Report on the Deliberation Results

June 4, 2020

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

Brand Name	Vafseo Tablets 150 mg Vafseo Tablets 300 mg
Non-proprietary Name	Vadadustat (JAN*)
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	July 8, 2019

Results of Deliberation

In its meeting held on May 29, 2020, the First Committee on New Drugs concluded that the product may be approved 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, and the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

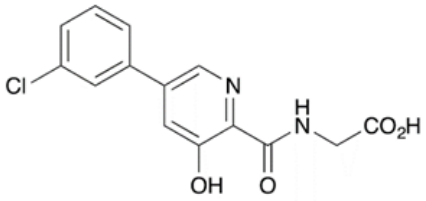
Review Report

May 18, 2020
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	Vafseo Tablets 150 mg Vafseo Tablets 300 mg
Non-proprietary Name	Vadadustat
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	July 8, 2019
Dosage Form/Strength	Each film-coated tablet contains 150 or 300 mg of vadadustat.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{14}H_{11}ClN_2O_4$

Molecular weight: 306.70

Chemical name: [5-(3-Chlorophenyl)-3-hydroxypyridine-2-carboxamido]acetic acid

Items Warranting Special Mention	None
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with renal anemia, 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.

Indication

Renal anemia

Dosage and Administration

The usual starting dose for adults is 300 mg of vadadustat orally administered once daily. The subsequent dose may be adjusted according to the patient's condition. The maximum dose should not exceed 600 mg.

Approval Condition

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

Attachment

Review Report (1)

April 8, 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	Vafseo Tablets 150 mg Vafseo Tablets 300 mg
Non-proprietary Name	Vadadustat
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	July 8, 2019
Dosage Form/Strength	Each film-coated tablet contains 150 or 300 mg of vadadustat.
Proposed Indication	Renal anemia

Proposed Dosage and Administration

The usual starting dose for adults is 300 mg of vadadustat orally administered once daily. The subsequent dose may be adjusted according to the course and severity of anemia. The maximum dose should not exceed 600 mg.

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List of Abbreviations

See Appendix.

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

Renal anemia is caused by decreased production of erythropoietin (EPO) due to renal impairment and gives rise to cardiac load associated with shortness of breath, palpitation, fatigability, anorexia, and cardiac output increased. In the drug treatment of renal anemia, erythropoiesis-stimulating agent (ESA)[1)] is mainly used, but all of these are injections and have been reported to cause anti-EPO antibody positive pure red-cell aplasia ("2015 JSDT Guideline for Renal Anemia in Chronic Kidney Disease" edited by the Japanese Society for Dialysis Therapy).

Vafseo is an oral preparation containing the active pharmaceutical ingredient of vadadustat discovered by Akebia Therapeutics, Inc. and inhibits hypoxia inducible factor (HIF)-prolyl hydroxylase (PH). HIF is a transcription factor consisting of 2 subunits (HIF-α and HIF-β) and activated in a hypoxic environment to induce adaptive responses to the hypoxic condition by enhancing erythropoiesis. In a normoxic environment, on the other hand, HIF-α is hydroxylated by HIF-PH and degraded by proteasomes (*Mol Cell.* 2008;30:393-402, *Cell Death Differ.* 2008;15:635-41, etc.). Because vadadustat inhibits HIF-PH and thereby activates the HIF pathway to increase EPO production, which can enhance erythropoiesis, it was expected to be effective in the treatment of renal anemia and thus has been developed as the therapeutic drug.

The applicant has submitted a marketing application for vadadustat, claiming that the efficacy and safety were demonstrated in Japanese clinical studies in patients with renal anemia.

As of February 2020, vadadustat has not been approved in foreign countries.

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 solid. The general properties of the drug substance, including description, solubility, hygroscopicity, thermal analysis, dissociation constant, and partition coefficient, have been determined. Although the drug substance at the development stage was found in 4 crystal forms ([redacted], [redacted], [redacted], and [redacted]), only [redacted] has been obtained at the commercial production scale.

Its chemical structure has been elucidated by elemental analysis, mass spectrometry (MS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectrum (NMR) (^{1}H-NMR, ^{13}C-NMR), ultraviolet-visible spectroscopy (UV/VIS), and single crystal X-ray diffractometry.

2.1.2 Manufacturing process

The drug substance is synthesized from the starting materials of [redacted].

1) Recombinant human erythropoietin (rHuEPO), darbepoetin alfa (genetical recombination) (DA), and continuous erythropoietin receptor activator (CERA)

For the drug substance, critical quality attributes (CQAs) were identified, and material attributes and process parameters affecting the CQAs were investigated. Based on the investigation results, the control strategy has been constructed (Table 1).

Table 1. Outline of control strategy of drug substance

CQA	Control method
[redacted]	[redacted]

The critical step [redacted]. In addition, [redacted] and a mixture of [redacted] and [redacted] are controlled as the critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR, high performance liquid chromatography [HPLC]), purity (elemental impurities [inductively coupled plasma-mass spectrometry (ICP-MS)], related substances [HPLC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, crystal forms, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows main stability studies conducted on the drug substance. The photostability testing has shown that the drug substance is photostable.

Table 2. Main stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 pilot-scale batches	25°C	60%RH	(double-layered) polyethylene bag + polyethylene drum	18 months
Accelerated testing	3 pilot-scale batches	40°C	75%RH		6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when stored at room temperature in the double-layered polyethylene bags placed in a polyethylene drum, in accordance with the Guideline on Evaluation of Stability Data (International council for harmonisation of technical requirements for pharmaceuticals for human use [ICH] Q1E guideline). Long-term testing will be continued for [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet each containing 150 or 300 mg of the drug substance. The drug product contains microcrystalline cellulose, sodium starch glycolate, hypromellose, light anhydrous silicic acid, magnesium stearate, and Opadry II White (150 mg tablets only) or Opadry II Yellow (300 mg tablets only) as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through the process comprised of [redacted], tableting, coating, storage, and package/labeling/testing/storage.

