, 0.89] | — |
| 5 mg (N = 2) | 2661.150 ± 119.855 | −1731.850 ± 363.806 | −1.124 ± 0.5010 | −0.2664 [−1.46, 0.93] | — |
| 10 mg (N = 8) | 4209.963 ± 2862.896 | −1438.625 ± 2079.287 | −0.553 ± 0.6930 | 0.3049 [−0.46, 1.07] | — |

Mean ± SD, Difference of means [90% CI], —: Not applicable
a: Pooled vericiguat 2.5 mg, 5 mg, and 10 mg groups
b: t-test, one-sided significance level of 5%

Table 38. Incidences of clinical efficacy events up to Week 12 (Study 15371, FAS)

| Overall population | Placebo (N = 92) | Vericiguat 1.25 mg (N = 91) | Vericiguat 2.5 mg (N = 91) | Vericiguat 5 mg (N = 91) | Vericiguat 10 mg (N = 91) |
|---|---|---|---|---|---|
| CV death or HF hospitalization (first event) | 19.6 (18) | 18.7 (17) | 19.8 (18) | 12.1 (11) | 11.0 (10) |
| CV death | 3.3 (3) | 4.4 (4) | 2.2 (2) | 2.2 (2) | 2.2 (2) |
| HF hospitalization (first event) | 17.4 (16) | 17.6 (16) | 17.6 (16) | 9.9 (9) | 9.9 (9) |
| All-cause mortality | 3.3 (3) | 4.4 (4) | 3.3 (3) | 3.3 (3) | 2.2 (2) |
| Japanese subgroup | Placebo (N = 5) | Vericiguat 1.25 mg (N = 8) | Vericiguat 2.5 mg (N = 5) | Vericiguat 5 mg (N = 4) | Vericiguat 10 mg (N = 8) |
| CV death or HF hospitalization (first event) | 40.0 (2) | 0 (0) | 20.0 (1) | 25.0 (1) | 0 (0) |
| CV death | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| HF hospitalization (first event) | 40.0 (2) | 0 (0) | 20.0 (1) | 25.0 (1) | 0 (0) |
| All-cause mortality | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

Incidence % (n)

Regarding safety, among the overall population, the incidences of adverse events[6)] were 71.7% (66 of 92 subjects) in the placebo group, 65.9% (60 of 91 subjects) in the vericiguat 1.25 mg group, 68.9% (62 of 90 subjects) in the vericiguat 2.5 mg group, 68.1% (62 of 91 subjects) in the vericiguat 5 mg group, and 61.5% (56 of 91 subjects) in the vericiguat 10 mg group, and adverse events reported by ≥5% of subjects in any group

[6)] Adverse events that started or worsened after start of study drug up to 5 days after the end of treatment with study drug (TEAEs). Any adverse events leading to death in the study period are listed. In Study 15371, errors were found after the final database lock, and 23 adverse events occurring before start of study drug were treated as TEAEs and 5 adverse events that should have been treated as TEAEs originally were not treated as TEAEs. These errors were not considered to affect evaluation, and the analysis results based on the final database lock are presented. Among the adverse events that should have been treated as TEAEs originally, 3 adverse events reported by 1 subject in the placebo group (cellulitis, upper respiratory tract infection, chronic heart failure) are not included in the presented analysis results.

are shown in Table 39. Among the Japanese subgroup, the incidences of adverse events were 80.0% (4 of 5 subjects) in the placebo group, 50.0% (4 of 8 subjects) in the vericiguat 1.25 mg group, 60.0% (3 of 5 subjects) in the vericiguat 2.5 mg group, 75.0% (3 of 4 subjects) in the vericiguat 5 mg group, and 37.5% (3 of 8 subjects) in the vericiguat 10 mg group. Among the Japanese subgroup, adverse events reported by ≥2 subjects were anaemia (1 in the 1.25 mg group, 1 in the 10 mg group), chronic cardiac failure (1 in the placebo group, 1 in the 2.5 mg group), ventricular tachycardia (1 in the 1.25 mg group, 1 in the 5 mg group), constipation (1 in the placebo group, 1 in the 1.25 mg group, 1 in the 5 mg group), nasopharyngitis (1 in the 5 mg group, 1 in the 10 mg group), hypoaesthesia (1 in the 1.25 mg group, 1 in the 2.5 mg group), and hypotension (1 in the 2.5 mg group, 1 in the 10 mg group).

Table 39. Adverse events reported by ≥5% of subjects in any group (Study 15371, Safety population [Overall population])

| MedDRA PT | Placebo (N = 92) | Vericiguat 1.25 mg (N = 91) | Vericiguat 2.5 mg (N = 90) | Vericiguat 5 mg (N = 91) | Vericiguat 10 mg (N = 91) |
|---|---|---|---|---|---|
| Anaemia | 2.2 (2) | 3.3 (3) | 0 (0) | 3.3 (3) | 5.5 (5) |
| Cardiac failure | 9.8 (9) | 15.4 (14) | 15.6 (14) | 3.3 (3) | 3.3 (3) |
| Cardiac failure chronic | 7.6 (7) | 3.3 (3) | 11.1 (10) | 5.5 (5) | 4.4 (4) |
| Abdominal pain upper | 2.2 (2) | 5.5 (5) | 2.2 (2) | 1.1 (1) | 0 (0) |
| Dyspepsia | 0 (0) | 1.1 (1) | 0 (0) | 1.1 (1) | 5.5 (5) |
| Nausea | 3.3 (3) | 5.5 (5) | 3.3 (3) | 1.1 (1) | 1.1 (1) |
| Asthenia | 3.3 (3) | 0 (0) | 2.2 (2) | 5.5 (5) | 2.2 (2) |
| Oedema peripheral | 3.3 (3) | 2.2 (2) | 2.2 (2) | 1.1 (1) | 5.5 (5) |
| Urinary tract infection | 2.2 (2) | 5.5 (5) | 3.3 (3) | 1.1 (1) | 1.1 (1) |
| Hyperuricaemia | 1.1 (1) | 0 (0) | 2.2 (2) | 5.5 (5) | 0 (0) |
| Hypokalaemia | 3.3 (3) | 6.6 (6) | 2.2 (2) | 2.2 (2) | 5.5 (5) |
| Dizziness | 5.4 (5) | 3.3 (3) | 2.2 (2) | 2.2 (2) | 5.5 (5) |
| Acute kidney injury | 3.3 (3) | 5.5 (5) | 2.2 (2) | 1.1 (1) | 3.3 (3) |
| Cough | 6.5 (6) | 8.8 (8) | 4.4 (4) | 4.4 (4) | 4.4 (4) |
| Dyspnoea | 5.4 (5) | 2.2 (2) | 3.3 (3) | 3.3 (3) | 5.5 (5) |
| Hypotension | 6.5 (6) | 5.5 (5) | 5.6 (5) | 4.4 (4) | 15.4 (14) |

Incidence % (n)

Among the overall population, the incidences of adverse events leading to death were 5.4% (5 of 92 subjects) in the placebo group (cardiac failure [2 subjects]; and cardiac arrest; respiratory failure and cardiogenic shock; and sudden death [1 subject each]), 6.6% (6 of 91 subjects) in the vericiguat 1.25 mg group (cardiac failure; chronic cardiac failure; and death [2 subjects each]), 4.4% (4 of 90 subjects) in the vericiguat 2.5 mg group (death [2 subjects]; and chronic obstructive pulmonary disease; and pneumococcal sepsis [1 subject each]), 2.2% (2 of 91 subjects) in the vericiguat 5 mg group (multi-organ failure and pneumonia; and sudden death [1 subject each]), and 4.4% (4 of 91 subjects) in the vericiguat 10 mg group (cardiac failure; sudden death; congestive cardiac failure; and chronic cardiac failure [1 subject each]), and all those events were considered unrelated to study drug. Among the Japanese subgroup, no adverse events leading to death were reported.

Among the overall population, the incidences of serious adverse events were 32.6% (30 of 92 subjects) in the placebo group, 28.6% (26 of 91 subjects) in the vericiguat 1.25 mg group, 28.9% (26 of 90 subjects) in the vericiguat 2.5 mg group, 22.0% (20 of 91 subjects) in the vericiguat 5 mg group, and 27.5% (25 of 91 subjects) in the vericiguat 10 mg group. Those reported by ≥3% of subjects in any group were cardiac failure (8.7% in the placebo group, 14.3% in the vericiguat 1.25 mg group, 11.1% in the vericiguat 2.5 mg group, 3.3% in the vericiguat 5 mg group, 3.3% in the vericiguat 10 mg group), chronic cardiac failure (5.4%, 2.2%, 5.6%, 3.3%, 4.4%), congestive cardiac failure (1.1%, 2.2%, 3.3%, 2.2%, 3.3%), and acute kidney injury (3.3%, 4.4%, 2.2%,

1.1%, 3.3%). The incidences of serious adverse events related to study drug were 3.3% (3 of 92 subjects) in the placebo group (cardiac failure; fluid overload; and acute kidney injury [1 subject each]), 1.1% (1 of 91 subjects) in the vericiguat 1.25 mg group (fall), 1.1% (1 of 90 subjects) in the vericiguat 2.5 mg group (arthralgia), 1.1% (1 of 91 subjects) in the vericiguat 5 mg group (gastrointestinal haemorrhage), and 4.4% (4 of 91 subjects) in the vericiguat 10 mg group (abdominal pain; melaena; cholangitis and cholecystitis; and hypotension [1 subject each]). Among the Japanese subgroup, the incidences of serious adverse events were 20.0% (1 of 5 subjects) in the placebo group (chronic cardiac failure), 40.0% (2 of 5 subjects) in the vericiguat 2.5 mg group (chronic cardiac failure; and urinary retention [1 subject each]), 25.0% (1 of 4 subjects) in the vericiguat 5 mg group (acute cardiac failure), and 12.5% (1 of 8 subjects) in the vericiguat 10 mg group (gastric cancer), and all those events were considered unrelated to study drug.

Among the overall population, the incidences of adverse events leading to study drug discontinuation were 7.6% (7 of 92 subjects) in the placebo group, 9.9% (9 of 91 subjects) in the vericiguat 1.25 mg group, 10.0% (9 of 90 subjects) in the vericiguat 2.5 mg group, 7.7% (7 of 91 subjects) in the vericiguat 5 mg group, and 8.8% (8 of 91 subjects) in the vericiguat 10 mg group, and those reported by ≥2% of subjects in any group were cardiac failure (1.1%, 2.2%, 2.2%, 0%, 0%), acute kidney injury (3.3%, 0%, 0%, 1.1%, 1.1%), rash (0%, 0%, 2.2%, 0%, 1.1%), and metabolic acidosis (2.2%, 0%, 0%, 0%, 0%). Among the Japanese subgroup, no adverse events leading to study drug discontinuation were reported.

### 7.2.2 Global phase II study (Study 19334, CTD 5.3.5.1.11 [Reference data], June 2018 to November 2019)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 178 sites in Japan and foreign countries including the US and Europe to evaluate the efficacy and safety of vericiguat in patients with chronic heart failure with preserved LVEF (target sample size, approximately 735 randomized subjects).

Table 40 shows key inclusion and exclusion criteria.

Table 40. Key inclusion and exclusion criteria for Study 19334

| Inclusion criteria | Exclusion criteria |
|---|---|
| · Patients with chronic heart failure aged ≥45 years<br>· HF decompensation within 6 months prior to randomization (hospitalization for HF or IV diuretic treatment for HF without hospitalization)<br>· NYHA class Ⅱ or Ⅲ<br>· LVEF ≥45%<br>· NT-proBNP ≥300 pg/mL or BNP ≥100 pg/mL in sinus rhythm, or NT-proBNP ≥600 pg/mL or BNP ≥200 pg/mL in atrial fibrillation within 30 days prior to randomization | · Clinical instability at randomization[a]<br>· Previous diagnosis of LVEF <40%<br>· Use of IV inotropes at any time between index event and randomization<br>· eGFR <30 mL/min/1.73 $m^2$<br>· Hepatic insufficiency classified as Child-Pugh B or C<br>· Concurrent or anticipated use of long-acting or short-acting nitrates or NO donors[b]<br>· Concurrent or anticipated use of PDE5 inhibitors[c] |

a: (1) Any IV treatment (including IV diuretics or IV fluids) within 24 hours prior to randomization, (2) SBP ≥160 mmHg at randomization, (3) SBP <110 mmHg and/or DBP <40 mmHg and/or symptomatic hypotension at randomization, or (4) resting heart rate <50 or ≥100 bpm at randomization

b: isosorbide dinitrate, isosorbide-5-mononitrate, pentaerythritol tetranitrate, nicorandil, nitroglycerin, molsidomine, etc.

c: vardenafil, tadalafil, sildenafil, etc.

Placebo or vericiguat was to be administered orally once daily with food for 24 weeks. In the vericiguat groups, (1) vericiguat was to be started at 2.5 mg and up-titrated to 5 mg at Week 2, and to 10 mg at Week 4 (vericiguat 10 mg group), or (2) vericiguat was to be started at 2.5 mg and up-titrated to 5 mg at Week 2, to 10 mg at Week 4, and to 15 mg at Week 6 (vericiguat 15 mg group). The titration was to occur at all visits in accordance with the dose modification guidance presented in Table 41. If the patient did not reach the 15 mg dose step by the time of the Week 6 visit, or the dose was temporarily interrupted and when the investigator (sub-investigator) felt it was medically appropriate to resume it afterwards, up-titration was to be considered at any subsequent visit at the discretion of the investigator (sub-investigator). Upon temporary interruption of study drug due to intolerability, intake was to be resumed as soon as medically justified at the discretion of the investigator (sub-investigator), in accordance with the instructions for resumption of study drug intake presented in Table 42.

Table 41. Dose modification guidance for Study 19334

| Blood pressure assessment | Dose modification |
|---|---|
| If SBP ≥100 mmHg and SBP decrease is ≤20 mmHg from previous visit, and not yet on highest dose | Increase the dose by 1 step.<br>· 5 mg if on 2.5 mg<br>· 10 mg if on 5 mg<br>· 15 mg if on 10 mg |
| If SBP is between 90 mmHg and <100 mmHg, or SBP ≥100 mmHg and SBP decrease is >20 mmHg from previous visit, or if already on highest dose step (after 3 up-titrations) | Maintain the dose. |
| If SBP <90 mmHg without symptoms of hypotension | Decrease the dose.<br>· 2.5 mg if on 5 mg<br>· 5 mg if on 10 mg<br>· 5 mg if on 15 mg |
| If SBP <90 mmHg without symptoms of hypotension on 2.5 mg (starting dose or after down titration from a higher dose),<br>or if SBP <90 mmHg with symptoms of hypotension | Interrupt the dose. |

Table 42. Resumption of study drug intake for Study 19334

| Dose at time of interruption | Length of interruption | Restart dose | Dose level 1st titration (2 weeks after resumption) | Dose level 2nd titration (4 weeks after resumption) | Dose level 3rd titration (6 weeks after resumption) |
|---|---|---|---|---|---|
| 2.5 mg | Any | 2.5 mg | 5 mg | 10 mg | 10 mg or 15 mg |
| 5 mg | Any | 2.5 mg | 5 mg | 10 mg | 10 mg or 15 mg |
| 10 mg | >5 days | 2.5 mg | 5 mg | 10 mg | 10 mg or 15 mg |
| | ≤5 days | 5 mg | 10 mg | 10 mg or 15 mg | － |
| 10 or 15 mg | >5 days | 2.5 mg | 5 mg | 10 mg | 10 mg or 15 mg |
| | ≤5 days | 5 mg | 10 mg | 10 mg or 15 mg | － |

－: highest dose achieved in the second titration
If interruption occurred during the titration phase (before Week 6), restart at a scheduled visit, and If interruption occurred after Week 6, restart as soon as possible (with an unscheduled visit if required) and titrate according to Table 41.

Among 789 randomized subjects (41 Japanese subjects), 788 subjects (262 [15 Japanese subjects] in the placebo group, 262 [13 Japanese subjects] in the vericiguat 10 mg group, 264 [13 Japanese subjects] in the vericiguat 15 mg group) after excluding 1 subject who did not receive study drug (vericiguat 10 mg group) were included in the safety population. All of the 789 randomized subjects were included in the full analysis set (FAS), of whom all subjects who had at least 1 observed Kansas City Cardiomyopathy Questionnaire, Physical limitation score (KCCQ PLS) assessment were included in the primary efficacy analysis population. There were 117 withdrawals from the study (32 subjects [1 Japanese subject], 45 subjects [2 Japanese subjects], 40 subjects [0 Japanese subjects]), and the main reasons for withdrawals were consent withdrawal (41 subjects)

(10 subjects, 12 subjects, 19 subjects), adverse events (37 subjects) (10 subjects, 16 subjects, 11 subjects), and death (22 subjects) (4 subjects, 11 subjects, 7 subjects).

There were no statistically significant differences in the primary efficacy endpoint of KCCQ PLS changes from baseline to Week 24 between the placebo group and either vericiguat 10 or 15 mg group. Among the overall population, the incidences of all-cause mortality as an exploratory endpoint during the study period were 2.7% (7 of 262 subjects) in the placebo group, 5.7% (15 of 263 subjects) in the vericiguat 10 mg group, and 3.8% (10 of 264 subjects) in the vericiguat 15 mg group, and the incidences of CV death were 1.5% (4 of 262 subjects) in the placebo group (stroke [2 subjects]; and cardiac failure; and others [1 subject each]), 4.6% (12 of 263 subjects) in the vericiguat 10 mg group (cardiac failure [6 subjects]; sudden death [5 subjects]; and stroke [1 subject]), and 3.0% (8 of 264 subjects) in the vericiguat 15 mg group (sudden death [5 subjects]; and cardiac failure [3 subjects]).

Regarding safety, among the overall population, the incidences of adverse events[7)] were 65.6% (172 of 262 subjects) in the placebo group, 62.2% (163 of 262 subjects) in the vericiguat 10 mg group, and 65.2% (172 of 264 subjects) in the vericiguat 15 mg group, and those reported by ≥3% of subjects in any group are shown in Table 43. Among the Japanese subgroup, the incidences of adverse events were 73.3% (11 of 15 subjects) in the placebo group, 69.2% (9 of 13 subjects) in the vericiguat 10 mg group, and 61.5% (8 of 13 subjects) in the vericiguat 15 mg group.

Table 43. Adverse events reported by ≥3% of subjects in any group (Study 19334, Safety population [Overall population])

| MedDRA PT | Placebo (N = 262) | Vericiguat 10 mg (N = 262) | Vericiguat 15 mg (N = 264) |
|---|---|---|---|
| Anaemia | 3.4 (9) | 3.1 (8) | 5.7 (15) |
| Atrial fibrillation | 2.7 (7) | 3.4 (9) | 3.8 (10) |
| Nausea | 0.8 (2) | 3.4 (9) | 1.5 (4) |
| Constipation | 1.5 (4) | 0.8 (2) | 3.0 (8) |
| Oedema peripheral | 3.1 (8) | 6.1 (16) | 3.8 (10) |
| Bronchitis | 3.1 (8) | 1.9 (5) | 1.9 (5) |
| Nasopharyngitis | 2.7 (7) | 3.1 (8) | 2.7 (7) |
| Pneumonia | 3.4 (9) | 1.9 (5) | 3.4 (9) |
| Respiratory tract infection | 1.9 (5) | 1.9 (5) | 3.0 (8) |
| Hyperkalaemia | 4.6 (12) | 1.9 (5) | 2.7 (7) |
| Hyperuricaemia | 1.1 (3) | 2.7 (7) | 3.0 (8) |
| Hypokalaemia | 3.1 (8) | 1.9 (5) | 2.7 (7) |
| Arthralgia | 3.1 (8) | 0.4 (1) | 2.3 (6) |
| Dizziness | 4.2 (11) | 3.1 (8) | 2.7 (7) |
| Headache | 4.2 (11) | 1.9 (5) | 2.3 (6) |
| Acute kidney injury | 4.2 (11) | 2.3 (6) | 1.9 (5) |
| Dyspnoea | 5.3 (14) | 2.7 (7) | 1.9 (5) |
| Hypertension | 4.6 (12) | 1.9 (5) | 4.2 (11) |
| Hypotension | 6.1 (16) | 6.9 (18) | 9.5 (25) |

Incidence % (n)

Among the overall population, the incidences of adverse events leading to death were 1.9% (5 of 262 subjects) in the placebo group (thalamus haemorrhage; epiglottitis; acute respiratory failure and pulmonary embolism; oesophageal varices; and hypotension [1 subject each]), 4.2% (11 of 262 subjects) in the vericiguat 10 mg group (acute hepatic failure; pulmonary oedema; thalamus haemorrhage; cardiovascular disorder; cardiac

[7)] Adverse events that started or worsened after start of study drug up to 5 days after the end of treatment with study drug. Any adverse events leading to death in the study period are listed.

failure; pneumonia; sudden death; pulmonary sepsis; bacterial pneumonia and acute kidney injury; death; and bacteraemia [1 subject each]), and 1.9% (5 of 264 subjects) in the vericiguat 15 mg group (aortic aneurysm and aortic stenosis; death; pelvic mass, hypoglycaemia, and hyponatraemia; septic shock and pneumonia; and sudden cardiac death [1 subject each]), and hypotension in the placebo group and pulmonary oedema in the vericiguat 10 mg group were considered related to study drug.