For the drug product, CQAs were identified, and material attributes and process parameters affecting the CQAs were investigated. Based on the investigation results, the control strategy has been constructed (Table 3).

Table 3. Outline of control strategy of drug product

CQA	Control method
[redacted]	[redacted]

The critical step [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows main stability studies conducted on the drug product. The long-term and accelerated testing [redacted]. The photostability testing has shown that the drug product is photostable.

Table 4. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	2 pilot-scale batches, 1 small-scale batch	25°C	60%RH	Polyvinyl chloride film/aluminum foil + aluminum-laminated bag + carton	18 months
Accelerated testing	2 pilot-scale batches, 1 small-scale batch	40°C	75%RH		6 months

Based on the above, a shelf life of 30 months has been proposed for the drug product when filled in a polyvinyl chloride film/aluminum foil sheet, packaged in an aluminum-polyethylene-laminated bag in

a carton and stored at room temperature, in accordance with the ICH Q1E guideline. Long-term testing will be continued for [redacted] 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 drug product is adequately controlled.

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

In primary pharmacodynamic studies, HIF-PH inhibition, EPO production induction, and erythropoiesis enhancement in rats were investigated. In secondary pharmacodynamic studies, the effects on enzymes other than HIF-PH and pulmonary arterial pressure were investigated. The effects on the central nervous system, cardiovascular system, respiratory system, and renal and urinary system were investigated in safety pharmacology studies. Unless otherwise specified, vehicles used in *in vivo* studies were 25% dimethyl sulfoxide (DMSO) and 1% methylcellulose for mice, a solution containing 0.25% hydroxypropylmethylcellulose and 0.1% polysorbate 80 for rats, and 1% methylcellulose for dogs.

3.1 Primary pharmacodynamics

3.1.1 HIF-PH inhibition

3.1.1.1 *In vitro* inhibition against human HIF-PH (Common technical document [CTD] 4.2.1.1-1 and 4.2.1.1-2, Studies AKB-6548-NC-[redacted] and AKB-6548-NC-[redacted])

Inhibition of vadadustat against human recombinant prolyl hydroxylase domain enzyme (PHD) 1, PHD2, and PHD3 was investigated. The half maximal inhibitory concentration (IC_{50}) values of vadadustat against human PHD1, PHD2, and PHD3 were 15.4, 11.8, and 7.6 nmol/L, respectively. Vadadustat inhibited all PHDs to a similar extent. In addition, inhibition of the *O*-glucuronate conjugate, a metabolite of vadadustat against human PHD2, was investigated, and the IC_{50} value was 2.31 μmol/L (approximately 1/200 inhibition of vadadustat).

3.1.2 EPO production induction

3.1.2.1 *In vitro* EPO production induction (CTD 4.2.1.1-3, Study [redacted]04989)

Hep3B cells, human hepatoma cell line, were incubated with vadadustat at 3 to 30 μmol/L to measure HIF-1α and HIF-2α protein amounts as well as vascular endothelial growth factor (VEGF) concentration. In addition, EPO concentrations were also measured after incubation with vadadustat at 0.1 to 100 μmol/L. Vadadustat increased the HIF-1α and HIF-2α protein amounts, and EPO concentration in a concentration-dependent manner. Vadadustat, on the other hand, did not affect the VEGF concentration.

3.1.2.2 EPO production induction in mice (CTD 4.2.1.1-4, Study [redacted]-0302)

Vadadustat at 30, 90, or 270 mg/kg was orally administered 3 times daily to male mice for 4 days, and blood EPO concentrations were measured. The blood EPO concentrations (mean ± standard deviation [SD]) at 2 hours after the last dose of the 4-day treatment in the vehicle control group, and the vadadustat 30, 90, and 270 mg/kg groups were below the detection limit (94 pg/mL), 125 ± 152, 175 ±

152, and 1,461 ± 968 pg/mL, respectively. Vadadustat tended to increase the blood EPO concentration in a dose-dependent manner.

3.1.2.3 EPO production induction in rats (CTD 4.2.1.1-10, Study 6901491)

A single dose of 30 or 90 mg/kg of vadadustat was orally administered to male rats, and blood EPO concentrations were measured. The blood EPO concentrations (mean ± SD) at 6 hours after the administration were 50 ± 8 pg/mL in the vehicle control group, 265 ± 37 pg/mL in the vadadustat 30 mg/kg group, and 9,265 ± 2,086 pg/mL in the vadadustat 90 mg/kg group. Vadadustat tended to increase the blood EPO concentration in a dose-dependent manner.

3.1.3 Erythropoiesis enhancement

3.1.3.1 Erythropoiesis enhancement in mice (CTD 4.2.1.1-4 and 4.2.1.1-5, Studies [redacted]-0302 and [redacted]-0446)

Vadadustat at 30, 90, or 270 mg/kg was orally administered 3 times daily to male mice for 4 days, and a reticulocyte percentage after the last dose was measured. Although no clear effect of vadadustat was observed in comparison between the vadadustat 30 or 90 mg/kg group and vehicle control group, the percentage in the vadadustat 270 mg/kg group was higher than that in the vehicle control group at any timepoint with the highest value found at 8 hours after the last dose (Table 5). In addition, the reticulocyte percentage did not clearly differ between different 4-day vadadustat regimens in which the dose of 270 mg/kg was administered as 1 dose, 2 divided doses (twice daily), or 3 divided doses (3 times daily).

Table 5. Reticulocyte percentage after 4-day treatment in mice

Dose		Reticulocyte percentage		
		2 hours after last dose	8 hours after last dose	24 hours after last dose
Vehicle control		1.13 ± 0.57	1.30 ± 0.26	1.85 ± 0.21
Vadadustat (mg/kg)	30	1.82 ± 0.66	1.15 ± 0.49	2.38 ± 0.75
	90	1.86 ± 0.31	1.80 ± 0.12	1.72 ± 0.37
	270	3.45 ± 1.34	5.55 ± 0.49	4.67 ± 0.81

n = 2 to 6, mean ± SD

3.1.3.2 Erythropoiesis enhancement in rats (CTD 4.2.1.1-10, Study 6901491)

Vadadustat at 30 or 90 mg/kg was orally administered once daily to male rats for 2 weeks, and erythrocyte count, reticulocyte percentage, and hemoglobin (Hb) and hematocrit (Hct) values after the last dose were measured. Values on all the parameters were higher in the vadadustat 90 mg/kg group than in the vehicle control group (Table 6).

Table 6. Erythrocyte count, reticulocyte count, and Hb and Hct values after 2 weeks of treatment in rats

Dose		Erythrocyte count (10^6/μL)	Reticulocyte count (10^9/μL)	Hb value (g/dL)	Hct value (%)
Vehicle control		7.5 ± 0.2	314 ± 37	14.9 ± 0.7	43.6 ± 1.4
Vadadustat (mg/kg)	30	7.7 ± 0.5	308 ± 84	15.8 ± 0.7	45.6 ± 2.0
	90	8.8 ± 0.6	706 ± 118	19.9 ± 1.1	59.2 ± 3.9

n = 10 to 12, mean ± SD

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors and enzymes (CTD 4.2.1.2-1 and 4.2.1.2-2, Studies 14651 and 100043777)

Effects of vadadustat at 10 μmol/L on 112 types of receptors and 42 types of enzymes were investigated. Vadadustat at 10 μmol/L inhibited angiotensin-converting enzyme (ACE) activity by 60%, activated calcium/calmodulin-dependent protein kinase (CAMK) 2α by 89%, and inhibited ligand-binding to peripheral benzodiazepine (BZD) receptor activity by 70%.

Using rabbit aorta, effects of vadadustat at 0.3 to 300 μmol/L on ACE activity and ligand-binding to peripheral BZD receptor were investigated. Vadadustat inhibited ACE activity with the IC_{50} value of 72 μmol/L, which was 87 times C_{max} (254 ng/mL)[2)] of plasma-protein unbound of unchanged vadadustat in healthy adults who orally received multiple dose of vadadustat at the maximum recommended clinical dose of 600 mg/day. Vadadustat did not inhibit ligand-binding to peripheral BZD receptor at up to 300 μmol/L.

The applicant's explanation:
Based on the above, vadadustat was unlikely to inhibit ACE activity and ligand-binding to peripheral BZD receptor in clinical use. In addition, vadadustat was unlikely to activate CAMK2α when administered in humans because vadadustat is hardly transferred to the central nervous system [see Section 4.2], no clinical signs were observed in safety pharmacology studies [see Section 3.3], and no abnormal behaviors were observed in toxicity studies [see Sections 5.1 and 5.2].

3.2.2 Effects on pulmonary arterial pressure (CTD 4.2.1.2-3, Study 021-1802)

Vadadustat at 30 or 90 mg/kg was orally administered once daily to male rats for 29 days, and the effect on pulmonary arterial pressure was investigated. In the vadadustat 90 mg/kg group, systolic, diastolic, and mean pulmonary arterial pressures as well as heart rate were higher than those in the vehicle control group. In addition, the Fulton index,[3)] which indicates right cardiac hypertrophy, was not affected.

The applicant explained that although right ventricular hypertrophy and hypertrophy of the endovascular layer were observed in model animals with pulmonary hypertension, vadadustat posed a low risk of pulmonary hypertension in clinical use because no such findings were observed in the above study and 2-year treatment toxicity studies of vadadustat [see Sections 5.1 and 5.2].

3.3 Safety pharmacology

The applicant submitted safety pharmacology studies shown in Table 7.

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2) Calculated from C_{max} (84,800 ng/mL) of unchanged vadadustat in plasma and protein binding rate
3) Fulton index = (total weight of right atrium and right ventricle)/(total weight of left atrium, left ventricle, and ventricular septum)

Table 7. Outline of safety pharmacology studies

Organ	Test system	Endpoints and methods	Dose of vadadustat	Regimen	Findings	Attached document CTD (Study)
Central nervous system	Rat (10 males/ group)	FOB	120, 180, 360 mg/kg[a)]	Single oral dose	No effects were found at up to the highest dose of 360 mg/kg.	4.2.1.3-1 (1008-2361)
Cardiovascular system	HEK293 cells (7 samples/ group)	hERG current	9.5, 28.4, 94.8, 284.4 μmol/L	*In vitro*	Vadadustat at 9.5, 28.4, 94.8, and 284.4 μmol/L inhibited the current by 17.6%, 21.6%, 26.9%, and 21.0%.	4.2.1.3-2 (701205-2)
	Rat (6 males/ group)	Blood pressure (systolic, diastolic, and mean), heart rate, body temperature	120, 180, 360 mg/kg[a)]	Single oral dose	Increased heart rate was observed in all the doses, and decreased blood pressure and body temperature were observed at ≥180 mg/kg.	4.2.1.3-3 (1008-2391)
	Dog (4 males/ group)	Blood pressure (systolic, diastolic, and mean), heart rate, body temperature, activity, and electrocardiogram	60, 120, 360 mg/kg	Single oral dose	Decreased blood pressure and increased heart rate were observed at all the doses.	4.2.1.3-4 (1008-2382)
Respiratory system	Rat (6 males/ group)	Respiratory rate, minute volume of ventilation, and tidal volume	120, 180, 360 mg/kg[a)]	Single oral dose	Increased minute volume of ventilation and tidal volume were observed at 360 mg/kg.	4.2.1.3-5 (1008-2371)
Renal and urinary system	Rat (10 males/ group)	Urine volume, urine electrolytes (Na^+, K^+, Cl^-), urine protein, creatinine, ureotelic amount, urine pH, water intake, creatinine clearance	120, 180, 360 mg/kg[a)]	Single oral dose	No effects were found on any endpoint at up to the highest dose of 360 mg/kg.	4.2.1.3-6 (0209[redacted])

a) Vehicle was 1% methylcellulose.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacology

The applicant's explanation on pharmacology of vadadustat:

Vadadustat inhibits HIF-PH, which is involved in degradation of HIF. HIF is a transcription factor consisting of 2 subunits (HIF-α and HIF-β). In a normoxic environment, HIF is hydroxylated by HIF-PH and degraded by proteasomes (*J Biol Chem.* 2004;279:38458-65), while in a hypoxic environment, HIF-PH which uses oxygen as a cofactor is suppressed, inhibiting degradation of HIF and thereby activating HIF pathway.

In the normal kidney, a hypoxic environment activates the HIF pathway, enhancing production of EPO, which stimulates erythropoiesis. In patients with renal failure, EPO is not sufficiently produced even in a hypoxic environment owing to the renal impairment (*Nephrol Dial Transplant.* 2007;22:2900-8, *N Eng J Med.* 1998;339:1054-62). Accordingly, vadadustat activates the HIF pathway, enhancing EPO production, which leads to increased erythropoiesis and Hb value, and thus is considered to be effective in treatment of renal anemia.

Studies from which data have been submitted in this application showed that vadadustat inhibited human HIF-PH and thereby induced EPO production, and it increased the erythrocyte count, reticulocyte count, Hb value, and Hct value in rats, and thus vadadustat is expected to alleviate renal anemia by activating the HIF pathway.

Based on results on primary pharmacodynamics submitted in this application and applicant's discussion, PMDA concluded that vadadustat inhibits HIF-PH and thereby activates the HIF pathway to increase the Hb value, and thus it is effective in treatment of renal anemia.

3.R.2 Safety pharmacology

The applicant's explanation on findings in the safety pharmacology studies:
For the cardiovascular system, vadadustat suppressed human ether-a-go-go related gene (hERG) current. In addition, increased heart rate and decreased blood pressure were observed in rats and dogs, and the safety margin (total drug concentration) was 2 and 0.2 times C_{max} (84,800 ng/mL) of unchanged vadadustat in healthy adults who orally received multiple dose of vadadustat at the maximum recommended clinical dose of 600 mg/day. Of the above findings, vasodilation is induced by activation of the HIF pathway in the tissue (*Cell.* 1997;89:9-12, *Essays in Biochem.* 2007;43:105-19). Thus, the decreased blood pressure is considered attributable to vasodilation, which HIF stabilization resulted from vadadustat's HIF-PH inhibition potentially led to vasodilation based on the same mechanism as the normal one in response to a hypoxic environment, and the increased heart rate is considered as a reflex response to the decreased blood pressure. In clinical studies conducted so far, however, no adverse drug reactions of hypotension and blood pressure decreased have been reported. In dogs, no effects on electrocardiogram were observed at up to the highest dose of 360 mg/kg.

For the respiratory system, increases in minute volume of ventilation and tidal volume unassociated with changes in respiratory rate were observed in rats, and the safety margin (total drug concentration) was 3 times C_{max} (84,800 ng/mL) of unchanged vadadustat in healthy adults who orally received multiple dose of vadadustat at the maximum recommended clinical dose of 600 mg/day. For the above findings, activation of the HIF pathway enhances production of EPO and endothelin, which induce changes in oxygen sensitivity of chemoreceptors in the carotid body and increased afferent output from the carotid body to the central nervous system (*Respir Physiol Neurobiol.* 2008;164:282-7). Thus, the increases in minute volume of ventilation and tidal volume are considered attributable to activation of the HIF pathway.

Based on the above discussion and results from safety pharmacology studies shown in Table 7, vadadustat is considered unlikely to affect the central nervous system, cardiovascular system, respiratory system, and renal and urinary system in clinical use.

PMDA accepted the applicant's explanation.

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

Unlabeled vadadustat or ^{14}C-vadadustat was administered to mice, rats, rabbits, and dogs to investigate the pharmacokinetics. Plasma concentrations of unchanged vadadustat and its metabolites (*O*-glucuronate conjugate and acylglucuronide conjugate) were measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation of plasma concentrations was 60 ng/mL in mice, 5 ng/mL in rats and rabbits, and 2 ng/mL in dogs for unchanged vadadustat; 20 ng/mL in mice and 10 ng/mL in rats for the *O*-glucuronate conjugate; and 20 ng/mL in mice and 5 ng/mL in rats for the acylglucuronide conjugate. When ^{14}C-vadadustat was used, the radioactivity measurement was performed using a liquid scintillation counter, quantitative whole-body autoradiography, or radioactivity detector.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1, 4.2.2.2-2, 4.2.2.2-4, and 4.2.2.2-5, Studies 6901595, [redacted]1129, 6901603, and [redacted]1132)

Table 8 shows pharmacokinetic parameters of unchanged vadadustat after a single oral or intravenous administration of vadadustat to male and female rats. No clear differences were observed in the pharmacokinetics of vadadustat between male and female rats.

Table 8. Plasma pharmacokinetic parameters of unchanged vadadustat after a single administration of vadadustat to rats

Sex	Route of administration	Dose of vadadustat (mg/kg)	C_{max}[a)] (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	Bioavailability[b)] (%)
Male	Oral	20	23,100 ± 2,490	2.0	104,000	2.3	75
	Intravenous	5.57	-	-	38,500	0.9	-
Female	Oral	20	33,300 ± 16,500	0.5	103,000	1.1	117
	Intravenous	5.57	-	-	24,600	1.1	-

Mean in 3 animals at each timepoint; -, not determined

a) Mean ± SD

b) ($AUC_{0-\infty}$ after oral administration/oral dose)/($AUC_{0-\infty}$ after intravenous administration/intravenous dose) × 100

Table 9 shows pharmacokinetic parameters of unchanged vadadustat after a single oral or intravenous administration of vadadustat to male and female dogs. No clear differences were observed in the pharmacokinetics of vadadustat between male and female dogs.