Among the overall population, the incidences of serious adverse events were 18.3% (48 of 262 subjects) in the placebo group, 17.6% (46 of 262 subjects) in the vericiguat 10 mg group, and 20.5% (54 of 264 subjects) in the vericiguat 15 mg group, and those reported by ≥1% of subjects in any group were anaemia (0.4% in the placebo group, 1.1% in the vericiguat 10 mg group, 0.8% in the vericiguat 15 mg group), atrial fibrillation (0.4%, 1.5%, 1.5%), cellulitis (0%, 0%, 1.1%), pneumonia (1.5%, 1.1%, 2.7%), urinary tract infection (1.1%, 0%, 0.4%), acute kidney injury (1.5%, 1.1%, 1.1%), chronic obstructive pulmonary disease (0.4%, 0.4%, 1.5%), and hypotension (1.5%, 0.8%, 1.1%). The incidences of serious adverse events related to study drug were 1.1% (3 of 262 subjects) in the placebo group (hypotension [2 subjects]; and renal failure [1 subject]), 1.5% (4 of 262 subjects) in the vericiguat 10 mg group (hypotension; hypotension and syncope; acute kidney injury; and pulmonary oedema [1 subject]), and 1.1% (3 of 264 subjects) in the vericiguat 15 mg group (syncope; acute kidney injury; and hypotension [1 subject each]).

Among the overall population, the incidences of adverse events leading to study drug discontinuation were 2.7% (7 of 262 subjects) in the placebo group, 3.4% (9 of 262 subjects) in the vericiguat 10 mg group, and 4.5% (12 of 264 subjects) in the vericiguat 15 mg group, and those reported by ≥2 subjects in any group were pneumonia (0.4%, 0.8%, 0%) and hypotension (0%, 0.4%, 1.1%).

Among the Japanese subgroup, the incidences of adverse events leading to death were 6.7% (1 of 15 subjects) in the placebo group, 7.7% (1 of 13 subjects) in the vericiguat 10 mg group, and 0% (0 of 13 subjects) in the vericiguat 15 mg group, and the incidences of serious adverse events were 20.0% (3 of 15 subjects), 7.7% (1 of 13 subjects), and 23.1% (3 of 13 subjects), respectively. All those events were considered unrelated to study drug.

## 7.3 Phase III study

### 7.3.1 Global phase III study (Study 16493, CTD 5.3.5.1.5, September 2016 to September 2019)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 694 sites in Japan and foreign countries including the US and Europe to evaluate the efficacy and safety of vericiguat in patients with chronic heart failure with reduced LVEF on standard HF therapy (target sample size, approximately 4872 randomized subjects, a total of 782 CV death events required[8)]).

Table 44 shows key inclusion and exclusion criteria.

[8)] If the median follow-up time was <10 months when 782 CV death events had been observed, the study was to continue until a median follow-up time of 10 months was reached.

Table 44. Key inclusion and exclusion criteria for Study 16493

| Inclusion criteria | Exclusion criteria |
|---|---|
| · Patients with chronic heart failure aged ≥18 years<br>· Previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF without hospitalization within 3 months prior to randomization<br>· NYHA class Ⅱ to Ⅳ<br>· LVEF <45%<br>· NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL (≥192 pg/mL in Japan) in sinus rhythm, or NT-proBNP ≥1600 pg/mL or BNP ≥500 pg/mL (≥319 pg/mL in Japan) in atrial fibrillation within 30 days prior to randomization | · Administration of any IV treatment within 24 hours prior to randomization, or SBP <100 mmHg or symptomatic hypotension at the time of randomization<br>· eGFR <15 mL/min/1.73 $m^2$ or chronic dialysis<br>· Severe hepatic insufficiency<br>· Concurrent or anticipated use of long-acting nitrates or NO donors [a]<br>· Concurrent or anticipated use of PDE5 inhibitors[b] |

a: isosorbide dinitrate, isosorbide-5-mononitrate, pentaerythritol tetranitrate, nicorandil, transdermal nitroglycerin patch, molsidomine, etc.
b: vardenafil, tadalafil, sildenafil, etc.

Placebo or vericiguat was to be administered orally once daily with food. Vericiguat was to be started at 2.5 mg and up-titrated to 5 mg at Week 2 and to the target dose of 10 mg at Week 4. The titration was to occur at all visits in accordance with the dose modification guidance presented in Table 45. If the patient did not reach the target dose, up-titration was to be considered at any subsequent visit at the discretion of the investigator (sub-investigator). Upon interruption of study drug due to intolerability, intake was to be resumed as soon as medically justified at the discretion of the investigator (sub-investigator), in accordance with the instructions for resumption of study drug intake presented in Table 46. If the patient did not tolerate the target dose of study drug, the investigator was to consider whether medications not shown to provide an outcome benefit in clinical studies (e.g., diuretics) can be reduced before reducing the dose of study drug.

The mean duration of exposure to study drug (range) was 374.7 (1-966) days in the placebo group and 375.5 (1-964) days in the vericiguat group among the overall population and 369.4 (5-885) days in the placebo group and 407.7 (13-894) days in the vericiguat group among the Japanese subgroup. The proportion of subjects titrated to the 10-mg target dose at some point in the study was 84.1% in the placebo group and 81.9% in the vericiguat group among the overall population and 83.4% in the placebo group and 83.9% in the vericiguat group among the Japanese subgroup. The proportion of subjects who reached the 10-mg dose by Week 8 and stayed on the 10-mg dose for at least 80% of the treatment period was 63.8% in the placebo group and 61.6% in the vericiguat group among the overall population and 56.7% in the placebo group and 63.4% in the vericiguat group among the Japanese subgroup.

Table 45. Dose modification guidance for Study 16493

| Blood pressure assessment | Dose modification |
|---|---|
| SBP ≥100 mmHg on 2.5 or 5 mg | Increase the dose by 1 step.<br>· 5 mg if on 2.5 mg<br>· 10 mg if on 5 mg |
| SBP ≥100 mmHg on 10 mg,<br>or SBP ≥90 and <100 mmHg | Maintain the dose. |
| SBP <90 mmHg without symptoms of hypotension on 5 or 10 mg | Decrease the dose by 1 step.<br>· 2.5 mg if on 5 mg<br>· 5 mg if on 10 mg |
| SBP <90 mmHg with or without symptoms of hypotension on 2.5 mg | Interrupt the dose. |

Table 46. Resumption of study drug intake for Study 16493

| Dose at time of interruption | Length of interruption | Restart dose | Dose level 1st titration (2 weeks after resumption) | Dose level 2nd titration (4 weeks after resumption) |
|---|---|---|---|---|
| 2.5 mg | Any | 2.5 mg | 5 mg | 10 mg |
| 5 mg | Any | 2.5 mg | 5 mg | 10 mg |
| 10 mg | >5 days | 2.5 mg | 5 mg | 10 mg |
| | ≤5 days | 5 mg | 10 mg | 10 mg |

If interruption occurred during the titration phase (before Week 4), restart at a scheduled visit, and if interruption occurred after Week 4, restart as soon as possible (with an unscheduled visit if required) and titrate according to Table 45.

Enrolled subjects were assigned randomly in a 1:1 ratio to placebo or vericiguat. Randomization was stratified by region and race.[9)] The intension-to-treat (ITT) population included 5050 randomized subjects (2524 [158 Japanese subjects] in the placebo group, 2526 [161 Japanese subjects] in the vericiguat group), which was used as the primary efficacy analysis population. Of whom, 5034 subjects who received at least 1 dose of study drug (2515 [157 Japanese subjects] in the placebo group, 2519 [161 Japanese subjects] in the vericiguat group) were included in the safety population. There were 1161 withdrawals from the study (587 subjects [18 Japanese subjects] in the placebo group, 574 subjects [30 Japanese subjects] in the vericiguat group), and the main reasons for withdrawals were death (1093 subjects) (552 subjects [15 Japanese subjects] in the placebo group, 541 subjects [30 Japanese subjects] in the vericiguat group).

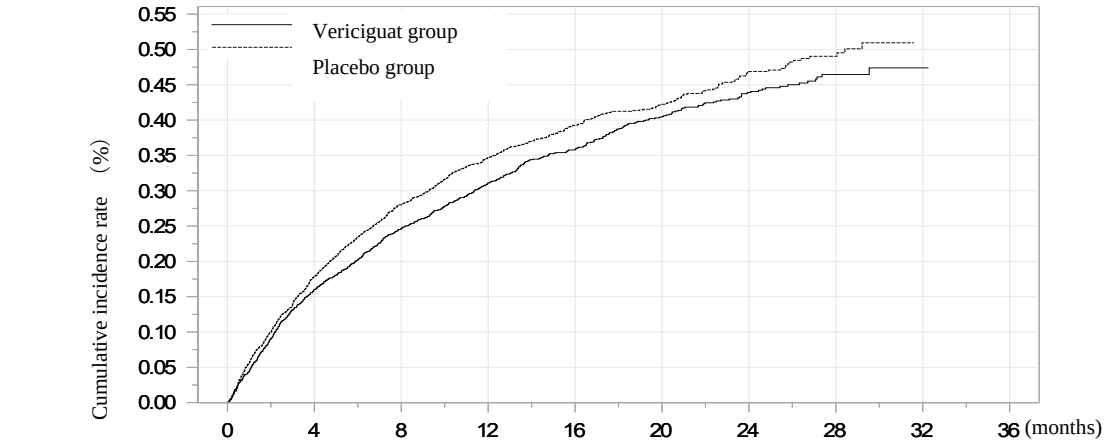
The primary efficacy endpoint was the time to the first occurrence of the composite endpoint of CV death or HF hospitalization. Table 47 shows the results of the primary efficacy endpoint and its components and all-cause mortality. Subjects receiving vericiguat experienced significantly fewer primary composite events compared to those receiving placebo (log-rank test, stratified by the strata used in randomization [region and race], $P = 0.019$). Kaplan-Meier curves for the primary composite endpoint: time to the first occurrence of CV death or HF hospitalization are shown in Figure 1 (the overall population) and Figure 2 (the Japanese subgroup).

Table 47. Incidences of clinical efficacy events (Study 16493, ITT population)

| Overall population | Placebo (N = 2524) | Vericiguat (N = 2526) | Hazard ratio[a] [95% CI] |
|---|---|---|---|
| CV death or HF hospitalization (first event) | 38.5 (972) | 35.5 (897) | 0.90 [0.82, 0.98] |
| CV death | 17.5 (441) | 16.4 (414) | 0.93 [0.81, 1.06] |
| HF hospitalization (first event) | 29.6 (747) | 27.4 (691) | 0.90 [0.81, 1.00] |
| All-cause mortality | 21.2 (534) | 20.3 (512) | 0.95 [0.84, 1.07] |
| **Japanese subgroup** | **Placebo (N = 158)** | **Vericiguat (N = 161)** | **Hazard ratio[b] [95% CI]** |
| CV death or HF hospitalization (first event) | 31.0 (49) | 30.4 (49) | 0.93 [0.63, 1.39] |
| CV death | 7.0 (11) | 14.3 (23) | 2.01 [0.98, 4.12] |
| HF hospitalization (first event) | 27.8 (44) | 23.6 (38) | 0.82 [0.53, 1.26] |
| All-cause mortality | 9.5 (15) | 15.5 (25) | 1.60 [0.85, 3.04] |

Incidence % (n)
a: Estimated from a Cox proportional hazards model including stratification factors used for randomization.
b: Estimated from a Cox proportional hazards model not including stratification factors used for randomization.

9) Eastern Europe (including Israel and South Africa)/Western Europe/North America (Black)/North America (Non-black)/Latin and South America/Asia Pacific (including Australia)

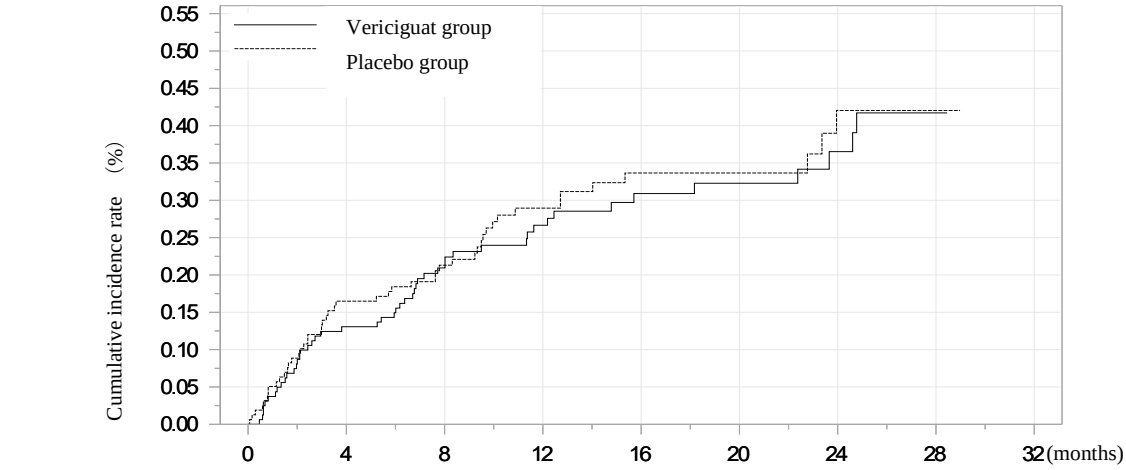



**Number of subjects at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Vericiguat group | 2526 | 2099 | 1621 | 1154 | 826 | 577 | 348 | 125 | 1 | 0 |
| Placebo group | 2524 | 2053 | 1555 | 1097 | 772 | 559 | 324 | 110 | 0 | 0 |

Figure 1. Time to the first occurrence of CV death or HF hospitalization

(Kaplan-Meier curves: Study 16493, ITT population [overall population])




**Number of subjects at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vericiguat group | 161 | 139 | 108 | 79 | 57 | 42 | 26 | 1 | 0 |
| Placebo group | 158 | 130 | 104 | 71 | 45 | 33 | 18 | 3 | 0 |

Figure 2. Time to the first occurrence of CV death or HF hospitalization

(Kaplan-Meier curves: Study 16493, ITT population [Japanese subgroup])

Regarding safety, among the overall population, the incidences of adverse events[10)] were 81.0% (2036 of 2515 subjects) in the placebo group and 80.5% (2027 of 2519 subjects) in the vericiguat group, and adverse events reported by ≥3% of subjects in either group are shown in Table 48. Among the Japanese subgroup, the

[10)] Adverse events that started or worsened after start of study drug up to 14 days after the end of treatment with study drug.

incidences of adverse events were 89.8% (141 of 157 subjects) in the placebo group and 90.1% (145 of 161 subjects) in the vericiguat group, and adverse events reported by ≥5% of subjects in either group are shown in Table 49.

Table 48. Adverse events reported by ≥3% of subjects in either group (Study 16493, Safety population [overall population])

| MedDRA PT | Placebo (N = 2515) | Vericiguat (N = 2519) |
|---|---|---|
| Hypotension | 14.1 (354) | 15.4 (388) |
| Cardiac failure | 9.9 (250) | 8.9 (224) |
| Anaemia | 5.7 (143) | 7.6 (192) |
| Dizziness | 6.0 (150) | 6.7 (169) |
| Pneumonia | 7.2 (180) | 6.4 (161) |
| Acute kidney injury | 5.0 (127) | 5.3 (134) |
| Dyspnoea | 5.1 (129) | 5.3 (133) |
| Diarrhoea | 4.9 (124) | 5.2 (130) |
| Nasopharyngitis | 5.0 (127) | 4.8 (121) |
| Upper respiratory tract infection | 4.6 (115) | 4.8 (120) |
| Cough | 4.2 (105) | 4.4 (111) |
| Hyperkalaemia | 5.6 (140) | 4.4 (111) |
| Syncope | 3.5 (88) | 4.0 (101) |
| Oedema peripheral | 3.8 (95) | 3.9 (98) |
| Nausea | 2.7 (67) | 3.8 (96) |
| Hypokalaemia | 3.5 (87) | 3.7 (94) |
| Renal failure | 3.5 (89) | 3.7 (92) |
| Bronchitis | 4.5 (112) | 3.5 (87) |
| Urinary tract infection | 3.9 (98) | 3.5 (89) |
| Atrial fibrillation | 3.8 (96) | 3.5 (89) |
| Chronic kidney disease | 3.6 (90) | 3.5 (88) |
| Headache | 2.4 (61) | 3.4 (86) |
| Gout | 3.8 (96) | 3.3 (83) |
| Hyperuricaemia | 2.9 (72) | 3.1 (77) |
| Chronic obstructive pulmonary disease | 2.3 (58) | 3.0 (76) |
| Constipation | 3.1 (77) | 2.9 (74) |

Incidence % (n)

Table 49. Adverse events reported by ≥5% of subjects in either group (Study 16493, Safety population [Japanese subgroup])

| MedDRA PT | Placebo (N = 157) | Vericiguat (N = 161) |
|---|---|---|
| Nasopharyngitis | 28.0 (44) | 24.8 (40) |
| Cardiac failure | 12.7 (20) | 10.6 (17) |
| Constipation | 10.2 (16) | 10.6 (17) |
| Diarrhoea | 7.0 (11) | 8.7 (14) |
| Hyperkalaemia | 3.8 (6) | 8.1 (13) |
| Back pain | 5.7 (9) | 8.1 (13) |
| Dehydration | 10.8 (17) | 6.8 (11) |
| Hypotension | 10.2 (16) | 6.8 (11) |
| Anaemia | 6.4 (10) | 6.8 (11) |
| Pneumonia | 8.9 (14) | 5.6 (9) |
| Nausea | 3.8 (6) | 5.6 (9) |
| Insomnia | 3.8 (6) | 5.6 (9) |
| Cough | 3.2 (5) | 5.6 (9) |
| Pruritus | 3.2 (5) | 5.0 (8) |
| Cataract | 5.1 (8) | 5.0 (8) |
| Hepatic function abnormal | 3.8 (6) | 5.0 (8) |
| Skin abrasion | 1.9 (3) | 5.0 (8) |
| Dizziness | 7.0 (11) | 3.7 (6) |
| Hyperuricaemia | 5.7 (9) | 3.7 (6) |
| Diabetes mellitus | 7.0 (11) | 3.1 (5) |
| Epistaxis | 5.1 (8) | 3.1 (5) |
| Bronchitis | 5.7 (9) | 2.5 (4) |
| Periodontitis | 5.1 (8) | 1.2 (2) |

Incidence % (n)

Among the overall population, the incidences of adverse events leading to death were 3.4% (85 of 2515 subjects) in the placebo group and 3.3% (83 of 2519 subjects) in the vericiguat group, and those reported by ≥4 subjects in either group were cardiac failure (0.6% in the placebo group, 0.4% in the vericiguat group), pneumonia (0.6%, 0.3%), acute kidney injury (0.2%, 0.2%), sepsis (0.2%, 0.2%), septic shock (0.1%, 0.2%), and congestive cardiac failure (0.2%, 0.0%). Of which, acute kidney injury reported by 1 subject in the vericiguat group was considered related to study drug. Among the Japanese subgroup, the incidences of adverse events leading to death were 0.6% (1 of 157 subjects) in the placebo group (subarachnoid haemorrhage) and 2.5% (4 of 161 subjects) in the vericiguat group (pneumonia [2 subjects]; and bacterial pneumonia; and marasmus [1 subject each]), and all those events were considered unrelated to study drug.

Among the overall population, the incidences of serious adverse events were 34.8% (876 of 2515 subjects) in the placebo group and 32.8% (826 of 2519 subjects) in the vericiguat group, and those reported by ≥2% of subjects in either group were cardiac failure (4.4%, 3.2%), pneumonia (4.5%, 4.0%), and acute kidney injury (2.0%, 2.5%). Of which, the events reported by 0.8% (20 of 2515) of subjects in the placebo group (hypotension [7 subjects]; acute kidney injury [3 subjects]; syncope [2 subjects]; and cognitive disorder; generalised tonic-clonic seizure; renal failure; angioedema; bullous dermatitis; gouty arthritis and gout; hypotension and orthostatic hypotension; and acute kidney injury, cardiac failure, and hypotension [1 subject each]) and the events reported by 1.2% (30 of 2519) of subjects in the vericiguat group (hypotension [7 subjects]; acute kidney injury [4 subjects]; ventricular tachycardia; dizziness; and syncope [2 subjects each]; and gingival bleeding; upper gastrointestinal haemorrhage; liver injury; blood creatinine increased; enthesopathy and gout; axonal neuropathy; haematuria; nephropathy; chronic kidney disease; presyncope; hypotension and renal failure; fall and hypotension; and acute kidney injury, chronic kidney disease, hyperkalaemia, and metabolic acidosis [1 subject each]) were considered related to study drug. Among the Japanese subgroup, the incidences of serious adverse events were 36.3% (57 of 157 subjects) in the placebo group and 31.7% (51 of 161 subjects) in the vericiguat group, and those reported by ≥2% of subjects in either group were cardiac failure (3.8%, 3.7%), cataract (2.5%, 2.5%), and pneumonia (6.4%, 2.5%). Of which, ventricular tachycardia reported by 1 subject in the vericiguat group was considered related to study drug.