Table 9. Plasma pharmacokinetic parameters of unchanged vadadustat after a single administration of vadadustat to dogs

Sex	Route of administration	Dose of vadadustat (mg/kg)	n	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)
Male	Oral	30	3	50,900 ± 4,550	0.5 ± 0.0	135,000[a)]	3.2[a)]
	Intravenous	5	3	-	-	NC	NC
Female	Oral	30	3	62,800 ± 21,600	0.4 ± 0.1	112,000 ± 29,700	4.2 ± 2.9
	Intravenous	5	3	-	-	19,200[b)]	2.7[b)]

Mean ± SD; -, Not determined; NC, Not Calculated

a) n = 1

b) Mean in 2 animals

Table 10 shows pharmacokinetic parameters of plasma radioactivity after a single oral administration of ^{14}C-vadadustat to male and female rats and male and female dogs. No clear differences were observed in the pharmacokinetics of vadadustat between males and females of either rats or dogs.

Table 10. Pharmacokinetic parameters of plasma radioactivity after a single oral administration of vadadustat

	Sex	Dose of vadadustat (mg/kg)	n	C_{max} (ng eq./mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng eq.•h/mL)	$t_{1/2}$ (h)
Rat	Male	50	3	153,239 ± 9,666	0.5 ± 0.0	643,813 ± 38,268	9.3 ± 8.9
	Female	50	3	184,043 ± 6,221	0.8 ± 0.3	890,585 ± 49,541	5.4 ± 1.1
Dog	Male	50	3	117,843 ± 12,020	1.0 ± 0.0	283,937 ± 34,826	22.2 ± 7.0
	Female	50	3	128,550 ± 7,912	0.7 ± 0.3	310,202 ± 7,875	18.9 ± 8.2

Mean ± SD

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study in rats (CTD 4.2.3.2-8, Study 2008611)

Vadadustat was orally administered to male and female rats for 6 months in a toxicity study to investigate toxicokinetics. Table 11 shows plasma pharmacokinetic parameters of unchanged vadadustat. C_{max} and AUC_{0-t} of unchanged vadadustat almost increased dose-proportionally. No clear differences were observed in the pharmacokinetics of vadadustat between male and female rats.

Table 11. Plasma pharmacokinetic parameters of unchanged vadadustat after repeated oral administration of vadadustat for 6 months to rats

Sex	Dose of vadadustat (mg/kg/day)	Timepoint	C_{max}[a)] (ng/mL)	t_{max} (h)	AUC_{0-t} (ng•h/mL)
Male	20	Day 1	12,590 ± 2,982	1.0	52,000
		Day 182	28,180 ± 4,562	1.0	118,000
	40	Day 1	36,120 ± 10,820	1.0	160,100
		Day 182	42,140 ± 7,515	1.0	250,500
	60	Day 1	50,400 ± 1,720	1.0	301,000
		Day 182	37,040 ± 6,343	2.0	231,800
Female	20	Day 1	16,770 ± 2,384	1.0	54,590
		Day 182	33,780, 39,240[b)]	1.0	130,800
	40	Day 1	46,770 ± 4,340	1.0	144,600
		Day 182	57,450 ± 18,560	2.0	285,300
	60	Day 1	66,180 ± 810.1	1.0	242,300
		Day 182	55,590 ± 13,260	1.0	422,600

Mean in 3 animals at each timepoint
a) Mean ± SD
b) Measured values in 2 animals

4.1.2.2 Repeated-dose study in dogs (CTD 4.2.3.2-13, Study 20008612)

Vadadustat was orally administered for 9 months to male and female dogs in a toxicity study to investigate toxicokinetics. Table 12 shows plasma pharmacokinetic parameters of unchanged vadadustat. C_{max} and AUC_{0-t} of unchanged vadadustat almost increased dose-proportionally. No clear differences were observed in the pharmacokinetics of vadadustat between male and female dogs.

Table 12. Plasma pharmacokinetic parameters of unchanged vadadustat after repeated oral administration of vadadustat for 9 months to dogs

Sex	Vadadustat dose (mg/kg/day)	Timepoint	C_{max}[a)] (ng/mL)	t_{max} (h)	AUC_{0-t} (ng•h/mL)
Male	10	Day 1	6,081 ± 4,808	1.0	10,560
		Day 274	2,563 ± 1,802	1.0	4,563
	25	Day 1	34,700 ± 17,420	1.0	64,800
		Day 274	24,060 ± 10,180	1.0	39,780
	50	Day 1	73,820 ± 14,460	1.0	139,200
		Day 274	47,870 ± 9,164	1.0	76,960
Female	10	Day 1	2,474 ± 1,630	1.0	6,513
		Day 274	3,850 ± 2,310	1.0	8,019
	25	Day 1	6,714 ± 3,275	1.0	12,170
		Day 274	30,580 ± 9,556	1.0	46,270
	50	Day 1	29,120 ± 23,050	1.0	51,360
		Day 274	68,170 ± 22,780	1.0	119,800

Mean in 3 animals at each timepoint
a) Mean ± SD

4.1.3 *In vitro* membrane permeability (CTD 4.2.2.2-7, Study [redacted]1R2)

Membrane permeability of vadadustat was investigated using Caco-2 cells. After incubation of vadadustat (0.024-0.271 mg/mL) and highly membrane-permeable minoxidil (10 μmol/L), the apparent permeability coefficient from the apical surface to the basolateral surface (P_{app} A→B) were 5.02 to 24.6 × 10^{-6} cm/s and 4.31 to 7.88 × 10^{-6} cm/s, respectively. The applicant explained that vadadustat was considered to have high membrane permeability.