Among the overall population, the incidences of adverse events leading to study drug discontinuation were 6.3% (158 of 2515 subjects) in the placebo group and 6.6% (167 of 2519 subjects) in the vericiguat group, and those reported by ≥0.2% of subjects in either group were cardiac failure (0.2%, 0.2%), dyspepsia (0.1%, 0.2%), nausea (0.0%, 0.2%), pneumonia (0.2%, 0.1%), dizziness (0.1%, 0.4%), syncope (0.2%, 0.0%), acute kidney injury (0.4%, 0.4%), chronic kidney disease (0.6%, 0.3%), renal failure (0.4%, 0.2%), hypotension (1.3%, 1.9%), and blood creatinine increased (0.0%, 0.2%). Among the Japanese subgroup, the incidences of adverse events leading to study drug discontinuation were 3.8% (6 of 157 subjects) in the placebo group and 5.0% (8 of 161 subjects) in the vericiguat group, and those reported by ≥2 subjects in either group were hypotension (1.3%, 0%).

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Clinical positioning of vericiguat

The applicant's explanation about the clinical positioning of vericiguat in the treatment of chronic heart failure in Japan:

β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) have been established as standard of care for chronic heart failure. Despite the use of these existing therapies, some patients continue to experience HF decompensation. Thus, a new treatment as an addition to the patient's existing therapies is needed to reduce HF events. Also in recent clinical studies in patients with chronic heart failure with reduced LVEF (*N Engl J Med*. 2014; 371: 993-1004, *N Engl J Med*. 2019; 381: 1995-2008, *JAMA*. 2013; 309: 1125-35), the risk of the composite endpoint of CV death or HF hospitalization was particularly high in patients with worsening chronic HF than in patients with more stable chronic HF, indicating that there is an unmet medical need for patients treated with the current Japanese guideline-recommended standard therapies for chronic heart failure.

cGMP is a signaling molecule that regulates critical physiological processes such as cardiac contractility, vascular tone, and cardiac remodeling. HF is associated with impaired synthesis of NO and decreased activity of sGC. Deficiency in sGC-derived cGMP contributes to myocardial and vascular dysfunction (*J Am Coll Cardiol*. 2012; 60: 1455-69, *Nitric Oxide*. 2018; 76: 105-12, etc.). Vericiguat restores the relative cGMP deficiency by directly stimulating sGC to augment the levels of intracellular cGMP. It has a mechanism of action not currently addressed by existing drugs used in the treatment of chronic heart failure.

Study 16493 demonstrated the efficacy and safety of vericiguat. The study included patients with chronic heart failure with LVEF <45% on standard therapy for chronic heart failure who had a previous HF hospitalization within 6 months or IV diuretic treatment for HF without hospitalization within 3 months. The results of the primary efficacy endpoint in the Japanese subgroup were consistent with those in the overall population, and also as to safety, there were no events of particular concern in the Japanese subgroup compared with the overall population.

Based on the above, vericiguat is expected to be added to standard therapy in patients with chronic heart failure with reduced LVEF on available standard therapy for chronic heart failure.

PMDA's view:

In Study 16493 in patients with chronic heart failure with reduced LVEF on standard therapy for chronic heart failure, vericiguat was superior to placebo in reducing the risk of the primary efficacy endpoint (the primary composite endpoint of CV death or HF hospitalization [the first event]), and vericiguat had clinically acceptable safety [see Section "7.R.2 Efficacy" and Section "7.R.3 Safety"].

Also in Japanese patients on standard therapy for chronic heart failure, vericiguat was suggested to have the clinically meaningful efficacy and acceptable safety [see Section "7.R.2.2 Efficacy of vericiguat in Japanese patients"]. Thus, offering vericiguat as an addition to standard therapies, mainly with renin-angiotensin-

aldosterone system (RAAS) inhibitors or β-blockers, to clinical practice in Japan has its significance because vericiguat is a treatment option with a novel mode of action for patients with chronic heart failure with reduced LVEF.

### 7.R.2 Efficacy

#### 7.R.2.1 Results of efficacy assessment

The applicant's explanation about the efficacy of vericiguat:

According to the results of Study 16493, the hazard ratio of the primary composite endpoint of CV death or HF hospitalization (the first event) for vericiguat vs. placebo [95% CI] was 0.90 [0.82, 0.98], demonstrating the superiority of vericiguat over placebo in reducing the risk of the primary composite endpoint. The hazard ratios of the components of the primary composite endpoint for vericiguat vs. placebo [95% CI] were 0.93 [0.81, 1.06] for CV death and 0.90 [0.81, 1.00] for HF hospitalization. Moreover, the hazard ratio of a secondary endpoint of all-cause mortality for vericiguat vs. placebo [95% CI] was 0.95 [0.84, 1.07]. These results by clinical efficacy event were also largely consistent with the results of the primary efficacy endpoint. The above results demonstrated the efficacy of vericiguat in patients with chronic heart failure with reduced LVEF.

PMDA asked the applicant to explain whether the clinically meaningful efficacy of vericiguat was demonstrated, even though the hazard ratio of the primary endpoint for vericiguat vs. placebo (0.90) in Study 16493 was different from that expected at the time of planning the study.

The applicant's explanation:

Study 16493 was designed, assuming that the clinically meaningful efficacy of vericiguat is demonstrated by achieving a hazard ratio of the primary endpoint for vericiguat vs. placebo of 0.8, based on the results of clinical studies of other agents in patients with chronic heart failure (*JAMA*. 2013; 309: 1125-35, *N Engl J Med*. 2014; 371: 993-1004) and Study 15371, a global phase II study of vericiguat. As it was considered that there is an unmet medical need particularly for patients with chronic heart failure at higher risk of worsening HF event compared with patients with more stable chronic heart failure, Study 16493 enrolled patients with chronic heart failure who had a previous worsening HF event defined as a previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF without hospitalization within 3 months prior to randomization. At the time of planning the study, the expected event rate of the primary endpoint in the placebo group after 12 months was 23%, and the expected event rate of CV death was 11%, whereas the annual event rate for the primary endpoint in the placebo group was 37.8%, and the annual event rate for CV death was 13.9%, which were higher than expected. In Study 16493, the median time from the index event to randomization (range) was 32.0 (2-621) days, and many patients were enrolled within a short period of time after their index event. Compared with patients with chronic heart failure included in the clinical studies of other agents, the proportion of subjects with NYHA class III or IV was higher and baseline NT-proBNP was also higher. Such patient characteristics were considered to be a cause of the higher than expected hazard ratio for vericiguat vs. placebo. In Study 16493, the proportion of subjects who reported the use of standard therapies for chronic heart failure at baseline was high, and subjects in both groups continued on standard therapies

throughout the study period on the whole. Although patients at higher than expected risk of HF event enrolled in Study 16493 produced unexpected efficacy results, vericiguat, when added to optimal background standard of HF care, was shown to reduce the risk of the composite endpoint of CV death or HF hospitalization and CV death in a population with a previous worsening HF event at higher risk of HF event, demonstrating the clinically meaningful efficacy of vericiguat.

PMDA asked the applicant to explain the possibility of generalizability of the results of Study 16493 to patients with chronic heart failure, including patients with more stable chronic HF who were not eligible for the study.

The applicant's explanation:
In Study 16493, the pre-specified subgroup analyses of the primary endpoint according to the time from the index event to randomization showed almost consistent efficacy of vericiguat across the subgroups (Table 50).

Table 50. Incidences of primary endpoint events by time from index event to randomization (Study 16493, ITT population)

| | Placebo<br>N = 2524 | Vericiguat<br>N = 2526 | Hazard ratio[a] [95% CI] |
|---|---|---|---|
| HF hospitalization within 3 months | 41.1 (701/1705) | 39.5 (660/1673) | 0.93 [0.84, 1.04] |
| HF hospitalization within 3-6 months | 36.2 (151/417) | 31.1 (141/454) | 0.85 [0.67, 1.07] |
| IV diuretic treatment for HF without hospitalization within 3 months | 29.9 (120/402) | 24.1 (96/399) | 0.78 [0.60, 1.02] |

Incidence % (No. of subjects with event/No. of subjects analyzed)
a: Estimated from a Cox proportional hazards model including stratification factors used for randomization, treatment group, subgroup, and treatment group-subgroup interaction term

There was no trend towards decreasing efficacy of vericiguat in a population with a long duration between HF hospitalization and randomization within the scope investigated. Thus, the efficacy of vericiguat is expected also in patients with more stable (≥6 months after HF hospitalization) chronic heart failure who were not eligible for Study 16493.

PMDA's view:
In Study 16493, vericiguat significantly reduced the primary composite endpoint event of CV death or HF hospitalization (the first event) compared with placebo, and vericiguat reduced the risk of event compared with placebo for all of the components of the primary endpoint, i.e., CV death and HF hospitalization, and a secondary endpoint of all-cause mortality (Table 47). Though the hazard ratio of the primary endpoint for vericiguat vs. placebo was higher than that expected at the time of planning the study, the applicant's explanation that the possible cause was more patients at higher risk of event enrolled than expected is appropriate to some extent. Given that the hazard ratio was <1 also in a population that had an index event within 3 months prior to randomization (Table 50), and that the hazard ratio in a population with a longer duration between their index event and randomization was not substantially different from that expected at the time of planning the study etc., the results indicate that the clinically meaningful efficacy of vericiguat is attained in patients with chronic heart failure with reduced LVEF. The applicant's explanation (as there was no trend towards decreasing efficacy in a population with a long duration between HF hospitalization and

randomization, when added to optimal background standard of HF care, the efficacy of vericiguat is expected also in patients with more stable chronic heart failure who were not eligible for Study 16493) is also appropriate.

### 7.R.2.2 Efficacy of vericiguat in Japanese patients

PMDA asked the applicant to explain the appropriateness of participation of Japan in a global study, Study 16493, along with the intrinsic and extrinsic ethnic factors studied.

The applicant's explanation:

With a view to participation of Japan in a global study, Japanese and foreign guidelines on chronic heart failure were compared, which showed no clear differences in the diagnosis of and recommended standard therapies for heart failure between Japan and overseas, except that some drugs were unapproved in Japan. Since phase II and III studies of vericiguat enrolled patients with chronic heart failure who experienced a recent worsening HF event, acute heart failure registry data in Japan and overseas were reviewed for patient characteristics (*Am Heart J*. 2010; 159: 949-55, *J Am Coll Cardiol*. 2006; 47: 76-84, etc.). There seemed no major differences between Japan and overseas, except that the proportion of patients with ischemic heart disease as the underlying etiology was low in Japan. With respect to differences in the PK of vericiguat between Japanese and non-Japanese populations, based on the PPK analysis of Study 15371, the mean estimated dose-normalized AUC and $C_{max}$ were approximately 20% and approximately 10% higher, respectively, in Japanese patients with chronic heart failure than in non-Asian patients in Study 16493, but the 90% confidence intervals almost overlapped. Thus, it was concluded that there are no major differences between Japanese and non-Japanese patients with chronic heart failure. Based on the above, there are no clear differences between Japanese and non-Japanese populations attributable to intrinsic and extrinsic ethnic factors that can impact the efficacy and safety of vericiguat, and participation of Japan in Study 16493 poses no major problem.

There were differences in patient characteristics between the overall population and the Japanese subgroup in Study 16493 for the mean age (67.3 years in the overall population, 73.0 years in the Japanese subgroup), the mean body weight (78.9 kg, 60.3 kg), the mean eGFR at randomization (61.5 mL/min/1.73 $m^2$, 55.8 mL/min/1.73 $m^2$), the proportion of subjects with LVEF <30% (49.3%, 38.6%), the proportion of subjects with NYHA class III (39.7%, 20.7 %), and the median time from the index event to randomization (32.0 days, 43.0 days). Subgroup analyses of efficacy and safety according to these factors were performed. In the overall population, there were no major differences in efficacy among the age (<65 years vs. ≥65 years and <75 years vs. ≥75 years), body weight (<60 kg vs. ≥60 kg and <90 kg vs. ≥90 kg) and renal function (eGFR [mL/min/1.73 $m^2$], ≤30 vs. >30 and ≤60 vs. >60) subgroups [for efficacy by LVEF, NYHA class, and time from the index event to randomization, see Section "7.R.2.5 Impact of LVEF on the efficacy of vericiguat," Section "7.R.2.3 Efficacy by severity of heart failure," and Section "7.R.2.1 Results of efficacy assessment"].

Table 51 shows baseline use of standard of care medications or devices for chronic heart failure. Sacubitril/valsartan and ivabradine were unapproved in Japan during the conduct of Study 16493, and there were differences in the proportion of subjects treated with MRA, triple therapy (β-blocker + RAS inhibitor + MRA), or implantable cardioverter defibrillator (ICD) between the overall population and the Japanese

subgroup. Subgroup analyses according to the use of these therapies showed no trend towards differences in efficacy between the subgroups (Table 52).

Based on the above, though there were differences in some baseline characteristics between Japanese and non-Japanese populations, these differences did not affect the efficacy results, and participation of Japan in the global study, Study 16493, is appropriate.

Table 51. Baseline use of standard of care for chronic heart failure (Study 16493, ITT population)

| | Overall population | | | Japanese subgroup | | |
|---|---|---|---|---|---|---|
| | Placebo (N = 2524) | Vericiguat (N = 2526) | Total (N = 5050) | Placebo (N = 158) | Vericiguat (N = 161) | Total (N = 319) |
| ACE inhibitor or ARB | 73.6 (1853) | 73.3 (1847) | 73.4 (3700) | 81.0 (128) | 81.4 (131) | 81.2 (259) |
| Sacubitril/Valsartan | 14.7 (371) | 14.3 (360) | 14.5 (731) | 0 (0) | 0 (0) | 0 (0) |
| β-blocker | 93.0 (2432) | 93.2 (2349) | 93.1 (4691) | 92.4 (146) | 95.7 (154) | 94.0 (300) |
| MRA | 71.4 (1798) | 69.3 (1747) | 70.3 (3545) | 53.8 (85) | 52.8 (85) | 53.3 (170) |
| Ivabradine | 5.7 (143) | 6.4 (161) | 6.0 (304) | 0 (0) | 0 (0) | 0 (0) |
| Two or more SOC medications | 91.7 (2309) | 91.2 (2300) | 91.4 (4609) | 86.7 (137) | 89.4 (144) | 88.1 (281) |
| Triple therapy[a] | 60.7 (1529) | 58.7 (1480) | 59.7 (3009) | 41.1 (65) | 40.4 (65) | 40.8 (130) |
| Diuretics (excluding MRA)[b] | 89.7 (2257) | 88.5 (2230) | 89.1 (4487) | 93.0 (146) | 90.1 (145) | 91.5 (291) |
| ICD | 27.9 (703) | 27.6 (696) | 27.8 (1399) | 15.2 (24) | 18.0 (29) | 16.6 (53) |
| Biventricular pacemaker | 14.6 (369) | 14.7 (370) | 14.7 (739) | 12.7 (20) | 16.8 (27) | 14.7 (47) |

Use of standard of care % (n)
a: β-blocker + RAS inhibitor (ACE inhibitor, ARB, or sacubitril/valsartan) + MRA
b: Safety population

Table 52. Incidence of the primary composite endpoint by use of standard therapies for chronic heart failure (Study 16493, ITT population)

| | | Placebo (N = 2524) | Vericiguat (N = 2526) | Hazard ratio[a] [95% CI] |
|---|---|---|---|---|
| MRA | Yes | 37.7 (677/1798) | 33.5 (586/1747) | 0.86 [0.77, 0.96] |
| | No | 40.8 (294/721) | 39.8 (308/774) | 0.98 [0.83, 1.15] |
| Sacubitril/Valsartan | Yes | 41.2 (153/371) | 37.2 (134/360) | 0.88 [0.70, 1.11] |
| | No | 38.1 (818/2148) | 35.2 (760/2161) | 0.90 [0.81, 0.99] |
| Ivabradine | Yes | 44.0 (70/159) | 38.7(67/173) | 0.87 [0.62, 1.21] |
| | No | 38.1 (902/2365) | 35.3 (830/2353) | 0.90 [0.82, 0.99] |
| Triple therapy[b] | Yes | 35.6 (545/1529) | 31.5 (466/1480) | 0.85 [0.75, 0.96] |
| | No | 43.0 (426/990) | 41.1 (428/1041) | 0.94 [0.82, 1.08] |
| ICD | Yes | 46.7 (328/703) | 40.8 (284/696) | 0.85 [0.72, 0.99] |
| | No | 35.4 (643/1816) | 33.4 (610/1825) | 0.92 [0.82, 1.03] |

Incidence % (No. of subjects with event/No. of subjects analyzed)
a: Estimated from a Cox proportional hazards model including stratification factors used for randomization, treatment group, subgroup, and treatment group-subgroup interaction term.
b: β-blocker + RAS inhibitor (ACE inhibitor, ARB, or sacubitril/valsartan) + MRA

The applicant's explanation about the efficacy of vericiguat in Japanese patients:
In the Japanese subgroup of Study 16493, the hazard ratio of the primary composite endpoint for vericiguat vs. placebo [95% CI] was 0.93 [0.63, 1.39], and subjects receiving vericiguat experienced fewer primary composite events compared to those receiving placebo (Table 47). The hazard ratios of the components of the primary composite endpoint for vericiguat vs. placebo [95% CI] were 2.01 [0.98, 4.12] for CV death and 0.82 [0.53, 1.26] for HF hospitalization (the first event), and the hazard ratio of a secondary endpoint of all-cause mortality was 1.60 [0.85, 3.84].

Possible causes for the higher incidences of CV death and all-cause mortality in the vericiguat group than in the placebo group among the Japanese subgroup were examined as follows. Considering that the between-

group difference in all-cause mortality was mainly attributable to the between-group difference in CV death, the discussion focused on CV death.

(a) Imbalances in patient characteristics between the treatment groups

Among the items as prognostic risk factors for heart failure mentioned in the 2016 European Society of Cardiology (ESC) guideline, the patient characteristic factors that were imbalanced between the treatment groups at randomization were assessed for their effects on the between-group difference in the incidence of CV death. As to the distribution of the risk factors assessed in Study 16493, there was a ≥3% difference in the distribution of the following items between the treatment groups in the Japanese subgroup: The imbalances in the distribution of 10 items were unfavorable to the vericiguat group (NYHA class III/IV, LVEF, ventricular tachycardia, myocardial infarction, sleep apnoea syndrome, cardiac resynchronization therapy, angina pectoris, NT-proBNP, HF duration, chronic kidney disease), and the imbalances in the distribution of 4 items were unfavorable to the placebo group (eGFR, atrial fibrillation, atrial flutter, diabetes mellitus). In the overall population of Study 16493, there was a ≥3% difference in the distribution between the treatment groups for 2 items (myocardial infarction, coronary artery disease) only, and there were no major differences in the distribution of these risk factors between the treatment groups. With regard to many of the items that were imbalanced between the treatment groups in the Japanese subgroup, the incidence of CV death was higher in subjects with the risk factors in the overall population. A similar trend was observed in the Japanese subgroup as well. Especially, the incidence of CV death in subjects with an NT-proBNP value higher than the median (24.8% [297 of 1198 subjects] in the placebo group, 26.5% [318 of 2102 subjects] in the vericiguat group) was higher than that in subjects with an NT-proBNP value equal to or lower than the median (11.1% [133 of 1193 subjects], 9.3% [113 of 1212 subjects]), and higher NT-proBNP values in the vericiguat group (3005.0 pg/mL) than in the placebo group (2707.0 pg/mL) among the Japanese subgroup may have been associated with the between-group difference in the incidence of CV death. The above findings suggested that more subjects with prognostic risk factors for heart failure at baseline in the vericiguat group than in the placebo group among the Japanese subgroup was a possible cause of the between-group difference in the incidence of CV death.

(b) Discussion on mortality rates based on comparison with the existing data

Table 53 shows the incidences of all-cause death in the Japanese subgroup of Study 16493 and the HF registries in Japan.

Table 53. Incidences of all-cause death in Japanese subgroup of Study 16493 and HF registries in Japan

| Registry/Study | Population | No. of patients analyzed | BNP (Median) | Cumulative 1-year[c] incidence of all-cause death |
|---|---|---|---|---|
| KCHF[a] | Patients with previous HF hospitalization | 1321 | 757 pg/ml | 29.3% |
| ATTEND[b] | Hospitalized patients with acute heart failure | 4842 | 706 pg/ml | 14.5% |
| WET-HF[b] | Hospitalized patients with acute heart failure | 2551 | 676 pg/ml | 15.3% |
| REALITY-AHF[b] | Hospitalized patients with acute heart failure | 1682 | 744 pg/ml | 17.7% |
| Study 16493 (Vericiguat group) | Japanese subgroup | 161 | 746.5 pg/ml | 13.5% |
| Study 16493 (Placebo group) | | 158 | | 6.9% |

a: *Circ Rep*. 2019; 1: 517-24, b: *J Am Heart Assoc*. 2018; 7: e008687
c: Cumulative incidence of all-cause death at 1 year after admission for KCHF and cumulative incidence of all-cause death between 30 days and 1 year after admission for ATTEND, WET-HF, and REALITY-AHF were calculated.

Due to differences in the population, duration of evaluation, and the method of approximation of mortality rate among the HF registries/clinical study listed in Table 53, care should be taken when interpreting the results. While the cumulative incidence of all-cause death at 1 year in the vericiguat group among the Japanese subgroup of Study 16493 was almost similar to those from the 4 HF registries in Japan, the cumulative incidence of all-cause death at 1 year in the placebo group tended to be lower. This supports the following possibilities: A higher incidence of CV death in the vericiguat group than in the placebo group among the Japanese subgroup of Study 16493 was incidental due to the limited number of patients; and as examined in the above (a), the imbalances in the distribution of prognostic risk factors for HF between the treatment groups was the cause of the between-group difference in the incidence of CV death.

(c) Association between CV death and study drug administration

The overall incidences of CV death through the last visit in Study 16493 were 18.3% (463 of 2524 subjects) in the placebo group and 17.7% (448 of 2526 subjects) in the vericiguat group among the overall population and 7.0% (11 of 158 subjects) in the placebo group and 17.4% (28 of 161 subjects) in the vericiguat group among the Japanese subgroup. Among those subjects with CV death, 45.8% (212 of 463) of subjects in the placebo group and 47.8% (214 of 448) of subjects in the vericiguat group in the overall population had CV death at ≥15 days after the end of study treatment and 63.6% (7 of 11) of subjects in the placebo group and 67.9% (19 of 28) of subjects in the vericiguat group in the Japanese subgroup had CV death at ≥15 days after the end of study treatment, and the proportions were higher in the Japanese subgroup than in the overall population. Among the Japanese subgroup, especially, there were more CV deaths occurring at ≥15 days after the end of study treatment in the vericiguat group than in the placebo group. Although the above findings suggested that CV deaths occurring at ≥15 days after the end of study treatment may have contributed to the between-group difference in the incidence of CV death in the Japanese subgroup, considering the time elapsed after the end of study treatment, the possibility that vericiguat was associated with increased CV deaths occurring at ≥15 days after the end of study treatment should be low.

Table 54 shows a breakdown of CV deaths in the overall population and the Japanese subgroup. "Heart failure" accounted for more than half of the causes of CV deaths in the Japanese subgroup. Individual subjects with CV death in the Japanese subgroup were evaluated for blood pressure, NYHA class, time course of NT-proBNP,

the occurrence of CV events, use of standard of care, use of study drug, complications, the occurrence of adverse events, etc. All of them had prognostic risk factors for HF.

Table 54. A breakdown of CV deaths (Study 16493, ITT population)

| | Overall population | | Japanese subgroup | |
|---|---|---|---|---|
| | Placebo (N = 2524) | Vericiguat (N = 2526) | Placebo (N = 158) | Vericiguat (N = 161) |
| CV death | 17.5 (441) | 16.4 (414) | 7.0 (11) | 14.3 (23) |
| Heart failure | 7.6 (191) | 6.5 (165) | 4.4 (7) | 8.1 (13) |
| Myocardial Infarction | 0.4 (11) | 0.4 (10) | 0 (0) | 0 (0) |
| Stroke | 0.6 (16) | 0.3 (7) | 0.6 (1) | 0 (0) |
| Other cardiovascular events | 0.4 (9) | 0.5 (13) | 0 (0) | 0 (0) |
| Sudden cardiac death | 4.5 (113) | 4.2 (107) | 1.3 (2) | 0.6 (1) |
| Unknown cause of death | 4.0 (101) | 4.4 (112) | 0.6 (1) | 5.6 (9) |

Incidence % (n)

Among the subjects with CV death, 0 of 11 subjects in the placebo group and 2 of 28 subjects in the vericiguat group had hypotension, and 1 of 11 subjects in the placebo group and 2 of 28 subjects in the vericiguat group had syncope, but none of these events led to a fatal outcome. Other adverse events that could lead to death were not specific to the vericiguat group.

Based on the above, subjects with CV death were at high risk of HF, and vericiguat is unlikely to increase CV death. There was no trend towards higher incidences of specific adverse events that could lead to death, including adverse events related to the pharmacological effects of vericiguat, in the vericiguat group.

In the above analyses (a)(b)(c), the number of subjects in the Japanese subgroup was limited, and evaluation based on the incidence of each efficacy endpoint event has limitations. Thus, the applicant explained the association between changes in NT-proBNP and reduction of CV deaths in Study 16493 as follows. Table 55 shows changes in NT-proBNP in the subgroups with or without CV death among the overall population or the Japanese subgroup of Study 16493.

Table 55. NT-proBNP changes in subgroups with or without CV death among overall population or Japanese subgroup (Study 16493, ITT population)

| | Placebo | | | Vericiguat | | |
|---|---|---|---|---|---|---|
| | N | NT-proBNP (pg/ml) | Change from baseline (pg/ml) | N | NT-proBNP (pg/ml) | Change from baseline (pg/ml) |
| Overall population | | | | | | |
| Subjects without CV death | | | | | | |
| Baseline | 2183 | 2724.0 | ― | 2210 | 2670.0 | ― |
| Week 16 | 2026 | 2173.0 | −223.0 | 2023 | 1942.0 | −465.0 |
| Week 32 | 1673 | 1996.0 | −297.0 | 1688 | 1777.5 | −478.0 |
| Week 48 | 1244 | 1930.5 | −313.0 | 1251 | 1678.0 | −558.5 |
| Week 96 | 425 | 1622.0 | −208.0 | 432 | 1546.0 | −593.0 |
| Week 144 | 1 | 1133.0 | 287.0 | 2 | 2866.5 | 1292.5 |
| Subjects with CV death | | | | | | |
| Baseline | 208 | 4624.0 | ― | 204 | 5357.0 | ― |
| Week 16 | 123 | 4142.0 | 233.0 | 111 | 4283.0 | −84.5 |
| Week 32 | 76 | 4237.5 | 333.5 | 67 | 3523.0 | 10.0 |
| Week 48 | 46 | 4101.5 | 8.0 | 43 | 3722.0 | 168.0 |
| Week 96 | 6 | 6857.0 | 3205.0 | 4 | 7758.0 | 4243.0 |
| Japanese subgroup | | | | | | |
| Subjects without CV death | | | | | | |
| Baseline | 152 | 2695.0 | ― | 148 | 2814.5 | ― |
| Week 16 | 147 | 2582.0 | 6.5 | 142 | 1873.5 | −459.0 |
| Week 32 | 118 | 2280.5 | −226.5 | 118 | 1803.0 | −526.5 |
| Week 48 | 89 | 2361.0 | −208.0 | 93 | 1732.0 | −583.5 |
| Week 96 | 27 | 1943.0 | −303.0 | 37 | 1757.0 | −793.0 |
| Subjects with CV death | | | | | | |
| Baseline | 5 | 3202.0 | ― | 11 | 5353.0 | ― |
| Week 16 | 3 | 2904.0 | 734.0 | 10 | 6990.5 | 90.0 |
| Week 32 | 3 | 4054.0 | 1266.0 | 7 | 4890.0 | 453.0 |
| Week 48 | 2 | 2921.5 | 1334.5 | 5 | 3722.0 | 409.0 |
| Week 96 | 1 | 4209.0 | 3205.0 | 2 | 7146.0 | 3486.5 |

Median, ―: Not applicable

Among the overall population, in both treatment groups, baseline NT-proBNP was lower and the reduction from baseline in NT-proBNP tended to be greater in subjects without CV death than in those with CV death. There was also a trend towards a greater reduction or a smaller increase in NT-proBNP in the vericiguat group than in the placebo group. The Japanese subgroup also showed a similar trend to that of the overall population, and an association between improvement of NT-proBNP by vericiguat and reduction of CV death events was suggested in the overall population and the Japanese subgroup.

Given the incidence of each event in the Japanese subgroup of Study 16493 and these considerations, the clinically meaningful efficacy of vericiguat is expected in the Japanese subgroup as in the overall population.

PMDA's view:

According to the applicant's explanation, with a view to participation of Japan in a global study, Study 16493, intrinsic and extrinsic ethnic factors other than the PK were studied, which concludes that there are no major differences between Japanese and non-Japanese populations attributable to intrinsic and extrinsic ethnic factors that can impact the efficacy of vericiguat. Though differences in the PK of vericiguat between Japanese and

non-Japanese populations were suggested [see Section "6.R.2 PK differences between Japanese and non-Japanese populations"], and there were differences in the use of some standard therapies for chronic heart failure and patient characteristics between the overall population and the Japanese subgroup of Study 16493, the considerations based on the results of Studies 15371 and 16493 [see Section "7.R.5 Dosage and administration"] and the results of subgroup analyses by patient characteristics presented by the applicant conclude that differences in the PK of vericiguat and patient characteristics between Japanese and non-Japanese populations do not significantly affect the efficacy evaluation of vericiguat. Then, Study 16493 demonstrated the superiority of vericiguat over placebo in reducing the primary composite events in the overall population, and the results in the Japanese subgroup were also consistent with those in the overall population. When focusing on the incidences of the components of the primary composite endpoint and all-cause mortality, the hazard ratio of clinically relevant CV death for vericiguat vs. placebo was >1 in the Japanese subgroup. However, it is difficult to say that the number of patients was sufficient to assess the consistency of the incidence of each component of the composite endpoint, and the applicant's explanation (more subjects with prognostic risk factors for HF at baseline enrolled in the vericiguat group than in the placebo group among the Japanese subgroup was a possible cause of inconsistency in the incidence of death between the Japanese subgroup and the overall population) is rational to a certain extent. Based on the above considerations, the overall conclusion is that the efficacy of vericiguat shown in the overall population is expected also in Japanese patients. Given that a causal relationship to study drug was denied by the investigator for most of CV deaths reported in the Japanese subgroup, and based on the changes in NT-proBNP in the overall population and the Japanese subgroup etc., there is no clear signal that treatment with vericiguat causes CV death. A final conclusion on the appropriateness of the above conclusion by PMDA will be made, taking account of comments from the Expert Discussion.

### 7.R.2.3 Efficacy by severity of heart failure

The applicant's explanation about the impact of the severity of chronic heart failure on the efficacy of vericiguat:

Table 56 shows the results of the primary endpoint by NYHA class in Study 16493.

Table 56. Incidence of the primary composite endpoint by NYHA class (Study 16493, ITT population)

| NYHA class | Placebo | Vericiguat | Hazard ratio[a] [95% CI] |
|---|---|---|---|
| Overall population | | | |
| Ⅱ | 32.2 (482/1497) | 30.1 (445/1478) | 0.92 [0.81, 1.04] |
| Ⅲ | 46.9 (466/993) | 42.4 (428/1010) | 0.87 [0.76, 0.99] |
| Ⅳ | 67.7 (21/31) | 65.7 (23/35) | 0.90 [0.46, 1.78] |
| Japanese subgroup | | | |
| Ⅱ | 31.5 (40/127) | 28.2 (35/124) | 0.85 [0.54, 1.34] |
| Ⅲ | 26.7 (8/30) | 38.9 (14/36) | 1.43 [0.60, 3.42] |
| Ⅳ | 100 (1/1) | 0 (0/0) | 0.00 [0.00, －] |

Incidence % (No. of subjects with event/No. of subjects analyzed), －: Not calculated

a: Estimated from a Cox proportional hazards model including stratification factors used for randomization, for the overall population.

Estimated from a Cox proportional hazards model not including stratification factors used for randomization, for the Japanese subgroup.

In the overall population, there was no trend towards differences in the efficacy of vericiguat among the NYHA class subgroups. In the Japanese subgroup, interpretation of the results from a small number of subjects in each subgroup has limitations. There was no trend towards differences in safety among the subgroups in the overall population.

Table 57 shows the results of the primary endpoint by baseline NT-proBNP quartile in Study 16493.

Table 57. Incidence of the primary composite endpoint by NT-proBNP quartile (Study 16493, ITT population)

| NT-proBNP (pg/mL) | Placebo | Vericiguat | Hazard ratio[a] [95% CI] |
|---|---|---|---|
| Overall population | | | |
| Q1 (≤1556) | 26.7 (161/604) | 21.4 (128/599) | 0.78 [0.62, 0.99] |
| Q2 (1556-2816) | 34.1 (201/589) | 26.9 (165/613) | 0.73 [0.60, 0.90] |
| Q3 (2816-5314) | 41.9 (257/613) | 36.3 (213/586) | 0.82 [0.69, 0.99] |
| Q4 (>5314) | 51.6 (302/585) | 73.6 (355/616) | 1.16 [0.99, 1.35] |
| Japanese subgroup | | | |
| Q1 (≤1556) | 22.2 (10/45) | 26.2 (11/42) | 1.14 [0.48, 2.69] |
| Q2 (1556-2816) | 23.5 (8/34) | 14.7 (5/34) | 0.53 [0.17, 1.63] |
| Q3 (2816-5314) | 39.0 (16/41) | 34.0 (16/47) | 0.80 [0.40, 1.61] |
| Q4 (>5314) | 40.5 (15/37) | 47.2 (17/36) | 1.25 [0.63, 2.51] |

Incidence % (n)

a: Estimated from a Cox proportional hazards model including stratification factors used for randomization, for the overall population. Estimated from a Cox proportional hazards model not including stratification factors used randomization, for the Japanese subgroup.

In the overall population, the efficacy of vericiguat relative to placebo was demonstrated with regard to the primary endpoint in subjects in the Q1, Q2, and Q3 of NT-proBNP, whereas the hazard ratio for vericiguat vs. placebo was >1 in subjects in the Q4 of NT-proBNP. Although the demographic and disease characteristics were generally consistent across the NT-proBNP quartile subgroups, subjects with the highest NT-proBNP levels at baseline tended to be older, have a higher NYHA class, have a lower BMI and eGFR, and a shorter duration between their index event and randomization than those with lower NT-proBNP levels at baseline. The highest NT-proBNP quartile (Q4) subgroup seemed to include patients with particularly severe and treatment-resistant HF among the patient population of this study, i.e. patients who had experienced a recent worsening HF event at high risk of event, which was suggested to be a possible cause of unfavorable efficacy results in subjects in the highest NT-proBNP quartile (Q4). However, given that NT-proBNP is a variable indicator, that multiple factors potentially associated with elevated NT-proBNP levels are assumed, and that interpretation of the results of the subgroup analysis based on post hoc cutoff values selected from the distribution of NT-proBNP values in subjects of Study 16493 has limitations, vericiguat may be used also in patients with the highest NT-proBNP levels.

PMDA's view:

In Study 16493, there was no trend towards major differences in the efficacy of vericiguat among the NYHA class II to IV subgroups in the overall population, suggesting the efficacy of vericiguat. In the Japanese subgroup, efficacy findings in the NYHA class II subgroup showed a trend similar to that of the overall population, while the hazard ratio of the primary composite endpoint was >1 in the NYHA class III and IV subgroups. However, interpretation of the results has limitations due to the very limited numbers of subjects

analyzed and events. There was no trend towards increasing incidence of the primary composite endpoint with increasing severity based on NYHA class in the placebo group in the Japanese subgroup. As examined in Section "7.R.2.2 Efficacy of vericiguat in Japanese patients," the imbalances in patient characteristics between the treatment groups in the Japanese subgroup may have been associated with the above results. It is not appropriate to conclude, based on the above analysis of a small number of patients, that the efficacy of vericiguat is not obtained in Japanese patients with NYHA class III or IV only.

According to the subgroup analysis by baseline NT-proBNP in the overall population of Study 16493, the hazard ratio of the primary composite endpoint for vericiguat vs. placebo was >1 in the highest NT-proBNP quartile. In the Japanese subgroup, the Q2, Q3, and Q4 of baseline NT-proBNP showed a similar trend to that of the overall population. Although the possibility that the efficacy of vericiguat is decreased in the highest NT-proBNP quartile cannot be ruled out, this is inconsistent with the results of analysis by NYHA class in the overall population of Study 16493, i.e., there was no trend towards decreasing efficacy with increasing severity. Thus, it is difficult to say that a consistent relationship was demonstrated between a measure of severity of heart failure and the efficacy of vericiguat. Taking also into account that the cutoff values for NT-proBNP used for the analysis are not considered clinically meaningful, etc., there is no need to restrict the use of vericiguat according to NT-proBNP levels based on this subgroup analysis.

Based on the above, there is no need to restrict the use of vericiguat according to the severity of chronic heart failure based on the results of the above subgroup analysis. However, as there is limited clinical experience with vericiguat in Japanese patients with NYHA class III or IV, it is necessary to collect post-marketing information on patients with NYHA class III or IV treated with vericiguat. A final conclusion on the appropriateness of the above conclusion by PMDA will be made, taking account of comments from the Expert Discussion.

#### 7.R.2.4 Efficacy by underlying etiology of HF

The applicant's explanation about the impact of the underlying etiology of heart failure on the efficacy of vericiguat:

Table 58 shows the results of the primary endpoint by HF etiology in Study 16493.

Table 58. Incidence of the primary composite endpoint by HF etiology (Study 16493, ITT population)

| HF etiology | Placebo | Vericiguat | Hazard ratio[a] [95% CI] |
|---|---|---|---|
| Overall population | | | |
| Ischemic | 40.9 (649/1586) | 38.9 (645/1657) | 0.92 [0.82, 1.02] |
| Non-ischemic | 34.4 (323/938) | 29.0 (252/869) | 0.82 [0.70, 0.97] |
| Japanese subgroup | | | |
| Ischemic | 29.5 (26/88) | 34.7 (33/95) | 1.18 [0.71, 1.98] |
| Non-ischemic | 32.9 (23/70) | 24.2 (16/66) | 0.63 [0.33, 1.20] |

Incidence % (No. of subjects with event/No. of subjects analyzed)

a: Estimated from a Cox proportional hazards model including stratification factors used for randomization, for the overall population.

Estimated from a Cox proportional hazards model not including stratification factors used for randomization, for the Japanese subgroup.

In the overall population, there was no trend towards differences in the efficacy of vericiguat between the HF etiology subgroups. In the Japanese subgroup, interpretation of the results from a small number of subjects in each subgroup has limitations. It is proposed that vericiguat stimulates sGC, independently of and synergistically with NO, to increase the levels of intracellular cGMP, thus improving hemodynamics such as blood pressure lowering and decreasing cardiac afterload. The efficacy of vericiguat should be expected, regardless of HF etiology, from the point of view of the mechanism of action. There was no trend towards differences in safety between the subgroups in the overall population.

PMDA's view:

Based on the subgroup analysis by HF etiology in the overall population of Study 16493, the efficacy of vericiguat is expected in patients with either ischemic or non-ischemic HF etiology. In the Japanese subgroup, the hazard ratio of the primary composite endpoint was <1 in the subgroup of patients with non-ischemic HF etiology, and >1 in the subgroup of patients with ischemic HF etiology. However, the numbers of patients analyzed and events in each subgroup were small, and interpretation of the results has limitations. Taking account of the mechanism of action of vericiguat, differences in efficacy according to HF etiology are unlikely. Given these points, the efficacy of vericiguat as assessed in Section "7.R.2.2 Efficacy of vericiguat in Japanese patients" is expected also in Japanese patients, regardless of HF etiology, as in the overall population.

### 7.R.2.5 Impact of LVEF on the efficacy of vericiguat

The applicant's explanation about the impact of LVEF on the efficacy of vericiguat:

Table 59 shows the results of the primary endpoint by LVEF in Study 16493.

Table 59. Incidence of the primary composite endpoint by LVEF (Study 16493, ITT population)

| LVEF | Placebo | Vericiguat | Hazard ratio[a] [95% CI] |
|---|---|---|---|
| Overall population | | | |
| <30% | 41.3 (529/1280) | 36.8 (445/1210) | 0.84 [0.74, 0.95] |
| ≥30% and <35% | 37.7 (174/461) | 37.3 (192/515) | 1.00 [0.81, 1.23] |
| ≥35% and <40% | 35.5 (148/417) | 31.4 (136/433) | 0.89 [0.70, 1.12] |
| ≥40% and <45% | 32.3 (117/362) | 33.2 (119/358) | 1.05 [0.81, 1.36] |
| Japanese subgroup | | | |
| <30% | 35.0 (21/60) | 31.7 (20/63) | 0.85 [0.46, 1.57] |
| ≥30% and <35% | 24.1 (7/29) | 27.8 (10/36) | 1.20 [0.46, 3.17] |
| ≥35% and <40% | 28.6 (10/35) | 27.8 (10/36) | 0.93 [0.38, 2.24] |
| ≥40% and <45% | 30.3 (10/33) | 34.6 (9/26) | 1.04 [0.42, 2.57] |

Incidence % (No. of subjects with event/No. of subjects analyzed)

a: Estimated from a Cox proportional hazards model including stratification factors used for randomization, for the overall population.
Estimated from a Cox proportional hazards model not including stratification factors used for randomization, for the Japanese subgroup.

In the overall population, the point estimate of the hazard ratio of the primary composite endpoint was >1 in the subgroup of LVEF ≥40% and <45%. Meanwhile, no consistent trend towards decreasing efficacy with higher LVEF was observed among the subgroups of LVEF <40%, and it is unlikely that the efficacy of vericiguat is not expected in the subgroup of LVEF ≥40% and <45% only. In the Japanese subgroup, interpretation of the results from a small number of subjects in each subgroup has limitations, but the Japanese subgroup exhibited no clearly different trend from that of the overall population. There was no trend towards differences in safety among the subgroups in the overall population.

Given the applicant's explanation, PMDA concludes that the efficacy of vericiguat assessed in Section "7.R.2.2 Efficacy of vericiguat in Japanese patients" is expected also in Japanese patients with chronic heart failure with reduced LVEF, regardless of LVEF.