4.2 Distribution

4.2.1 Tissue distribution in rats and dogs (CTD 4.2.2.3-1 and 4.2.2.3-2, Studies 0830[redacted] and 0831[redacted])

To male rats, ^{14}C-vadadustat was orally administered at 60 mg/kg as a single dose, and radioactivity concentrations in each tissue at 2, 4, 8, 12, and 24 hours post-dose were measured.[4)] The radioactivity concentration in any tissue reached the maximum at 2 hours post-dose and then decreased with time. The radioactivity concentrations were high in the kidney and liver at 2 hours post-dose, being 1.6 times and comparable to, respectively, that in plasma, and then decreased to 0.4% and 1.3%, respectively, of those at 2 hours post-dose by 24 hours post-dose. Vadadustat was hardly transferred into the brain and bone marrow, and the radioactivity concentrations in these organs at 2 hours post-dose were approximately 1/50 and 1/100, respectively, of that in plasma. In addition, because the plasma radioactivity concentrations were comparable to the blood radioactivity concentrations or higher, vadadustat was suggested to be hardly distributed into blood cells.

To male dogs, ^{14}C-vadadustat was orally administered at 60 mg/kg as a single dose, and radioactivity concentrations in each tissue at 2, 4, 8, 12, and 24 hours post-dose were measured.[5)] The radioactivity concentration in most of the tissues reached the maximum at 2 hours post-dose and then decreased with time. The radioactivity concentrations were high in the kidney and liver at 2 hours post-dose, being 1.9 and 1.5 times, respectively, that in plasma, and then decreased to 3.3% and 2.0%, respectively, of those at 2 hours post-dose by 24 hours post-dose. Vadadustat was hardly transferred

4) Radioactivity concentrations in plasma, blood, brain, eyeball, thymus, heart, lung, liver, kidney, spleen, pancreas, carcass, testis, adrenal gland, skin, mesenteric lymph node, femur, skeletal muscle, and bone marrow were measured.
5) Radioactivity concentrations in plasma, blood, brain, eyeball, thymus, heart, lung, liver, kidney, spleen, pancreas, testis, adrenal gland, mesenteric lymph node, femur, skeletal muscle, and bone marrow were measured.

into the brain, and the radioactivity concentration at 2 hours post-dose was approximately 1/100 of that in plasma. In addition, because the plasma radioactivity concentrations were comparable to the blood radioactivity concentrations or higher, vadadustat was suggested to be hardly distributed into blood cells.

4.2.2 Protein binding (CTD 4.2.2.3-3, Study [redacted]1137)

Plasma protein binding of vadadustat (3-300 μg/L) was investigated using plasma specimens from mice, rats, rabbits, and dogs, and the mean protein binding rate was 93.2% to 96.6%, 96.4% to 99.2%, 98.1% to 99.3%, and 95.6% to 98.2%, respectively. No concentration dependence was found.

4.2.3 Placental transfer and fetal transfer (CTD 4.2.2.3-5, Study [redacted]8106[redacted])

To pregnant rats on Gestation Day 18, ^{14}C-vadadustat was orally administered at 50 mg/kg as a single dose, and radioactivity concentrations in maternal and fetal tissues were measured. The radioactivity concentration reached the maximum at 1 hour post-dose in all the maternal (excluding amniotic fluid) and fetal tissues measured and then decreased with time. Because the radioactivity was detected in fetal tissues, vadadustat crossed the placenta and was transferred into fetuses.

4.3 Metabolism

4.3.1 *In vitro* investigation of metabolites (CTD 4.2.2.4-6 and 4.2.2.4-7, Studies 14739 and [redacted]4105)

Metabolism of vadadustat by Cytochrome P450 (CYP) was investigated using liver microsomes from mice, rats, dogs, and monkeys. The concentration of unchanged vadadustat did not decrease in either presence or absence of nicotinamide adenine dinucleotide phosphate (NADPH), and the applicant explained that CYP's contribution to metabolism of vadadustat was limited.

4.3.2 Proportions of unchanged vadadustat and its metabolites in plasma, urine, feces, and bile (CTD 4.2.2.4-1 to 4.2.2.4-5, Studies [redacted]1131, [redacted]1133, 20035235, [redacted]797035, and AKB-6548-NC-[redacted])

To male and female rats, ^{14}C-vadadustat was orally administered at 50 mg/kg as a single dose, and proportions of unchanged vadadustat and its metabolites in plasma, urine, and feces were determined. In addition, to bile-duct-cannulated male and female rats, ^{14}C-vadadustat was orally administered at 50 mg/kg as a single dose, and the proportion of unchanged vadadustat and its metabolites in bile was also determined. In plasma at up to 8 hours post-dose, unchanged vadadustat was the most abundant form, but a deglycine form of vadadustat was also observed at 4 hours post-dose and later. In urine at up to 24 hours post-dose, the *O*-glucuronate conjugate (2.3%-4.6% of the total administered radioactivity) and unchanged vadadustat (0.9%-2.6% of the total administered radioactivity) were mainly observed. In feces at up to 72 hours post-dose, unchanged vadadustat (13.1%-19.3% of the total administered radioactivity) and a deglycine form of vadadustat (10.3%-14.2% of the total administered radioactivity) were mainly observed. In bile at up to 24 hours post-dose, the *O*-glucuronate conjugate (22.6%-26.7% of the total administered radioactivity) and unchanged vadadustat (3.2%-4.0% of the total administered radioactivity) were mainly observed. In addition, the glutathione conjugate and its related metabolites were observed (the most abundant metabolite accounted for 10.1% of the total administered radioactivity).