### 7.R.3 Safety

Given the incidences of adverse events in Japanese and foreign clinical studies, the following considerations, and the efficacy of vericiguat shown in Section "7.R.2 Efficacy," PMDA concludes that vericiguat has clinically acceptable safety in patients with chronic heart failure.

#### 7.R.3.1 Differences in safety profile between Japanese and non-Japanese populations in global phase III study

The applicant's explanation about differences in the safety profile of vericiguat between Japanese and non-Japanese populations:

Table 60 shows the incidences of adverse events etc. in the overall population and the Japanese subgroup of Study 16493.

Table 60. Incidences of adverse events etc. (Study 16493[a])

| | Overall population | | Japanese subgroup | |
|---|---|---|---|---|
| | Placebo (N = 2515) | Vericiguat (N = 2519) | Placebo (N = 157) | Vericiguat (N = 161) |
| Adverse events | 81.0 (2036) | 80.5 (2027) | 89.8 (141) | 90.1 (145) |
| Study drug-related adverse events | 11.7 (294) | 14.6 (367) | 5.7 (9) | 8.1 (13) |
| Adverse events leading to death | 3.4 (85) | 3.3 (83) | 0.6 (1) | 2.5 (4) |
| Serious adverse events | 34.8 (876) | 32.8 (826) | 36.3 (57) | 31.7 (51) |
| Adverse events leading to treatment discontinuation | 6.3 (158) | 6.6 (167) | 3.8 (6) | 5.0 (8) |
| Adverse events leading to study drug interruption | 18.3 (460) | 19.2 (484) | 12.7 (20) | 14.9 (24) |
| Adverse events leading to dose reduction | 2.5 (62) | 2.9 (72) | 3.2 (5) | 0.6 (1) |
| | Overall population | | Japanese subgroup | |
| | Placebo (N = 2524) | Vericiguat (N = 2526) | Placebo (N = 158) | Vericiguat (N = 161) |
| Subjects who required a dose interruption at 1 or more visits | 16.4 (403) | 17.0 (419) | 28.2 (44) | 22.4 (36) |
| Subjects who required a dose decrease at 1 or more visits | 7.4 (181) | 8.9 (218) | 14.1 (22) | 13.0 (21) |

Incidence % (n)
a: Adverse events in the safety population and subjects who required a dose interruption or a dose decrease at 1 or more visits in the ITT population (subjects with a record of dose modification assessment in the case report form) are presented.

In the overall population and the Japanese subgroup, there were no major differences in the incidence of adverse events between the treatment groups. The safety profile in the Japanese subgroup was generally similar to that in the overall population, and there should be no clinically relevant differences. In the Japanese subgroup, the incidence of adverse events leading to death tended to be higher in the vericiguat group, but all those events were considered unrelated to study drug. The proportions of subjects who required a dose interruption or a dose decrease at 1 or more visits tended to be higher in the Japanese subgroup than in the overall population, but there were no major differences between the treatment groups. The results of subgroup analyses according to patient characteristics that differed between the overall population and the Japanese subgroup [see Section "7.R.2.2 Efficacy of vericiguat in Japanese patients"] showed no major differences in safety across the subgroups.

PMDA considers that there were no clinically relevant differences in safety profile between the Japanese subgroup and the overall population. Symptomatic hypotension and syncope, which were defined as adverse events of special interest in Study 16493, and anaemia, dyspepsia, nausea, and headache, which were reported at a higher incidence in the vericiguat group than in the placebo group, among adverse events reported by ≥2% of subjects in either group in the overall population, will be assessed in the following sections.

### 7.R.3.2 Hypotension-related events

The applicant's explanation about the risk of hypotension associated with vericiguat:
Since vericiguat lowers blood pressure via vasodilatation, symptomatic hypotension and syncope were defined as adverse events of special interest in Study 16493, and the study excluded patients with SBP <100 mmHg or symptomatic hypotension at randomization. Table 61 shows the incidences of symptomatic hypotension, syncope, hypotension-related adverse events,[11)] and syncope-related adverse events[12)] based on the investigator (sub-investigator)'s assessment in Study 16493.

[11)] MedDRA PTs: hypotension, diastolic hypotension, orthostatic hypotension, blood pressure decreased, blood pressure systolic decreased, blood pressure diastolic decreased, blood pressure ambulatory decreased, blood pressure systolic inspiratory decreased
[12)] MedDRA PTs: syncope, presyncope, loss of consciousness, circulatory collapse

Table 61. Incidences of symptomatic hypotension, syncope, and hypotension- and syncope-related adverse events (Study 16493, Safety population)

| | | Overall population | | Japanese subgroup | |
|---|---|---|---|---|---|
| | | Placebo (N = 2515) | Vericiguat (N = 2519) | Placebo (N = 157) | Vericiguat (N = 161) |
| Symptomatic hypotension | | 7.9 (198) | 9.1 (229) | 3.8 (6) | 5.0 (8) |
| Study drug-related events | | 3.7 (92) | 4.3 (108) | 0.6 (1) | 1.2 (2) |
| Serious events | | 1.5 (37) | 1.2 (30) | 0.6 (1) | 0 (0) |
| Events leading to treatment discontinuation | | 0.8 (20) | 1.1 (27) | 0.6 (1) | 0 (0) |
| Events leading to dose reduction | | 0.6 (16) | 0.8 (19) | 0.6 (1) | 0.6 (1) |
| Events leading to study drug interruption | | 3.0 (75) | 4.0 (102) | 2.5 (4) | 1.9 (3) |
| Severity | Mild | 2.4 (61) | 4.0 (102) | 0.6 (1) | 2.5 (4) |
| | Moderate | 3.8 (95) | 3.7 (93) | 2.5 (4) | 2.5 (4) |
| | Severe | 1.7 (42) | 1.3 (34) | 0.6 (1) | 0 (0) |
| Hypotension-related adverse events | | 14.9 (375) | 16.4 (412) | 10.8 (17) | 8.1 (13) |
| Syncope | | 3.5 (87) | 4.0 (101) | 1.9 (3) | 3.1 (5) |
| Study drug-related events | | 0.4 (11) | 0.3 (7) | 0 (0) | 0.6 (1) |
| Serious events | | 1.3 (33) | 1.7 (43) | 0.6 (1) | 0.6 (1) |
| Events leading to treatment discontinuation | | 0.2 (6) | 0.0 (1) | 0 (0) | 0 (0) |
| Events leading to dose reduction | | 0.0 (1) | 0 (0) | 0 (0) | 0 (0) |
| Events leading to study drug interruption | | 0.5 (12) | 0.7 (17) | 0 (0) | 0 (0) |
| Severity | Mild | 0.8 (19) | 0.9 (22) | 0.6 (1) | 2.5 (4) |
| | Moderate | 1.4 (35) | 1.3 (34) | 0.6 (1) | 0 (0) |
| | Severe | 1.3 (33) | 1.8 (45) | 0.6 (1) | 0.6 (1) |
| Syncope-related adverse events | | 3.8 (95) | 4.4 (111) | 1.9 (3) | 3.1 (5) |

Incidence % (n)

The incidence of symptomatic hypotension was slightly higher in the vericiguat group than in the placebo group, which is considered attributable primarily to a higher incidence of mild events in the vericiguat group. No events leading to death were reported, and there were no major differences in the incidence of serious events or events leading to treatment discontinuation between the treatment groups. As events that may have occurred as a consequence of symptomatic hypotension, falls or fractures[13)] that occurred within 2 days after the onset of symptomatic hypotension were reported by 0.3% of subjects in the placebo group and 0.2% of subjects in the vericiguat group, showing no difference between the treatment groups. With respect to syncope, there were no major differences in the incidence of adverse events or serious adverse events between the treatment groups, and the incidence of adverse events leading to treatment discontinuation was minimal. As events that may have occurred as a consequence of syncope, falls or fractures[13)] that occurred within 2 days after the onset of syncope were reported by 0.6% of subjects in the placebo group and 0.5% of subjects in the vericiguat group, showing no difference between the treatment groups.

The characteristics of patients with hypotension-related adverse events or syncope-related adverse events were compared with the characteristics of patients without those adverse events. No noteworthy patient characteristics were identified in either the overall population or the Japanese subgroup. The incidence of hypotension-related adverse events by concomitant use of ACE inhibitors/ARB, β-blockers, MRA, diuretics

[13)] (1) MedDRA High Level Group Terms (HLGTs): bone and joint injuries, fractures, (2) MedDRA High Level Terms (HLTs): cerebral injuries NEC, (3) MedDRA PTs: fall, back injury, face injury, head injury, limb injury, lip injury, mouth injury, nasal injury, neck injury, oral contusion, tooth fracture, tooth injury

other than MRA, sacubitril/valsartan, or nitrates was assessed. In the overall population, there was a trend towards a higher incidence in the vericiguat group than in the placebo group in the subgroups with concomitant use of all of these medications, but the differences were minimal. There were no major differences between the treatment groups in the subgroup without concomitant use of these medications.

Based on the above, although the incidences of symptomatic hypotension and hypotension-related adverse events were higher in the vericiguat group than in the placebo group in Study 16493, these are expected events based on the mechanism of action of vericiguat, most events were non-serious, and all patients with syncope recovered. Thus, the risks of these events should be acceptable. However, the package insert will include the following precautionary statements: Following administration of vericiguat, symptomatic hypotension may occur in patients at risk of symptomatic hypotension, e.g., decreased blood volume, severe left ventricle outflow tract obstruction, hypotension at rest, autonomic dysregulation, a history of hypotension, and use of antihypertensives or nitrates; If symptomatic hypotension occurs, dose adjustment of diuretics and treatment of other factors such as decreased blood volume should be considered. If such measures do not resolve symptomatic hypotension, dose reduction or interruption of vericiguat should be considered.

PMDA's view:
Given the mechanism of action of vericiguat, hypotension-related symptoms and syncope are expected risks associated with vericiguat. Since the incidences of symptomatic hypotension, syncope, and related adverse events all tended to be higher in the vericiguat group than in the placebo group in Study 16493, attention should be paid to the possible occurrence of hypotension and syncope during treatment with vericiguat. On the other hand, taking account of the seriousness, outcomes, etc., of the events observed in the clinical study, these risks are manageable and clinically acceptable, considering the expected efficacy of vericiguat. Given that up-titration of vericiguat etc. depended on SBP and the absence of symptoms of hypotension in Study 16493, it is necessary to advise that blood pressure should be monitored regularly during treatment with vericiguat to decide dose modifications, and that if an excessive decrease in blood pressure or syncope occurs, appropriate measures should be taken, e.g., dose reduction or discontinuation of vericiguat. Particular care should be taken when using vericiguat in patients with risk factors for hypotension, including patients with SBP <100 mmHg or symptomatic hypotension who were excluded from Study 16493 because decreased blood pressure is more likely to occur. Thus, the applicant's measures (the package insert will advise that vericiguat should be administered with caution, closely monitoring the patient's condition, etc.) are largely appropriate. The safety of vericiguat in combination with nitrates or PDE5 inhibitors will be assessed in Section "7.R.3.5 Concomitant medications." The precautionary statements in the package insert will be finalized, taking also account of comments from the Expert Discussion. It is necessary to collect post-marketing information on the incidence of hypotension-related adverse events, including symptomatic hypotension and syncope.

#### 7.R.3.3 Other adverse events

Focusing on anaemia, dyspepsia, nausea, and headache, which were reported at a higher incidence in the vericiguat group than in the placebo group, among adverse events reported by ≥2% of subjects in either

vericiguat or placebo group, the applicant explained the incidences of anaemia-related adverse events, gastrointestinal disorder-related adverse events, and headache as follows (Table 62).

Table 62. Adverse events reported at a higher incidence in the vericiguat group than in the placebo group (Study 16493, Safety population)

| | Overall population | | Japanese subgroup | |
|---|---|---|---|---|
| | Placebo (N = 2515) | Vericiguat (N = 2519) | Placebo (N = 157) | Vericiguat (N = 161) |
| Anaemia-related adverse events | 7.4 (185) | 9.6 (243) | 7.0 (11) | 7.5 (12) |
| Study drug-related events | 0.1 (1) | 0 (0) | 0 (0) | 0 (0) |
| Serious events | 1.1 (28) | 1.9 (48) | 0.6 (1) | 1.2 (2) |
| Events leading to treatment discontinuation | 0.3 (8) | 0.4 (11) | 0 (0) | 0 (0) |
| Gastrointestinal disorder-related adverse events | 11.2 (281) | 13.0 (327) | 19.1 (30) | 21.7 (35) |
| Study drug-related events | 1.0 (24) | 1.6 (60) | 0 (0) | 1.2 (2) |
| Serious events | 0.4 (10) | 0.5 (12) | 0.6 (1) | 0 (0) |
| Events leading to treatment discontinuation | 0.7 (18) | 1.4 (36) | 0 (0) | 0 (0) |
| Headache | 2.4 (61) | 3.4 (86) | 2.5 (4) | 4.3 (7) |
| Study drug-related events | 0.4 (9) | 0.4 (10) | 0 (0) | 0 (0) |
| Serious events | 0.0 (1) | 0.0 (1) | 0 (0) | 0 (0) |
| Events leading to treatment discontinuation | 0.0 (1) | 0 (0) | 0 (0) | 0 (0) |

Incidence % (n)

For all of anaemia-related adverse events, gastrointestinal disorder-related adverse events, and headache, the treatment difference was small, and most events were non-serious. With respect to anaemia-related laboratory changes, the incidences of "a decrease in hematocrit of 10 percentage points with a value that was below the lower limit of normal" and "a decrease in haemoglobin ≥3.0 g/dL with a value below the lower limit of normal" were slightly higher in the vericiguat group than in the placebo group, and a similar trend was observed. Although the mechanism of development of anaemia associated with vericiguat is not fully understood, cases of anaemia have been reported also with the currently approved sGC stimulator, riociguat. Though the incidences of serious anaemia-related adverse events and anaemia-related adverse events leading to treatment discontinuation were slightly higher in the vericiguat group than in the placebo group, all those events were considered unrelated to study drug. Approximately 80% of serious anaemia-related adverse events did not require dose modification of study drug, and approximately 70% had an outcome of "recovered/resolved or improved." Two-thirds of anaemia-related adverse events leading to treatment discontinuation resolved. Furthermore, among subjects with anaemia-related adverse events, 13 of 28 subjects in the placebo group and 31 of 49 subjects in the vericiguat group had blood transfusions, showing no major difference between the treatment groups. Dyspepsia, nausea, and headache are considered related to the mode of action of vericiguat, and all those events have been reported also with the currently approved sGC stimulator, riociguat. The package insert should list the incidences of these events as other adverse reactions.

PMDA's view:

Gastrointestinal disorder-related adverse events and headache, which were reported at a higher incidence in the vericiguat group than in the placebo group in Study 16493, are expected from the mode of action of vericiguat, and attention should be paid to the possible occurrence of these adverse events. While the specific mechanism of development of anaemia-related adverse events is unknown, such events have been reported also with the currently approved sGC stimulator, riociguat, and a precautionary statement about anaemia is necessary. On the other hand, since most of these adverse events observed in the clinical study were non-serious, and a small number of cases led to study drug discontinuation, these risks are clinically acceptable, considering the expected efficacy of vericiguat. The applicant's measures (the incidences of these adverse events will be listed in the OTHER ADVERSE REACTIONS section of the package insert) are appropriate, but a final conclusion will be made, taking account of comments from the Expert Discussion.

### 7.R.3.4 Use in patients with renal impairment

The applicant's explanation about the use of vericiguat in patients with renal impairment:

Table 63 shows the incidences of adverse events by renal function at baseline in Study 16493. Patients who had an eGFR <15 mL/min/1.73 $m^2$ or chronic dialysis were excluded from Study 16493.

Table 63. Incidences of main adverse events by renal function (Study 16493, Safety population)

| Overall population | | | | | | |
|---|---|---|---|---|---|---|
| Baseline eGFR (mL/min/1.73 $m^2$) | ≤30 | | >30 and ≤60 | | >60 | |
| | Placebo (N = 246) | Vericiguat (N = 259) | Placebo (N = 1064) | Vericiguat (N = 1054) | Placebo (N = 1172) | Vericiguat (N = 1161) |
| Adverse events | 85.4 (210) | 86.5 (224) | 83.5 (888) | 82.8 (873) | 77.8 (912) | 77.3 (897) |
| Study drug-related adverse events | 11.8 (29) | 19.7 (51) | 12.8 (136) | 14.4 (152) | 10.3 (121) | 13.5 (157) |
| Adverse events leading to death | 6.5 (16) | 6.2 (16) | 3.7 (39) | 3.6 (38) | 2.4 (28) | 2.3 (27) |
| Serious adverse events | 47.2 (116) | 42.1 (109) | 39.8 (423) | 36.9 (389) | 27.6 (324) | 27.2 (316) |
| Adverse events leading to dose reduction, Adverse events leading to study drug interruption | 35.8 (88) | 30.1 (78) | 26.3 (280) | 28.8 (304) | 19.3 (226) | 22.1 (257) |
| Adverse events leading to treatment discontinuation | 13.4 (33) | 11.6 (30) | 7.0 (74) | 7.6 (80) | 4.0 (47) | 4.6 (53) |
| Hypotension-related adverse events[a] | 14.6 (36) | 18.9 (49) | 16.9 (180) | 17.7 (187) | 13.0 (152) | 14.6 (170) |
| Symptomatic hypotension[b] | 8.9 (22) | 11.2 (29) | 9.2 (98) | 10.2 (108) | 6.1 (72) | 7.5 (87) |
| Syncope[b] | 4.1 (10) | 4.2 (11) | 3.6 (38) | 4.6 (48) | 3.2 (37) | 3.5 (41) |
| Gastrointestinal disorder-related adverse events[c] | 15.4 (38) | 13.9 (36) | 12.7 (135) | 14.8 (156) | 9.0 (105) | 11.1 (129) |
| Headache | 1.6 (4) | 3.5 (9) | 2.6 (28) | 3.9 (41) | 2.4 (28) | 3.0 (35) |
| Anaemia-related adverse events[d] | 11.8 (29) | 15.1 (39) | 8.9 (95) | 11.5 (121) | 5.2 (61) | 6.9 (80) |
| Japanese subgroup | | | | | | |
| Baseline eGFR (mL/min/1.73 $m^2$) | ≤30 | | >30 and ≤60 | | >60 | |
| | Placebo (N = 22) | Vericiguat (N = 19) | Placebo (N = 82) | Vericiguat (N = 86) | Placebo (N = 53) | Vericiguat (N = 56) |
| Adverse events | 86.4 (19) | 89.5 (17) | 91.5 (75) | 89.5 (77) | 88.7 (47) | 91.1 (51) |
| Study drug-related adverse events | 4.5 (1) | 5.3 (1) | 8.5 (7) | 7.0 (6) | 1.9 (1) | 10.7 (6) |
| Adverse events leading to death | 4.5 (1) | 10.5 (2) | 0 (0) | 2.3 (2) | 0 (0) | 0 (0) |
| Serious adverse events | 36.4 (8) | 47.4 (9) | 40.2 (33) | 32.6 (28) | 30.2 (16) | 25.0 (14) |
| Adverse events leading to dose reduction, Adverse events leading to study drug interruption | 36.4 (8) | 21.1 (4) | 19.5 (16) | 22.1 (19) | 9.4 (5) | 17.9 (10) |
| Adverse events leading to treatment discontinuation | 9.1 (2) | 10.5 (2) | 3.7 (3) | 4.7 (4) | 1.9 (1) | 3.6 (2) |
| Hypotension-related adverse events[a] | 13.6 (3) | 0 (0) | 15.9 (13) | 10.5 (9) | 1.9 (1) | 7.1 (4) |
| Symptomatic hypotension[b] | 9.1 (2) | 0 (0) | 4.9 (4) | 5.8 (5) | 0 (0) | 5.4 (3) |
| Syncope[b] | 0.0 (0) | 5.3 (1) | 1.2 (1) | 2.3 (2) | 3.8 (2) | 3.6 (2) |
| Gastrointestinal disorder-related adverse events[c] | 18.2 (4) | 26.3 (5) | 22.0 (18) | 18.6 (16) | 15.1 (8) | 25.0 (14) |
| Headache | 4.5 (1) | 5.3 (1) | 3.7 (3) | 2.3 (2) | 0 (0) | 7.1 (4) |
| Anaemia-related adverse events[d] | 13.6 (3) | 21.1 (4) | 7.3 (6) | 5.8 (5) | 3.8 (2) | 5.4 (3) |

Incidence % (n)

a: MedDRA PTs: hypotension, diastolic hypotension, orthostatic hypotension, blood pressure decreased, blood pressure systolic decreased, blood pressure diastolic decreased, blood pressure ambulatory decreased, blood pressure systolic inspiratory decreased

b: Determined by the investigator (sub-investigator).

c: MedDRA PTs: diarrhoea, nausea, vomiting, dyspepsia, constipation

d: MedDRA PTs: anaemia, anaemia macrocytic, anaemia of chronic disease, iron deficiency anaemia, microcytic anaemia, autoimmune haemolytic anaemia, blood loss anaemia, haemolytic anaemia, hypochromic anaemia, nephrogenic anaemia, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, pancytopenia, pernicious anaemia, haematocrit decreased, haemoglobin decreased, red blood cell count decreased

In the overall population, the incidences of all adverse events in the vericiguat group tended to increase with decreasing eGFR, but there were no major differences between the treatment groups in all subgroups. A similar

trend was observed also in the Japanese subgroup. In the subgroup with renal impairment with eGFR ≤30 mL/min/1.73 $m^2$, the incidences of hypotension-related adverse events and anaemia-related adverse events were slightly higher in the vericiguat group than in the placebo group. With respect to hypotension-related adverse events, there were no major differences in the incidence of serious or severe events between the treatment groups, and those events resolved/improved with ongoing study therapy or after study drug interruption/discontinuation etc. in approximately 90% of subjects. With respect to anaemia-related adverse events, although serious or severe events were more frequently reported in the vericiguat group, all events were considered unrelated to study drug, and in approximately 70% to 80% of subjects, those events did not require dose modifications and resolved/improved. Thus, these events are clinically acceptable.

Four subjects in the vericiguat group had baseline eGFR <15 mL/min/1.73 $m^2$ (baseline eGFR was 11.0, 12.8, 14.5, and 14.9 mL/min/1.73 $m^2$, respectively). All those subjects died during the study period due to worsening of the primary disease or sepsis after the end of study treatment. The dose was up-titrated to 10 mg in all subjects except for 1 subject who discontinued study drug on Day 16 (on vericiguat 5 mg), and no adverse events leading to dose reduction or hypotension-related adverse events were reported during the study treatment period.

Based on the above, as there were no evident safety concerns in patients with renal impairment with eGFR ≥15 mL/min/1.73 $m^2$, no dose adjustment or precautionary statement in the package insert for these patient populations is necessary at present. On the other hand, patients with eGFR <15 mL/min/1.73 $m^2$ or on dialysis were excluded from Study 16493, and the efficacy and safety of vericiguat in these patients have not been evaluated. Thus, the package insert will advise that a decision to use vericiguat should be made carefully, and that vericiguat should be used with caution, closely monitoring the patient's condition such as blood pressure.

PMDA's view:
A trend towards increasing vericiguat exposure in patients with renal impairment was shown [see Section "6.R.3 Use in patients with renal impairment"]. In addition, in Study 16493, the incidence of adverse events tended to increase with decreasing eGFR in the vericiguat group, but this trend was largely similar to that in the placebo group. Although the incidences of hypotension-related adverse events and anaemia-related adverse events tended to be higher in the vericiguat group than in the placebo group in the eGFR <30 mL/min/1.73 $m^2$ subgroup, given the severity, outcomes, etc. of the observed events, these findings raised no safety concerns that necessitate dose adjustment and a precautionary statement for patients with renal impairment with eGFR ≥15 mL/min/1.73 $m^2$ assessed in the clinical study. On the other hand, as discussed in Section "6.R.3 Use in patients with renal impairment," the extent of increase in vericiguat exposure in patients with eGFR <15 mL/min/1.73 $m^2$ or on dialysis is unclear. Given the following points etc., there is no need to contraindicate vericiguat in these patients.

- There was no trend towards a marked increase in vericiguat exposure in patients with eGFR <15 mL/min/1.73 $m^2$ enrolled in Study 16493, though small in number, and no significant safety concerns related to vericiguat were identified in this patient population.

- Vericiguat is cleared via multiple routes such as metabolism in the kidneys and liver and biliary excretion, in addition to glomerular filtration in the kidneys.
- Vericiguat is started at a low dose and up-titration and dose modification occur, monitoring the patient's condition.
- The tolerability of vericiguat 10 mg once daily (a starting dose of 10 mg) in Japanese healthy adult subjects has been demonstrated [see Section "7.1.1 Japanese phase I study"]

However, as there is very limited clinical experience with vericiguat, a conclusion cannot be reached on the safety of vericiguat in patients with eGFR <15 mL/min/1.73 $m^2$ or on dialysis. A decision to use vericiguat in this patient population should be made carefully, and vericiguat should be used, closely monitoring the patient's condition. It is also necessary to collect post-marketing information on the safety of vericiguat in patients with renal impairment. A final conclusion on the appropriateness of the above conclusion by PMDA will be made, taking account of comments from the Expert Discussion.

### 7.R.3.5 Concomitant medications

#### 7.R.3.5.1 Concomitant use with nitrates or NO donors

Given that coadministration of the currently approved sGC stimulator, riociguat, with nitrates or NO donors (nitroglycerin, amyl nitrite, isosorbide dinitrate, nicorandil, etc.) is contraindicated, PMDA asked the applicant to explain the safety of vericiguat in combination with nitrates or NO donors.

The applicant's explanation:
Nitroglycerin, which is classified as a short-acting nitrate, is commonly used for the symptomatic treatment of coronary artery disease, a common comorbidity in patients with chronic heart failure. Thus, prior to Study 16493, drug interaction studies in non-Japanese healthy adult subjects and patients with stable coronary artery disease (Studies 17115 and 17849) [see Section "6.2.4.6.1 Study in healthy adult subjects" and Section "6.2.4.6.2 Study in patients with stable coronary artery disease"] investigated pharmacodynamic drug interactions and safety/tolerability.

In Study 17115 in healthy adult subjects, when a single oral dose of vericiguat 5 mg was followed 4 hours later by a single sublingual dose of nitroglycerin 0.2 mg, the mean maximum change in SBP was −11.34 mmHg. Following administration of nitroglycerin 0.2 mg alone, the mean maximum change in SBP was −11.72 mmHg. The treatment difference (the least-square mean [90% CI]) was −0.74 [−4.38, 2.89] mmHg, and no clear effect of coadministration was observed.

In Study 17849 in patients with coronary artery disease, when at steady state following multiple oral doses of vericiguat 10 mg, a single dose of nitroglycerin 0.4 mg was administered at 4 hours after administration of vericiguat, the mean maximum change in SBP was −8.9 mmHg. After administration of nitroglycerin alone, the mean maximum change in SBP was −6.0 mmHg. The treatment difference (the least-square mean [90% CI]) was −4.44 [−9.80, 0.91] mmHg, and no clear effect of coadministration was observed. The incidences of adverse events were 91.7% (22 of 24 subjects) after coadministration of vericiguat and nitroglycerin and 91.7%

(11 of 12 subjects) after administration of nitroglycerin alone. Serious adverse events occurred in 2 of 24 subjects (constipation; and symptomatic sinoatrial block) after coadministration of vericiguat and nitroglycerin and 1 of 12 subjects (myocardial infarction) after administration of nitroglycerin alone, but these events were considered unrelated to study drug. Adverse events leading to study drug discontinuation occurred in 1 of 21 subjects (postural dizziness) after coadministration of vericiguat 10 mg and nitroglycerin and 1 of 12 subjects (orthostatic intolerance) after administration of nitroglycerin alone.

Based on the above results, coadministration of sublingual nitroglycerin tablet or sublingual nitroglycerin spray as indicated for angina attacks, was allowed in Study 16493, and the proportions of subjects who used these short-acting nitrates during the study period were 12.9% (319 of 2474 subjects) in the placebo group and 10.8% (269 of 2487 subjects) in the vericiguat group. Coadministration of vericiguat with short-acting nitrates was deemed to be well-tolerated by the investigator in most cases, and none of these subjects were considered intolerant due to symptomatic hypotension or syncope.

In a drug interaction study of vericiguat with long-acting nitrates (isosorbide mononitrate) in patients with stable coronary artery disease (Study 18582), at steady state following multiple doses of isosorbide mononitrate 60 mg, vericiguat was up-titrated from 2.5 to 5 and then to 10 mg, and each was administered for 14 days. When vericiguat was given 1 hour after administration of isosorbide mononitrate on the first and last days of each dose step of vericiguat, the mean maximum change in SBP was −32.2 to −25.7 mmHg. After administration of isosorbide mononitrate alone, the mean maximum change in SBP was −30.2 to −21.0 mmHg. The treatment difference (the least-square mean [90% CI]) was −5.08 [−9.55, −0.61] to −1.41 [−6.65, 3.82] mmHg, and coadministration with vericiguat resulted in greater decreases in blood pressure compared with isosorbide mononitrate alone. However, SBP decreases of 2 to 5 mmHg during coadministration were small, and there was no clear relationship between SBP changes and the dose of vericiguat. Regarding safety, the incidences of adverse events were 92.3% (24 of 26 subjects) following coadministration of vericiguat and isosorbide mononitrate and 66.7% (8 of 12 subjects) following administration of isosorbide mononitrate alone. Following coadministration of vericiguat 2.5 mg and isosorbide mononitrate, 1 subject experienced 2 serious adverse events (acute coronary syndrome and unstable angina), but those events were considered unrelated to study drug. Symptomatic blood pressure decrease with SBP <90 mmHg or symptoms of hypotension were not observed, and coadministration of vericiguat and isosorbide mononitrate was well tolerated. As Study 18582 was conducted in parallel with Study 16493, concurrent use of long-acting nitrates or NO donors was prohibited in Study 16493. However, 96 subjects in the placebo group and 67 subjects in the vericiguat group deviated from the protocol and used long-acting nitrates or NO donors, and the duration of coadministration (median [range]) in the vericiguat group was 109.0 (1-1518) days (25 subjects) for oral isosorbide mononitrate, 3.0 (1-19) days (17 subjects) for nitroglycerin injection, 13.0 (1-790) days (8 subjects) for transdermal nitroglycerin patch, and 36.0 (1-302) days (8 subjects) for oral isosorbide dinitrate, etc. Table 64 shows the incidences of adverse events by concomitant use of long-acting nitrates or NO donors in Study 16493. There were no differences in the incidences of symptomatic hypotension/syncope or other adverse events between the vericiguat and placebo groups across these subgroups, and no clear differences between the subgroups with and without concomitant long-acting nitrates or NO donors were observed.

Table 64. Incidences of adverse events by concomitant use of long-acting nitrates or NO donors (Study 16493, Safety population)

| | With concomitant medications | | Without concomitant medications | |
|---|---|---|---|---|
| | Placebo (N = 96) | Vericiguat (N = 67) | Placebo (N = 2419) | Vericiguat (N = 2452) |
| Adverse events | 93.8 (90) | 95.5 (64) | 80.4 (1946) | 80.1 (1963) |
| Study drug-related adverse events | 14.6 (14) | 11.9 (8) | 11.6 (280) | 14.6 (359) |
| Serious adverse events | 53.1 (51) | 55.2 (37) | 34.1 (825) | 32.2 (789) |
| Adverse events leading to dose reduction, Adverse events leading to study drug interruption | 26.0 (25) | 31.3 (21) | 24.0 (581) | 25.8 (632) |
| Adverse events leading to treatment discontinuation | 6.3 (6) | 9.0 (6) | 6.3 (152) | 6.6 (161) |
| Symptomatic hypotension/Syncope | 17.7 (17) | 16.4 (11) | 10.3 (250) | 12.3 (301) |
| Symptomatic hypotension | 14.6 (14) | 10.4 (7) | 7.6 (184) | 9.1 (222) |
| Syncope | 5.2 (5) | 6.0 (4) | 3.4 (82) | 4.0 (97) |

Incidence % (n)

In the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD), the use of nitrates of approximately 23% was reported (*J Cardiol*. 2013; 62: 95-101). It is envisaged that chronic heart failure patients with ischemic etiology may need a nitrate or NO donor temporarily or for a certain period of time for concurrent angina, and it is important to offer an option of nitrates/NO donors to be coadministered with vericiguat.

Based on the above, both vericiguat and nitrates/NO donors lower blood pressure, and the package insert should appropriately advise that symptomatic hypotension may occur when coadministered with nitrates, and that there is limited clinical experience with coadministration of vericiguat with long-acting nitrates. Meanwhile, as no serious risk associated with coadministration of vericiguat with nitrates or NO donors has been identified at present, there is no need to contraindicate coadministration.

PMDA's view:

As to short-acting nitrates, the decreases in blood pressure during coadministration were not necessarily large in Studies 17115 and 17849, and Study 16493 raised no particular safety concerns about coadministration. As to long-acting nitrates, given that the decreases in blood pressure during coadministration were not necessarily large in Study 18582, and that symptomatic blood pressure decrease with SBP <90 mmHg or symptoms of hypotension were not observed etc., there were no clear tolerability issues following coadministration with vericiguat within the scope investigated. In addition, taking also into account that Study 16493 suggested no particular safety concerns about coadministration of vericiguat with long-acting nitrates or NO donors, and that nitrates have been used for the treatment of comorbidity in patients with chronic heart failure in clinical practice, coadministration with long-acting nitrates or NO donors should not be contraindicated at present. However, since the enhanced blood pressure lowering effect is expected from the standpoint of mode of action, and there is limited clinical experience with chronic coadministration of vericiguat with long-acting nitrates or NO donors in patients with chronic heart failure, etc., the package insert should advise the following: Vericiguat should be administered with caution when coadministered with nitrates; The need for coadministration should

be determined carefully; As discussed in Section "7.R.3.2 Hypotension-related events," vericiguat should be coadministered with nitrates carefully, continuously monitoring blood pressure and the patient's condition. It is also necessary to collect post-marketing information on the safety of vericiguat when coadministered with nitrates or NO donors. A final conclusion on the appropriateness of the above conclusion by PMDA will be made, taking also account of comments from the Expert Discussion.

#### 7.R.3.5.2 Concomitant use with PDE5 inhibitors

Given that concomitant administration of the currently approved sGC stimulator, riociguat, with PDE5 inhibitors (sildenafil, vardenafil hydrochloride hydrate, tadalafil) is contraindicated, PMDA asked the applicant to explain the safety of vericiguat in combination with PDE5 inhibitors.

The applicant's explanation:

In a drug interaction study of vericiguat with a PDE5 inhibitor, sildenafil, in non-Japanese healthy adult subjects, Study 17743 [see Section "6.2.4.8 Drug interaction study with sildenafil"], single doses of 25, 50, and 100 mg of sildenafil were administered at steady state following multiple doses of vericiguat 10 mg. The mean maximum change in SBP was −15.8 to −9.5 mmHg. Following administration of sildenafil alone, the mean maximum change in SBP was −11.0 to −10.2 mmHg. The treatment differences (the least-square mean [90% CI]) were −4.8021 [−8.0878, −1.5164], −0.5991 [−3.3596, 2.1614], and −5.3642 [−9.3076, −1.4209] mmHg, respectively, and coadministration with vericiguat resulted in greater decreases in SBP, compared with sildenafil alone. The incidences of adverse events were 100% (16 of 16 subjects) after coadministration of vericiguat and sildenafil and 43.8% (7 of 16 subjects) after administration of sildenafil alone, and no serious adverse events were reported. Following coadministration of vericiguat and sildenafil, the incidences of headache and head discomfort were high, but those events were generally mild in severity. Two subjects experienced adverse events associated with a decrease in SBP following coadministration of vericiguat and sildenafil 25 mg. One of them had syncope (blood pressure at the time of onset, 87/60 mmHg), and the other subject had headache (blood pressure at the time of onset, 85/46 mmHg), and both events were considered related to study drug. Although concurrent use of PDE5 inhibitors was prohibited in Study 16493, 6 subjects in the placebo group and 2 subjects in the vericiguat group deviated from the protocol and used PDE5 inhibitors. The 2 subjects in the vericiguat group (sildenafil 50 mg/day for 81 days in 1 subject, sildenafil 25 mg/day for 63 days in the other subject) did not experience symptomatic hypotension or syncope during coadministration. The DPC data[14)] were reviewed to describe the use of PDE5 inhibitors in patients with heart failure in Japan, and 0.07% to 0.26% of the patients used tadalafil or sildenafil for the treatment of either pulmonary arterial hypertension or impaired urination associated with prostatic hyperplasia.

Based on the above, both vericiguat and PDE5 inhibitors lower blood pressure, and the package insert should advise that the blood pressure lowering effect of vericiguat may be enhanced when coadministered with PDE5 inhibitors. Meanwhile, as no serious risk associated with coadministration of vericiguat with PDE5 inhibitors

[14)] Diagnosis Procedure Combination/Per-Diem Payment System. Period covered: January to December 2019 (the final data update date: July 28, 2020), hospitals covered: 399 hospitals (hospitals that provided data throughout the period covered), target disease (ICD-10): I50 heart failure, the number of patients with the target disease: 898319 patients

has been identified at present, there is no need to contraindicate coadministration of vericiguat with PDE5 inhibitors.

PMDA's view:
The decreases in blood pressure during coadministration in Study 17743 were similar to those during coadministration with long-acting nitrates. This is unlikely to become a clinically relevant problem, though comparison between the different studies has limitations [see Section "7.R.3.5.1 Concomitant use with nitrates or NO donors"]. There were no clear tolerability issues following coadministration with PDE5 inhibitors within the scope investigated in Study 16493. Thus, there is no need to contraindicate coadministration of vericiguat with PDE5 inhibitors at present. However, the enhanced blood pressure lowering effect is expected from the standpoint of mode of action, there is very limited clinical experience with coadministration of vericiguat and PDE5 inhibitors in Study 16493, and a special situation where patients with chronic heart failure need concomitant PDE5 inhibitors is unlikely to occur. Given these points etc., the package insert should advise that vericiguat should be coadministered with PDE5 inhibitors only if considered necessary for therapeutic reasons after carefully balancing the expected therapeutic benefits with the possible risks. A final conclusion on the appropriateness of the above conclusion by PMDA will be made, taking account of comments from the Expert Discussion.

### 7.R.4 Indication and target population

The applicant's explanation about the indication and target population for vericiguat:
Study 16493 in patients with chronic heart failure with LVEF <45% on standard HF therapy demonstrated the efficacy and safety of vericiguat. Since no data evaluating the efficacy and safety of vericiguat in patients with chronic heart failure with preserved LVEF are available in the present application, the target population for vericiguat should be patients with chronic heart failure as those included in Study 16493. Based on the above, the indication statement of "Chronic heart failure (only in patients who are receiving standard treatment for chronic heart failure)" was proposed, and then in order to define the preferred population to be treated with vericiguat, the PRECAUTIONS CONCERNING INDICATION section will advise that eligible patients must be selected by physicians with a full understanding of the characteristics (left ventricular ejection fraction) of patients enrolled in the clinical study.

With regard to the use of vericiguat in patients with chronic heart failure with preserved LVEF, PMDA asked the applicant to explain whether a precaution or information should be provided, taking account of the results of a clinical study of vericiguat in patients with chronic heart failure with preserved LVEF.

The applicant's explanation:
A 24-week treatment period and a 4-week safety follow-up period were included in Study 19334, a global phase IIb study in patients with chronic heart failure with preserved LVEF. The incidences of all-cause mortality were 2.7% (7 of 262 subjects) in the placebo group, 5.7% (15 of 263 subjects) in the vericiguat 10 mg group, and 3.8% (10 of 264 subjects) in the vericiguat 15 mg group. Although the incidence of all-cause mortality was higher for vericiguat compared with placebo, no dose-dependency was observed. Patients with

chronic heart failure with preserved LVEF are known to be a diverse population with many comorbidities that influence the risk of death. Based on registry data, "older age, NYHA class Ⅲ/Ⅳ status, aortic stenosis, peripheral artery disease, atrial fibrillation, and chronic kidney disease" have been reported as predictors for mortality in patients with chronic heart failure with preserved LVEF (*Eur J Heart Fail*. 2017; 19: 1574-85). Although most of the subjects who died in Study 19334 had at least 1 of these predictors, there were no major differences in subject characteristics including disease characteristics and the frequency of comorbidities among the treatment groups. Since the duration of Study 19334 was short, and a small number of subjects were evaluated in Study 19334, the available information for evaluating the efficacy and safety of vericiguat in patients with chronic heart failure with preserved LVEF is limited at present, and comprehensive evaluation of the death cases and the currently available findings on vericiguat do not identify a causal relationship between vericiguat and an increased risk of death in patients with chronic heart failure with preserved LVEF. Taking also into account that the preferred population to be treated with vericiguat is patients with chronic heart failure with reduced LVEF, there is no need to provide a further precaution based on LVEF or information on the results of Study 19334.

PMDA's view:
Study 16493, which was used as the principal evidence for the efficacy and safety of vericiguat in the present application, demonstrated the efficacy of vericiguat when added to standard of care in patients with chronic heart failure with reduced LVEF, and its safety was also considered clinically acceptable [see Section "7.R.2 Efficacy" and Section "7.R.3 Safety"]. PMDA has to say that the efficacy and safety of vericiguat in patients with chronic heart failure with preserved LVEF are unknown because no confirmatory study that is large enough to appropriately evaluate the usefulness of vericiguat has been conducted. Based on the above, in order to define the preferred population to be treated with vericiguat at present, the following statements should be included in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections, and then the information on the results of Study 19334 in patients with chronic heart failure with preserved LVEF should be provided using information materials for healthcare professionals. The appropriate population for vericiguat, the indication, the specific statements in the PRECAUTIONS CONCERNING INDICATION section etc., will be finalized, taking account of comments from the Expert Discussion.

**Indication**
Chronic heart failure (only in patients who are receiving standard treatment for chronic heart failure)

**Precautions Concerning Indication**

- The efficacy and safety of vericiguat in patients with chronic heart failure with preserved left ventricular ejection fraction have not been established. Vericiguat should be used in patients with chronic heart failure with reduced left ventricular ejection fraction.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the characteristics (prior treatment, left ventricular ejection fraction, systolic blood pressure, etc.) of patients enrolled in the clinical study.