To male and female dogs, ^{14}C-vadadustat was orally administered at 50 mg/kg as a single dose, and proportions of unchanged vadadustat and its metabolites in plasma, urine, and feces were determined. In plasma at up to 8 hours post-dose, unchanged vadadustat was the most abundant form, but a deglycine form of vadadustat was also observed at 4 hours post-dose and later. In urine at up to 24 hours post-dose, the *O*-glucuronate conjugate (7.5%-11.3% of the total administered radioactivity) was mainly observed, and the amount of unchanged vadadustat was limited (<0.5% of the total administered radioactivity). In feces at up to 48 hours post-dose, unchanged vadadustat (67.1%-71.2% of the total administered radioactivity) was mainly observed.

A single dose of 80 mg/kg of vadadustat was orally administered to male rats and vadadustat at 25 to 200 mg/kg was orally administered to male and female mice for 91 days, proportions of unchanged vadadustat, the *O*-glucuronate conjugate, and acylglucuronide conjugate in plasma were determined. Percentages of exposure (AUC_{0-t}) to the *O*-glucuronate conjugate and that to the acylglucuronide conjugate with respect to that of unchanged vadadustat in plasma were 4.29% and 0.09%, respectively, in rats and up to 16.8% and 1.73%, respectively, in mice (Day 91 of administration).

4.4 Excretion

4.4.1 Excretion into urine, feces, and expired air in rats and dogs (CTD 4.2.2.5-1 and 4.2.2.5-2, Studies [redacted]1129 and [redacted]1132)

When a single dose of 50 mg/kg of ^{14}C-vadadustat was orally administered to male and female rats, proportions of the radioactivity excreted into urine, feces, and expired air until 168 hours post-dose were 12.3%, 86.1%, and 0%, respectively, in males as well as 12.0%, 86.6%, and 0%, respectively, in females. When a single dose of 50 mg/kg of ^{14}C-vadadustat was orally administered to male and female dogs, proportions of the radioactivity excreted into urine and feces until 168 hours post-dose were 14.6% and 84.1%, respectively, in males as well as 18.8% and 79.6%, respectively, in females. The applicant explained that unchanged vadadustat and its metabolites were mainly excreted into feces in rats and dogs, and some portions were excreted into urine.

4.4.2 Excretion into bile in rats (CTD 4.2.2.5-1, Study [redacted]1129)

When a single dose of 50 mg/kg of ^{14}C-vadadustat was orally administered to bile-duct-cannulated male and female rats, proportions of the radioactivity excreted into bile, urine, and feces until 72 hours post-dose were 80.4%, 13.8%, and 4.5%, respectively, in males as well as 82.9%, 8.5%, and 6.2%, respectively, in females. In addition, when the bile sample collected until 72 hours post-dose was administered into the duodenum in different bile-duct-cannulated male and female rats, proportions of the bile sample radioactivity excreted into bile, urine, and feces until 72 hours after the administration were 17.4%, 5.6%, and 76.1%, respectively, in males as well as 17.3%, 5.4%, and 76.4%, respectively, in females. The applicant explained that unchanged vadadustat and its metabolites were excreted into feces through bile in rats, and some portions of the vadadustat and its metabolites excreted into bile were suggested to be reabsorbed and enter enterohepatic circulation.

4.4.3 Excretion into milk (CTD 4.2.2.3-5, Study [redacted])

To female rats on Lactation Day 11, a single dose of 50 mg/kg of ^{14}C-vadadustat was orally administered, and excretion of the radioactivity into milk at 1, 4, 8, and 24 hours post-dose was investigated. The radioactivity concentration in milk reached the maximum at 4 hours post-dose (212,594 ng eq./mL, 9.63 times the plasma radioactivity concentration) and then decreased with time. Based on the $AUC_{0\text{-last}}$ value, the radioactivity concentration in milk was 6.13 times the plasma radioactivity concentration at 24 hours post-dose, indicating that vadadustat was transferred into milk.

4.R Outline of the review conducted by PMDA

PMDA concluded that data on the non-clinical pharmacokinetics of vadadustat have no particular problems.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies of vadadustat were conducted: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity, carcinogenicity studies, reproductive and developmental toxicity studies, and the other studies (*in vitro* hemolysis study and phototoxicity studies). Unless otherwise specified, *in vivo* studies used a solution containing 0.25% hydroxypropylmethylcellulose and 0.1% Tween 80 as vehicle.

5.1 Single dose toxicity

Single oral dose toxicity studies in rats and dogs were conducted (Table 13).

Table 13. Single dose toxicity

Test system	Route of administration	Dose (mg/kg)	Major findings[a)]	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (SD)	Oral	0,[b)] 400, 1,000, 2,000	≥400: High white blood cell count and neutrophil count, high triglyceride ≥1,000: Decreased body weight, high platelet count, hepatic vacuolation and inflammation 2,000: Enhanced erythropoiesis	>2,000	Reference 4.2.3.1-1
Male and female dogs (beagle)	Oral	300, 450, 700	≥450: Vomiting	>700	Reference 4.2.3.1-2

a) No necropsy was performed in the single oral dose toxicity study in dogs.
b) As vehicle, an aqueous solution containing 1% methylcellulose was used.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in rats (4 weeks, and 3 and 6 months) and dogs (4 weeks, and 3 and 9 months) were conducted (Table 14). Major toxicity findings were enhanced erythropoiesis (rats and dogs); thrombosis in multiple organs and tissues; necrosis and bleeding in the heart valve and glandular stomach; enhanced extramedullary hematopoiesis in the spleen (rats); and mononuclear and multinuclear cells infiltration as well as hypertrophic cells in the adrenal cortex (dogs). All the findings except for ones in the adrenal cortex were considered attributable to the pharmacological action of vadadustat or the secondary effects associated with the concerned action. In addition, no observed adverse effect levels (NOAELs) in the 6-month repeated oral dose toxicity study in rats and 9-month repeated oral dose toxicity study in dogs were 40 mg/kg/day, 50 mg/kg/day for male dogs, and 25 mg/kg/day for female dogs, respectively. The ratio of the exposure (C_{max} and AUC [see Section

4.1.2]) at the NOAEL in any of the above toxicity studies with respect to that in healthy adults who orally received multiple dose of vadadustat at the maximum clinical dose of 600 mg/day ([see Section 6.2.1] total drug concentration) was 0.5 to 0.7 and 0.4 to 0.5 in rats and 0.4 to 0.6 and 0.1 in dogs.