### 7.R.5 Dosage and administration

The applicant's explanation about dosing rationale for vericiguat:

A global phase II study in patients with chronic heart failure with reduced LVEF on standard HF therapy (Study 15371) was conducted to evaluate 4 dosing regimens of vericiguat (the vericiguat 1.25, 2.5, 5, and 10 mg groups) for pharmacodynamics, safety, etc. Vericiguat 2.5 mg appeared to be the minimally effective dose and did not result in a decrease in blood pressure in healthy adult subjects. Thus, in the vericiguat 5 mg and 10 mg groups, a starting dose of 2.5 mg was to be titrated at 2-week intervals to a target dose of 5 or 10 mg, dependent on SBP and clinical symptoms. There was a trend towards a dose-dependent reduction of NT-proBNP (log-transformed value), which is used as a biomarker for severity of HF in a clinical setting, and the greatest reduction in NT-proBNP was seen in the vericiguat 10 mg group (Table 37). A similar trend was observed also for the exploratory endpoint of the proportion of subjects with a composite event of CV death or HF hospitalization (Table 38). Regarding safety, the incidence of events suspected of hypotension[15)] was 4.4% to 6.7% in the placebo group and the vericiguat groups other than the 10 mg group, in contrast to 15.4% in the vericiguat 10 mg group. The incidence of syncope (MedDRA PT) was 0% to 2.2% in the placebo group and the vericiguat groups other than the 10 mg group, in contrast to 4.4% (4 of 91 subjects) in the vericiguat 10 mg group. Though the incidences of both events were high in the vericiguat 10 mg group, given a causal relationship to study drug, severity, outcome, etc., vericiguat was well tolerated in the vericiguat 10 mg group, and 71.8% of subjects in the vericiguat 10 mg group reached the target dose by Week 12. Based on these results, a titration regimen starting with 2.5 mg vericiguat followed by 2 dose doublings in 2-week intervals to reach the 10-mg target dose, dependent on mean sitting SBP and the symptoms of hypotension before intake of the dose, was selected for Study 16493 (Table 45).

For participation of Japan in Study 15371, it was concluded that the same dosing regimen can be selected for Japanese and non-Japanese subjects in Study 15371, from the safety standpoint, because the dosing regimen of 1/8 to 1/4 of 10 mg (vericiguat 10 mg was well tolerated in healthy adult subjects including Japanese subjects) as a starting dose and up-titration, dependent on SBP and clinical symptoms, was planned, etc., though vericiguat exposure was higher in Japanese subjects than in non-Japanese subjects in a phase I study in healthy adult subjects. Although the study showed no clear dose-response relationship for change in NT-proBNP (log-transformed value) in the Japanese subgroup, interpretation of the results is difficult due to the limited number of subjects in each treatment group. However, regarding safety, there were no major differences in the incidence of adverse events between the vericiguat and placebo groups, and the proportion of subjects who reached the target dose by Week 12 in the vericiguat 10 mg group was 62.5%, which was similar to that in the overall population. Thus, it was concluded that the same dosing regimen can be selected for Japanese and non-Japanese patients in Study 16493.

In Study 16493, the proportion of subjects who reached the 10-mg target dose in the vericiguat group was 81.9%, and the proportion of subjects who reached the 10-mg dose by Week 8 and stayed on the 10-mg dose for at least 80% of the treatment period was 61.6%. Also in the Japanese subgroup, the proportion of subjects

[15)] MedDRA Low Level Terms (LLTs): symptomatic hypotension, hypotensive episode, hypotension, orthostatic hypotension, asymptomatic hypotension

who reached the 10-mg target dose (83.9%) and the proportion of subjects who reached the 10-mg dose by Week 8 and stayed on the 10-mg dose for at least 80% of the treatment period (63.4%) were similar to those in the overall population. Vericiguat was well tolerated throughout the titration phase and the chronic maintenance phase [see Section "7.R.3 Safety"]. Based on the above, in Study 16493, titration of vericiguat up to the target maintenance dose of 10 mg was performed based on each subject's blood pressure and tolerability, and then the efficacy and safety of vericiguat were demonstrated. Also in the Japanese subgroup, the distribution of doses, efficacy, and safety of vericiguat similar to those in the overall population were demonstrated. Thus, the proposed dosing regimen using the same starting dose, target dose, rate of up-titration, and titration interval as those in Study 16493, is appropriate.

PMDA's view:

The starting dose, target dose, and method of up-titration to the target dose of vericiguat for Study 16493 were selected based on the results of a dose-finding study, Study 15371. In Study 16493, ≥60% of subjects were up-titrated to the target dose based on SBP etc. and stayed on the target dose, and the efficacy and safety of vericiguat were demonstrated [see Section "7.3.1 Global phase III study"]. As discussed in Section "6.R.2 PK differences between Japanese and non-Japanese populations," differences in the PK of vericiguat between Japanese and non-Japanese populations were suggested, and it is difficult to say that Study 15371 found the optimal dose for the Japanese subgroup. Meanwhile, given that the proportion of subjects who reached the target dose in the Japanese subgroup of Study 16493 was similar to that in the overall population, and based on the efficacy and safety results [see Section "7.3.1 Global phase III study"], it is appropriate to select the starting dose, target dose, and method of up-titration to the target dose of vericiguat proposed by the applicant, also for the Japanese population. However, as up-titration and dose modification occurred, according to the patient's condition such as SBP in Study 16493, the package insert should advise that up-titration and dose modification should occur according to the patient's condition such as SBP. Based on Section "6.R.1 Food effect" and the considerations in this section, the dosage and administration statement should be as shown below, and then the dose modification guidance used in the clinical study should be presented in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section. A final conclusion will be made, taking account of comments from the Expert Discussion.

**Dosage and Administration**

The usual adult starting dose is 2.5 mg of vericiguat administered orally once daily with food. The dose should be doubled every 2 weeks to 5 mg, and then to 10 mg. The dose should be decreased as appropriate according to blood pressure and the patient's condition.

### 7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing investigations of vericiguat:

Taking account of the mechanism of action of vericiguat and the incidence of symptomatic hypotension in Study 16493, "symptomatic hypotension" will be listed in the safety specification in the risk management plan (draft), and post-marketing surveillance to determine the incidence of hypotension-related events including symptomatic hypotension, the patient characteristic factors, etc., in clinical practice will be conducted.

PMDA's view:

The applicant's policy (post-marketing surveillance to determine the incidence of hypotension-related events, etc. in clinical practice will be conducted) is appropriate. As the information concerning the safety of vericiguat in patients with NYHA class Ⅲ or IV heart failure, patients with hepatic impairment, and patients with severe renal impairment, and the safety of vericiguat in combination with long-acting nitrates or NO donors is limited, etc., safety information from these patient groups, etc. should also be collected via the planned post-marketing surveillance. Taking account of the above, the objectives, the sample size, and the observation period of this surveillance should be determined. In accordance with "Risk Management Plan Guidance" (PFSB/SD Notification No.0411-1 and PFSB/ELD Notification No.0411-2 dated April 11, 2012), the details of post-marketing surveillance, including identification of safety specification, the appropriateness of risk classification, and the appropriateness of pharmacovigilance activities and risk minimization activities, will be finalized, taking account of comments from the Expert Discussion.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that vericiguat has efficacy in the treatment of chronic heart failure and acceptable safety in view of its benefits. Vericiguat is a sGC stimulator, and it is meaningful to make vericiguat available in clinical practice because it offers a treatment option with a novel mode of action for chronic heart failure. PMDA considers that the indication, dosage and administration, the precautionary statements in the package insert, post-marketing investigations, etc., should be further discussed.

PMDA has concluded that vericiguat may be approved if vericiguat is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

February 3, 2021

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Verquvo Tablets 2.5 mg, Verquvo Tablets 5 mg, Verquvo Tablets 10 mg |
| **Non-proprietary Name** | Vericiguat |
| **Applicant** | Bayer Yakuhin, Ltd. |
| **Date of Application** | June 5, 2020 |

**List of Abbreviations**

See Appendix.

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

### 1.1 Efficacy

As for efficacy in a global phase III study in patients with chronic heart failure with reduced LVEF (Study 16493), the expert advisors made the following comment:

> The lower bound of the 95% confidence interval for the hazard ratio of the primary composite endpoint for vericiguat versus placebo (0.82) was above the point estimate of the hazard ratio assumed when the study was planned (0.8). It is therefore difficult to consider that the study demonstrated robust efficacy as expected.

However, in the end, the expert advisors supported the following PMDA's conclusion:

> Vericiguat significantly reduced primary endpoint events compared with placebo, and these results are considered clinically meaningful [see Section "7.R.2.1 Results of efficacy assessment" in the Review Report (1)]. There was a trend towards lower risk of both CV death and all-cause mortality, which are considered clinically important, in the vericiguat group than in the placebo group [Review Report (1) Table 47]. Overall, the study showed that vericiguat can offer clinically meaningful efficacy, including efficacy against endpoints other than the primary endpoint, in patients with chronic heart failure with reduced LVEF.

In the Japanese subgroup of Study 16493, the incidence of "CV death" was higher in the vericiguat group than in the placebo group. The expert advisors made the following comment:

The number of patients was not sufficient to assess the consistency of the incidence of each component of the primary composite endpoint. That being said, according to a breakdown of CV deaths in the Japanese subgroup [Review Report (1) Table 54], the vericiguat group had more deaths of unknown cause than the placebo group, and such cases may include sudden cardiac deaths related to vericiguat. Thus, the following points should also be discussed, and then the applicant should be able to explain that vericiguat does not increase CV death.

- A causal relationship to vericiguat, taking account of the clinical courses of Japanese patients with CV death
- Despite the fact that vericiguat causes vasodilation, decreases in blood pressure are small. If this mechanism involves the compensatory activation of the sympathetic nervous system, the associated proarrhythmic effect may cause sudden cardiac death.
- Differences in patient characteristics between the Japanese subgroup and the overall population (e.g. the Japanese subgroup had a lower rate of ICD and were using lower doses of β-blockers) may have affected the between-group difference in sudden cardiac death in the Japanese subgroup.

PMDA asked the applicant to explain CV death associated with vericiguat.

The applicant's explanation:

As to the pro-arrhythmic risk of vericiguat, (a) the safety pharmacology studies showed that the $IC_{50}$ for the hERG current inhibition was 553 times the blood concentration (unbound) at the maximum clinical dose of vericiguat in humans, and (b) no ECG abnormalities were observed *in vivo* at a dose resulting in exposure approximately ≤26 times the blood concentration (unbound) at the maximum clinical dose of vericiguat. Thus, there are no concerns about the pro-arrhythmic effect of vericiguat in clinical use. In clinical studies in healthy subjects, patients with stable coronary artery disease, and patients with chronic heart failure with reduced LVEF, there was no clinically meaningful prolongation of QTc interval or vericiguat-related adverse effect on ventricular repolarization. Table 65 shows the incidences of ventricular tachycardia and ventricular fibrillation in Studies 15371 and 16493. There was no trend towards a higher incidence of ventricular arrythmia-related adverse events in the vericiguat group, suggesting no pro-arrhythmic effect of vericiguat.

Table 65. Incidences of ventricular tachycardia and ventricular fibrillation in Studies 15371 and 16493

| | Study 15371 | | | | | Study 16493 | |
|---|---|---|---|---|---|---|---|
| | Placebo (N = 92) | Vericiguat 1.25 mg (N = 91) | Vericiguat 2.5 mg (N = 90) | Vericiguat 5 mg (N = 91) | Vericiguat 10 mg (N = 91) | Placebo (N = 2515) | Vericiguat 10 mg (N = 2519) |
| Ventricular tachycardia | 2.2 (2) | 3.3 (3) | 0 (0) | 2.2 (2) | 2.2 (2) | 2.4 (60) | 1.7 (42) |
| Ventricular fibrillation | 0 (0) | 0 (0) | 0 (0) | 1.1 (1) | 0 (0) | 0.5 (12) | 0.5 (13) |

Incidence % (n)

Among 39 subjects resulting in CV death in the Japanese subgroup of Study 16493 (11 in the placebo group, 28 in the vericiguat group), 13 subjects had CV death within 14 days after the last dose of study drug (4 in the placebo group, 9 in the vericiguat group), and their relationship to study drug could not be ruled out, given temporal association. The detailed clinical courses of these 13 subjects were reviewed. CV death occurred

between Days 18 and 693 in the placebo group and between Days 65 and 749 in the vericiguat group, showing no imbalance between the treatment groups. The causes of CV deaths in the vericiguat group (MedDRA PTs) were cardiac failure (4 subjects); and pneumonia,[16)] acute cardiac failure, congestive cardiomyopathy, ventricular tachycardia, and death (1 subject each). Details of the clinical course in the subjects with acute cardiac failure and death were unknown. The deaths in the remaining 7 subjects were considered unrelated to vericiguat by the investigators. Among these events, ventricular tachycardia in the vericiguat group was classified as "sudden cardiac death," and congestive cardiac failure in the placebo group and acute cardiac failure, congestive cardiomyopathy, and death in the vericiguat group were classified as "death of unknown cause"; all of these cases may be sudden cardiac death, but none of the subjects had a history of ventricular tachycardia or ventricular fibrillation or experienced such events during the study period. In the 4 subjects in the vericiguat group, there was no relationship between the occurrence of events and blood pressure/heart rate/β-blockers over time during the study period, and there was no prolongation of QTcF interval.

Table 66 shows the incidences of the primary composite endpoint and its components by use of ICD in the overall population and the Japanese subgroup in Study 16493. In the overall population of subjects without ICD, the incidences of sudden cardiac death and death of unknown cause among CV deaths were similar in the vericiguat and placebo groups. In the Japanese subgroup, 9 deaths of unknown cause occurred in subjects without ICD in the vericiguat group; this number is larger than those in the placebo group and the subgroup with ICD. Six of the 9 subjects died ≥15 days after the last dose of study drug, and therefore their deaths are unlikely to be related to vericiguat. In the subjects who died within 14 days after the last dose of study drug, neither ventricular tachycardia nor ventricular fibrillation occurred during the study period. No information on ICD intervention was collected.

[16)] The patient was hospitalized on Day 720. A chest X-ray revealed pulmonary congestion, pleural effusion, and pneumonia, and was diagnosed with heart failure and pneumonia. Despite continued treatment of both diseases, the patient died on Day 743. While the investigator diagnosed that the final cause of death was pneumonia, Clinical Events Committee adjudicated the case as CV death (heart failure).

Table 66. Incidences of the primary composite endpoint and its components by use of ICD (Study 16493, ITT population)

| Overall population | | | Placebo | Vericiguat | Hazard ratio[a] [95% CI] |
|---|---|---|---|---|---|
| ICD use | Yes | Primary composite endpoint | 46.7 (328/703) | 40.8 (284/696) | 0.85 [0.72, 0.99] |
| | | CV death[c] | 23.2 (163/703) | 16.7 (116/696) | 0.69 [0.55, 0.88] |
| | | HF | 13.8 (97/703) | 8.8 (61/696) | － |
| | | Sudden cardiac death | 4.1 (29/703) | 2.3 (16/696) | － |
| | | Unknown cause of death | 3.7 (26/703) | 4.5 (31/696) | － |
| | | HF hospitalization | 37.1 (261/703) | 36.1 (251/696) | 0.94 [0.79, 1.12] |
| | No | Primary composite endpoint | 35.4 (643/1816) | 33.4 (610/1825) | 0.92 [0.82, 1.03] |
| | | CV death[c] | 15.3 (277/1816) | 16.2 (295/1825) | 1.06 [0.90, 1.24] |
| | | HF | 5.1 (93/1816) | 5.5 (101/1825) | － |
| | | Sudden cardiac death | 4.6 (84/1816) | 5.0 (91/1825) | － |
| | | Unknown cause of death | 4.1 (75/1816) | 4.4 (81/1825) | － |
| | | HF hospitalization | 26.7 (485/1816) | 23.9 (437/1825) | 0.87 [0.77, 1.00] |
| Japanese subgroup | | | Placebo | Vericiguat | Hazard ratio[b] [95% CI] |
| ICD use | Yes | Primary composite endpoint | 37.5 (9/24) | 31.0 (9/29) | 0.76 [0.30, 1.91] |
| | | CV death[c] | 8.3 (2/24) | 13.8 (4/29) | 1.10 [0.19, 6.31] |
| | | HF | 4.2 (1/24) | 10.3 (3/29) | － |
| | | Sudden cardiac death | 4.2 (1/24) | 3.4 (1/29) | － |
| | | HF hospitalization | 33.3 (8/24) | 27.6 (8/29) | 0.77 [0.29, 2.06] |
| | No | Primary composite endpoint | 29.9 (40/134) | 30.3 (40/132) | 0.97 [0.63, 1.50] |
| | | CV death[c] | 6.7 (9/134) | 14.4 (19/132) | 2.18 [0.99, 4.82] |
| | | HF | 4.5 (6/134) | 7.6 (10/132) | － |
| | | Sudden cardiac death | 0.7 (1/134) | 0 (0/132) | － |
| | | Unknown cause of death | 0.7 (1/134) | 6.8 (9/132) | － |
| | | HF hospitalization | 26.9 (36/134) | 22.7 (30/132) | 0.82 [0.50, 1,33] |

Incidence % (No. of subjects with event/No. of subjects analyzed), －: Not calculated
a: Estimated from a Cox proportional hazards model including stratification factors used for randomization.
b: Estimated from a Cox proportional hazards model not including stratification factors used for randomization.
c: Among CV deaths, HF, sudden cardiac death, and unknown cause of death are listed.

There are differences in the types of available β-blockers between Japan and other countries and in the recommended target doses between the Japanese guideline and the ESC guidelines 2016. Therefore, in subjects treated with β-blockers in Study 16493, the use of β-blockers was analyzed based on a percentage of the targe dose of the drug (% target dose) recommended by the Japanese guideline or the ESC guidelines 2016 for managing heart failure.[17)] As shown in Table 67, there were no differences in the distribution of % target dose between the Japanese and non-Japanese populations. Table 68 shows the incidences of the primary composite endpoint and its components by % target dose of β-blockers. In the subgroup without the use of β-blockers, the point estimates of the hazard ratios of the primary composite endpoint and CV death for vericiguat versus placebo were >1, but their 95% confidence intervals included 1. Compared with the subgroups with a higher % target dose, the subgroup without the use of β-blockers and the subgroup with >0% and ≤25% target dose showed a higher incidence of events in subjects receiving placebo. In both subgroups, baseline NT-proBNP (median) tended to be high, suggesting the possibility that the subgroup with a lower % target dose included more patients with severe and treatment-resistant HF.

17) The following were analyzed for the overall population: β-blockers (bisoprolol, bisoprolol fumarate, carvedilol, metoprolol acetate, nebivolol, nebivolol hydrochloride) and the target doses recommended by the ESC guidelines 2016. The following were analyzed for the Japanese subgroup: β-blockers (bisoprolol, bisoprolol fumarate, carvedilol) and the target doses recommended by the Japanese guideline. Patients were excluded from the analysis if they were taking 2 β-blockers at baseline or if they were taking the same drugs under different labels (e.g. the drug name/unit) unless the drugs were considered obviously identical. The subgroup with >100% target dose was excluded from assessment because the results could not be interpreted due to the small number of patients, and because the objective of using a dose higher than the target dose was unclear.

Table 67. Distribution of % target dose in subjects treated with β-blockers (Study 16493, ITT population)

| % target dose of β-blockers | Overall population | | Japanese subgroup | |
|---|---|---|---|---|
| | Placebo (N = 1929) | Vericiguat (N = 1924) | Placebo (N = 141) | Vericiguat (N = 148) |
| >0% and ≤25% | 48.2 (929) | 48.0 (923) | 48.9 (69) | 44.6 (66) |
| >25% and ≤50% | 30.8 (594) | 32.0 (616) | 27.7 (39) | 35.1 (52) |
| >50% and ≤100% | 19.5 (377) | 18.4 (354) | 20.6 (29) | 19.6 (29) |
| >100% | 1.5 (29) | 1.6 (31) | 2.8 (4) | 0.7 (1) |

Proportion of subjects % (n)

Table 68. Incidences of the primary composite endpoint and its components by % target dose of β-blockers (Study 16493, ITT population)

| Overall population | | Placebo | Vericiguat | Hazard ratio[a] [95% CI] |
|---|---|---|---|---|
| 0% (No use) | Primary composite endpoint | 41.8 (74/177) | 44.2 (76/172) | 1.07 [0.77, 1.48] |
| | CV death[c] | 21.5 (38/177) | 27.9 (48/172) | 1.42 [0.92, 2.19] |
| | HF | 11.3 (20/177) | 14.0 (24/172) | — |
| | Sudden cardiac death | 5.1 (9/177) | 7.0 (12/172) | — |
| | Unknown cause of death | 3.4 (6/177) | 5.2 (9/172) | — |
| | HF hospitalization | 32.8 (58/177) | 31.4 (54/172) | 0.93 [0.63, 1.36] |
| >0% and ≤25% | Primary composite endpoint | 42.0 (390/929) | 41.0 (378/923) | 0.97 [0.84, 1.12] |
| | CV death[c] | 20.1 (187/929) | 20.3 (187/923) | 0.99 [0.81, 1.22] |
| | HF | 9.1 (85/929) | 8.8 (81/923) | — |
| | Sudden cardiac death | 5.0 (46/929) | 4.8 (44/923) | — |
| | Unknown cause of death | 4.2 (39/929) | 5.3 (49/923) | — |
| | HF hospitalization | 32.5 (302/929) | 31.0 (286/923) | 0.95 [0.81, 1.12] |
| >25% and ≤50% | Primary composite endpoint | 36.0 (214/594) | 29.2 (180/616) | 0.78 [0.64, 0.95] |
| | CV death[c] | 14.8 (88/594) | 11.2 (69/616) | 0.76 [0.55, 1.04] |
| | HF | 5.9 (35/594) | 3.9 (24/616) | — |
| | Sudden cardiac death | 4.7 (28/594) | 3.6 (22/616) | — |
| | Unknown cause of death | 3.2 (19/594) | 3.2 (20/616) | — |
| | HF hospitalization | 27.4 (163/594) | 23.4 (144/616) | 0.81 [0.65, 1.02] |
| >50% and ≤100% | Primary composite endpoint | 38.7 (146/377) | 28.0 (99/354) | 0.64 [0.50, 0.83] |
| | CV death[c] | 17.5 (66/377) | 11.0 (39/354) | 0.58 [0.39, 0.87] |
| | HF | 6.1 (23/377) | 3.4 (12/354) | — |
| | Sudden cardiac death | 4.8 (18/377) | 1.7 (6/354) | — |
| | Unknown cause of death | 5.6 (21/377) | 4.8 (17/354) | — |
| | HF hospitalization | 29.2 (110/377) | 22.6 (80/354) | 0.69 [0.51, 0.92] |
| Japanese subgroup | | Placebo | Vericiguat | Hazard ratio[b] [95%CI] |
| 0% (No use) | Primary composite endpoint | 33.3 (4/12) | 42.9 (3/7) | 1.71 [0.38, 7.73] |
| | CV death[c] | 16.7 (2/12) | 42.9 (3/7) | 3.72 [0.61, 22.74] |
| | HF | 8.3 (1/12) | 28.6 (2/7) | — |
| | Unknown cause of death | 0 (0/12) | 14.3 (1/7) | — |
| | HF hospitalization | 25.0 (3/12) | 14.3 (1/7) | 0.66 [0.07, 6.31] |
| >0% and ≤25% | Primary composite endpoint | 36.2 (25/69) | 34.8 (23/66) | 0.96 [0.54, 1.68] |
| | CV death[c] | 10.1 (7/69) | 18.2 (12/66) | 1.91 [0.75, 4.84] |
| | HF | 5.8 (4/69) | 12.1 (8/66) | — |
| | Unknown cause of death | 1.4 (1/69) | 4.5 (3/66) | — |
| | HF hospitalization | 30.4 (21/69) | 27.3 (18/66) | 0.89 [0.48, 1.68] |
| >25% and ≤50% | Primary composite endpoint | 20.5 (8/39) | 26.9 (14/52) | 1.34 [0.56, 3.20] |
| | CV death[c] | 2.6 (1/39) | 5.8 (3/52) | 2.24 [0.23, 21.57] |
| | HF | 2.6 (1/39) | 1.9 (1/52) | — |
| | Unknown cause of death | 0 (0/39) | 3.8 (2/52) | — |
| | HF hospitalization | 20.5 (8/39) | 23.1 (12/52) | 1.15 [0.47, 2.82] |
| >50% and ≤100% | Primary composite endpoint | 27.6 (8/29) | 27.6 (8/29) | 0.87 [0.32, 2.33] |
| | CV death[c] | 3.4 (1/29) | 13.8 (4/29) | 3.64 [0.40, 32.73] |
| | HF | 3.4 (1/29) | 6.9 (2/29) | — |
| | Unknown cause of death | 0 (0/29) | 6.9 (2/29) | — |
| | HF hospitalization | 27.6 (8/29) | 24.1 (7/29) | 0.76 [0.27, 2.11] |

Incidence % (No. of subjects with event/No. of subjects analyzed), —: Not calculated

a: Estimated from a Cox proportional hazards model including stratification factors used for randomization.

b: Estimated from a Cox proportional hazards model not including stratification factors used for randomization.

c: Among CV deaths, HF, sudden cardiac death, and death of unknown cause are listed.

Based on the above, the use of ICD probably did not affect sudden cardiac death or death of unknown cause. There was a trend towards decreasing efficacy of vericiguat in the subgroup with a lower % target dose of β-blockers, but the distribution of % target dose of the drugs recommended in the region was similar in the Japanese and non-Japanese subgroups. Increased sudden cardiac deaths in the Japanese subgroup was unlikely to be due to differences in the proportion of subjects who had an ICD or in the distribution of the doses of β-blockers between Japan and other countries.

Based on the above discussion, vericiguat is unlikely to increase sudden cardiac death via its pro-arrhythmic effect in Japanese patients. Further, the results of the primary composite endpoint in the Japanese subgroup were consistent with those in the overall population. Thus, the expert advisors finally supported PMDA's conclusion that the efficacy of vericiguat is expected also in Japanese patients.

The document-based compliance inspection revealed deficiencies in evidential documents from a foreign study site participating in Study 16493. PMDA instructed the applicant to submit the results of sensitivity analysis conducted after excluding the data from the study site [see Section "2.1 PMDA’s conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment"]. PMDA confirmed that the analysis results were not clearly different from the results in the ITT population (Table 47 in the Review Report (1)) (Table 69). PMDA concluded that there were no major problems with evaluating the efficacy of vericiguat based on data from the ITT population of Study 16493.

Table 69. Incidences of clinical efficacy events
(Study 16493, A population excluding data from 1 study site where deficiencies in evidential documents were found)

| | Placebo (N = 2520) | Vericiguat (N = 2522) | Hazard ratio[a] [95% CI] |
|---|---|---|---|
| CV death or HF hospitalization (first event) | 38.5 (970) | 35.6 (897) | 0.90 [0.82, 0.99] |
| CV death | 17.5 (440) | 16.4 (414) | 0.93 [0.81, 1.06] |
| HF hospitalization (first event) | 29.6 (745) | 27.4 (691) | 0.90 [0.82, 1.00] |
| All-cause mortality | 21.2 (533) | 20.3 (512) | 0.95 [0.84, 1.07] |

Incidence % (n)
a: Estimated from a Cox proportional hazards model including stratification factors used for randomization.

## 1.2 Safety

### 1.2.1 Hypotension-related adverse events

PMDA's conclusions:

The incidences of hypotension and syncope in Study 16493 are clinically acceptable, considering the expected efficacy of vericiguat. The package insert should include the following precautionary statements and information:

- Vericiguat should be used with caution in patients with risk factors for hypotension, and their condition should be closely monitored.
- Blood pressure should be monitored regularly, and the dose should be adjusted according to the patient's condition such as blood pressure.
- Actions that should be taken when decreased blood pressure, etc. occurs.

The applicant should collect post-marketing information on the incidence of hypotension-related adverse events, and other data.

The expert advisors supported the above conclusions by PMDA.

### 1.2.2 Other adverse events

PMDA's conclusion:

The incidences of anaemia-related adverse events, gastrointestinal disorder-related adverse events, and headache in Study 16493 are clinically acceptable, considering the expected efficacy of vericiguat. At present, the incidences of these adverse events should be listed in the OTHER ADVERSE REACTIONS section of the package insert.

The expert advisors supported the above conclusion by PMDA.

### 1.2.3 Use in patients with renal impairment

PMDA's conclusions:

Given the incidence of adverse events by eGFR in Study 16493, dose adjustment and a precautionary statement for patients with renal impairment with eGFR ≥15 mL/min/1.73 $m^2$ are unnecessary. Patients with eGFR <15 mL/min/1.73 $m^2$ or on dialysis should not be excluded from treatment with vericiguat, given the pharmacokinetic profile, dosing regimen, and tolerated dose range of vericiguat, etc. The package insert should state that vericiguat exposure may be increased in patients with renal impairment, and that a decision to use vericiguat in patients with eGFR <15 mL/min/1.73 $m^2$ or on dialysis should be made carefully. The applicant should collect post-marketing information on the safety of vericiguat in patients with renal impairment.

The expert advisors supported the above conclusions by PMDA.

### 1.2.4 Use in patients with hepatic impairment

PMDA's conclusions:

Given the incidence of adverse events by hepatic function in Study 16493, dose adjustment and a precautionary statement for patients with mild or moderate hepatic impairment are unnecessary. Patients with severe hepatic impairment should not be excluded from treatment with vericiguat, given the pharmacokinetic profile, dosing regimen, and tolerated dose range of vericiguat, etc. The package insert should advise that a decision to use vericiguat in patients with severe hepatic impairment should be made carefully. The applicant should collect post-marketing information on the safety of vericiguat in patients with hepatic impairment.

The expert advisors supported the above conclusions by PMDA.

### 1.2.5 Concomitant medications

PMDA's conclusion:

When vericiguat is administered with nitrates/NO donors or PDE5 inhibitors, its blood pressure-lowering effect is expected to be enhanced in view of their mechanisms of action, and there is limited clinical experience with coadministration of vericiguat with these drugs. Thus, the package insert should state that vericiguat should be used with caution when co-administered with these drugs. The applicant should collect post-marketing information on the safety of vericiguat coadministered with these drugs.

The expert advisors supported the above conclusion by PMDA.

## 1.3 Indication and target population

PMDA's conclusion:

Since vericiguat offers a treatment option with a novel mode of action, it is meaningful to make vericiguat available as an add-on treatment to patients with chronic heart failure with reduced LVEF who are receiving standard treatment mainly with RAAS inhibitors or β-blockers in the clinical practice in Japan.

The expert advisors supported the above conclusion by PMDA.

PMDA's conclusion:

In the global phase II study in patients with chronic heart failure with preserved LVEF (Study 19334), all-cause deaths occurred more frequently in the vericiguat group than in the placebo group [see Section "7.2.2 Global phase II study" in the Review Report (1)]. PMDA has to say that the efficacy and safety of vericiguat in these patients are unknown. In order to define the population eligible for vericiguat therapy at present, the following statements should be used for INDICATION and PRECAUTIONS CONCERNING INDICATION. The results of Study 19334 in patients with chronic heart failure with preserved LVEF should be disseminated through information materials for healthcare professionals.

The expert advisors supported the above conclusion by PMDA.

**Indication**

Chronic heart failure (only in patients who are receiving standard treatment for chronic heart failure)

**Precautions Concerning Indication**

- The efficacy and safety of vericiguat in patients with chronic heart failure with preserved left ventricular ejection fraction have not been established. Vericiguat should be used in patients with chronic heart failure with reduced left ventricular ejection fraction.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the characteristics (prior treatment, left ventricular ejection fraction, systolic blood pressure, etc.) of patients enrolled in the clinical study.

### 1.4 Dosage and administration

PMDA's conclusion:

The starting dose, target dose, method of up-titration to the target dose of vericiguat, and the dose modification guidance for Study 16493 were selected based on the results of Study 15371, a dose-finding study. Based on the distribution of doses and the efficacy and safety results in Study 16493, the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections.

The expert advisors supported the above conclusion by PMDA.

**Dosage and Administration**

The usual adult starting dose is 2.5 mg of vericiguat administered orally once daily with food. The dose should be doubled every 2 weeks to 5 mg, and then to 10 mg. The dose should be decreased as appropriate according to the patient's condition such as blood pressure.

**Precautions Concerning Dosage and Administration**

Monitor blood pressure regularly, and apply the following dose modification guidance used in the clinical study.

Dose modification guidance used in clinical study

| Systolic blood pressure (mmHg)/symptoms of hypotension | Dose modification |
|---|---|
| Systolic blood pressure ≥100 mmHg | · If currently on 2.5 or 5 mg, increase the dose by 1 step.<br>· If currently on 10 mg, maintain the dose. |
| Systolic blood pressure ≥90 and <100 mmHg | Maintain the dose. |
| Systolic blood pressure <90 mmHg without symptoms of hypotension | · If currently on 2.5 mg, interrupt treatment.<br>· If currently on 5 or 10 mg, decrease the dose by 1 step. |
| Systolic blood pressure <90 mmHg with symptoms of hypotension | Interrupt treatment. |

### 1.5 Risk management plan (draft)

Based on the discussion in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for vericiguat should include the safety specification presented in Table 70, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 71 and a specified use-results survey presented in Table 72.

Table 70. Safety and efficacy specifications in the risk management plan (draft)

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| · Hypotension | · Concomitant use with nitrates or NO donors<br>· Concomitant use with PDE5 inhibitors | · Safety of vericiguat in patients with renal impairment<br>· Safety of vericiguat in patients with hepatic impairment<br>· Safety of vericiguat in patients with blood pressure <100 mmHg or symptomatic hypotension |
| Efficacy specification | | |
| None | | |

Table 71. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| · Early post-marketing phase vigilance<br>· Specified use-results survey | · Disseminate data gathered during early post-marketing phase vigilance<br>· Prepare and distribute information materials to healthcare professionals (Guide for healthcare professionals prescribing Verquvo Tablets)<br>· Prepare and distribute information materials to patients (Guide for patients taking Verquvo Tablets) |

Table 72. Outline of specified use-results survey (draft)

| | |
|---|---|
| Objective | To assess the safety etc. of vericiguat in clinical practice. |
| Survey method | Central registry system |
| Population | Patients with chronic heart failure treated with vericiguat |
| Observation period | 2 years |
| Planned sample size | 600 patients in the safety analysis population |
| Main survey items | The incidence of hypotension, patient characteristics (NYHA class, renal function, hepatic function, blood pressure, etc.), use of drugs for chronic heart failure, HF events (CV death, HF hospitalization, etc.), etc. |

## 2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The inspection revealed the following findings:

The sponsor knew deficiencies in evidential documents (e.g., falsification of the document concerning subject eligibility review, forged signature, and lack of implementation of the Attributable-Legible-Contemporaneous-Original-Accurate (ALCOA) principles) prepared in 1 study site (CTD 5.3.5.1.5). The sponsor, however, did not assess how the exclusion of data from the study site would affect the evaluation of vericiguat.

Since these deficiencies may affect the reliability of data from the study site, PMDA concluded that prior to PMDA's review, the sponsor must take the following actions to assure the robustness of the analysis results:

(a) Access the medical records at the study site and check the consistency between the records and the evidential data.

(b) Assess the impact of the deficiencies in the evidential documents on the analysis results presented in the clinical study report.

## 2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.5) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug substance is classified as a powerful drug. The drug product is not classified as a poisonous drug or a powerful drug.

**Indication**

Chronic heart failure (only in patients who are receiving standard treatment for chronic heart failure)

**Dosage and Administration**

The usual adult starting dose is 2.5 mg of vericiguat administered orally once daily with food. The dose should be doubled every 2 weeks to 5 mg, and then to 10 mg. The dose should be decreased as appropriate according to the patient's condition such as blood pressure.

**Approval Condition**

The applicant is required to develop and appropriately implement a risk management plan.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| ACE | Angiotensin converting enzyme |
| ADP | Adenosine diphosphate |
| ALBI | Albumin-bilirubin |
| ALCOA | Attributable-Legible-Contemporaneous-Original-Accurate |
| ALT | Alanine aminotransferase |
| ANP | Atrial natriuretic peptide |
| ARB | Angiotensin II receptor blocker |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| $AUC_{0-\infty}$ | Area under the concentration-time curve from zero to infinity |
| $AUC_{0-\infty,norm}$ | Area under the concentration-time curve from zero to infinity divided by dose per kg body weight |
| $AUC_{0-t}$ | Area under the concentration-time curve from zero to time t |
| $AUC_{\tau}$ | Area under the concentration-time curve for the actual dosing interval |
| BA | Bioavailability |
| BCRP | Breast cancer resistance protein |
| BE | Bioequivalence |
| BE guideline for different dosage form strengths | Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000. The guideline was amended by PFSB/ELD Notification No. 0319-1 dated March 19, 2020) |
| BE Guideline for Formulation Changes | Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No.67 dated February 14, 2000. The guideline was amended by PFSB/ELD Notification No. 0319-1 dated March 19, 2020) |
| BMI | Body mass index |
| BNP | Brain (B-type) natriuretic peptide |
| BSEP | Bile salt export pump |
| cGMP | Cyclic guanosine monophosphate |
| CHO | Chinese hamster ovary |
| CI | Confidence interval |
| CL | Total body clearance |
| $CL_{CR}$ | Creatinine clearance |
| $CL_R$ | Renal clearance |
| CL/F | Apparent total body clearance |
| $C_{max}$ | Maximum plasma concentration |
| $C_{max,norm}$ | Maximum plasma concentration divided by dose per kg body weight |
| $C_{max,ss}$ | Maximum plasma concentration at steady state |
| $C_{trough}$ | Trough concentration |
| CNGA2 | Cyclic nucleotide-gated channel alfa 2 |
| CPP | Critical process parameter |
| CQA | Critical quality attribute |
| CYP | Cytochrome P450 |
| DBP | Diastolic blood pressure |
| DEA/NO | Diethylamine/nitric oxide complex |
| DMSO | Dimethyl sulfoxide |
| +dP/dt | First derivative of ventricular pressure (left ventricular contractility) |
| $+dP/dt_{max}$ | Maximal first derivative of left ventricular pressure |
| $EC_{50}$ | Median/half maximum effective concentration |
| eGFR | Estimated glomerular filtration rate |

| | |
|---|---|
| ESC | European Society of Cardiology |
| ESC guidelines 2016 | ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2016 (*Eur Heart J*. 2016; 37: 2129-200) |
| FAS | Full analysis set |
| GC | Gas chromatography |
| GC-A | Receptor guanylyl cyclase GC-A |
| GC-B | Receptor guanylyl cyclase GC-B |
| GTP | Guanosine triphosphate |
| HEK | Human embryonic kidney |
| hERG | human ether-à go-go related gene |
| HPLC | High performance liquid chromatography |
| $IC_{20}$ | 20% inhibitory concentration |
| $IC_{50}$ | Half maximal inhibitory concentration |
| ICD | Implantable cardioverter defibrillator |
| ICH Q1E guideline | Guideline on Evaluation for Stability Data (PFSB/ELD Notification No. 0603004 dated June 3, 2003) |
| IR | Infrared absorption spectrum |
| ITT | Intention-to-treat |
| Japanese guideline | Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure (JCS 2017/JHFS 2017) |
| $k_a$ | Absorption rate constant |
| KCCQ PLS | Kansas City Cardiomyopathy Questionnaire, Physical limitation score |
| LC-MS/MS | Liquid chromatography coupled with tandem mass spectrometry |
| LLC-PK1 | Lewis lung carcinoma pork kidney cell line |
| L-NAME | NG-nitro-L-arginine methyl ester |
| LVEF | Left ventricular ejection fraction |
| LVDP | Left ventricular developed pressure |
| LVEDP | Left ventricular end-diastolic pressure |
| MATE | Multidrug and toxic compound |
| MDCK | Madin Darby canine kidney cell line |
| MedDRA PT | MedDRA Preferred Term |
| moxifloxacin | moxifloxacin hydrochloride |
| MRA | Mineralocorticoid receptor antagonist |
| mRNA | Messenger ribonucleic acid |
| NEC | Not Elsewhere Classified |
| NMR | Nuclear magnetic resonance spectrum |
| NO | Nitric oxide |
| NT-proBNP | N-terminal pro-B type natriuretic peptide |
| NYHA | New York Heart Association |
| NZW | New Zealand White |
| OAT | Organic anion transporter |
| OATP | Organic anion transporting polypeptide |
| OCT | Organic cation transporter |
| ODQ | 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one |
| $P_{app}$ | Apparent permeability coefficient |
| PBPK | Physiologically-based pharmacokinetics |
| PBS | Phosphate buffered saline |
| PDE | Phosphodiesterase |
| PE | Polyethylene |
| P-gp | P-glycoprotein |
| PK | Pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PPi | Pyrophosphoric acid |

| | |
|---|---|
| PPK | Population pharmacokinetics |
| PPS | Per protocol set |
| PTZ | Pentylenetetrazol |
| PVC | Polyvinyl chloride |
| PVDC | Polyvinylidene chloride |
| QbD | Quality by design |
| QTc | Corrected QT interval |
| QTcF | Fridericia-corrected QT Interval |
| RAAS | Renin-angiotensin-aldosterone system |
| RAS | Renin-angiotensin system |
| sacubitril/valsartan | sacubitril valsartan sodium hydrate |
| SBP | Systolic blood pressure |
| SCHH | Sandwich-cultured human hepatocytes |
| SD | Sprague-Dawley |
| SDS-PAGE | Sodium dodecyl sulfate-polyacrylamide gel electrophoresis |
| Ser | Serine |
| sGC | Soluble guanylate/guanylyl cyclase |
| sildenafil | sildenafil citrate |
| SNAP | S-nitroso-N-acetyl-D,L-penicillamine |
| SNP | Sodium nitroprussid |
| $SVO_2$ | Oxygen saturation in the coronary sinus |
| $t_{1/2}$ | Elimination half-life |
| $t_{max}$ | Time of maximum plasma concentration |
| TRAP-6 | Thrombin receptor activator Peptide 6 |
| $TXA_2$ | Thromboxane $A_2$ |
| UGT | Uridine diphosphate glucuronosyltransferase |
| UV-A | Ultraviolet A |
| UV/VIS | Ultraviolet/visible spectrum |
| VASP | Vasodilator-stimulated phosphoprotein |
| $V_{ss}$ | Volume of distribution at steady state |
| V/F | Apparent volume of distribution |
| Vz/F | Apparent volume of distribution during terminal phase |
| warfarin | warfarin potassium |