Table 14. Repeated-dose toxicity

Test system	Route of administration	Treatment period	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	Attached document CTD
Male and female rats (SD)	Oral	4 weeks (once daily) + 4 weeks of recovery	0, 40, 80, 120, 200	Death: 200 (3 of 19 males, 2 of 19 females) Hunchback position; unkempt fur; emaciation; gasping; urinary occult blood; pale mucosa; reduced body weight gain and decreased food consumption; thrombus, interstitium hyperplasia, and bleeding in the left atrioventricular valve; thrombus and bleeding in the lung; bleeding in the kidney, adrenal gland, and ileum; centrilobular hepatocyte degeneration in the liver; and lymphocyte depletion in the thymus ≥40: Enhanced erythropoiesis ≥80: Low platelet count; high unsaturated iron binding capacity and total iron binding capacity; low serum iron, glucose, and potassium; high weight of the lung; enhanced extramedullary hematopoiesis in the spleen; enhanced hematopoiesis in the bone marrow; and gastric congestion[a)] ≥120: Low urine pH; high potassium clearance in urine, high weight of the spleen, and gastric erosion[a)] 200: Tubular epithelium degeneration in the kidney Reversibility: Yes (decreased hematopoiesis in the bone marrow, lymphocyte depletion in the thymus, and interstitial hyperplasia and pigmented macrophages in the left atrioventricular valve were observed)	120	4.2.3.2-6
Male and female rats (SD)	Oral	3 months (once daily) + 3 months of recovery	0, 40, 80/70,[b)] 120/90[b)]	Death or moribund sacrifice: 80/70 (3 of 22 males) and 120/90 (2 of 22 males, 1 of 22 females) Abnormal general appearance; abnormal movement of hindlimbs; piloerection; red substances in the urogenital organs; decreased activity; fibrin thrombosis and necrosis in the heart, kidney, and skeletal muscle; thrombus, interstitial hyperplasia, bleeding, and pigmented macrophage infiltration in the heart valve; and bleeding and fibrin thrombus in the lung ≥40: Enhanced erythropoiesis; and low serum total iron binding capacity, glucose, and cholesterol ≥80/70: Erythema and swelling of the auricle; crust formation; abnormal color urine; high serum total bilirubin; low platelet count; bleeding, necrosis, and edema in the glandular stomach; enhanced extramedullary hematopoiesis in the spleen; and enhanced hematopoiesis in the bone marrow 120/90: Low body weight and food consumption; low serum iron; low urine pH; congestion and fibrin thrombus in the glandular stomach; and hypertrophy of adrenal cortex cells Reversibility: Yes (low red cell distribution width; and renal atrophy and fibrogenesis were observed)	40	4.2.3.2-7

Male and female rats (SD)	Oral	6 months (once daily) + 3 months of recovery	0, 20, 40, 60	Death or moribund sacrifice: 60 (7 of 26 males, 1 of 26 females) Abdominal distention; decreased activity; decreased body temperature; and bleeding, necrosis, and fibrin thrombus in the heart, kidney, lung, cecum, and ileum ≥20: Abnormal movement of hindlimbs; and dirty perifacial area ≥40: Erythema of the auricle and limbs; decreased feces; enhanced erythropoiesis; low platelet count and fibrinogen; low serum glucose and cholesterol; high serum total bilirubin; enhanced extramedullary hematopoiesis in the spleen; enhanced hematopoiesis in the bone marrow; and bleeding and necrosis in the glandular stomach 60: Piloerection; black feces; and low serum iron and total iron binding capacity Reversibility: Yes	40[c)]	4.2.3.2-8
Male and female dogs (beagle)	Oral	4 weeks (once daily) + 4 weeks of recovery	0, 30, 60, 60+Fe,[d)] 120	≥30: Low weight of the thymus; and mononuclear cell infiltration in the adrenal cortex[e)] ≥60 (including 60 + Fe): Enhanced erythropoiesis; low serum iron; high serum potassium, AST, LDH, and CK; atrophy of the thymus; and increased erythroid cells in the bone marrow 120: Vomiting; low body weight and food consumption; high platelet count; low glucose; small thymus; and multinuclear cell infiltration and single cell necrosis in the adrenal cortex Reversibility: Yes (mononuclear cell infiltration and multinuclear cell infiltration in the adrenal cortex, and decreased erythroid cells in the bone marrow were observed.)	30	4.2.3.2-11
Male and female dogs (beagle)	Oral	3 months (once daily) + 3 months of recovery	0, 25, 45, 90/65[f)]	≥25: High LDH; low serum glucose and serum iron; and mononuclear cell infiltration and multinuclear cell infiltration in the adrenal cortex[g)] ≥45: Erythema and swelling of the gingiva and auricle; enhanced erythropoiesis; high serum potassium; and increased erythroid cells in the bone marrow 90/65: Low body weight gain and food consumption; emaciation; unkempt fur; erythema of the skin; high basophil count; high CK; dark general color; and single cell necrosis in the adrenal cortex Reversibility: Yes (low erythrocyte count, hemoglobin, and hematocrit; and mononuclear cell infiltration and multinuclear cell infiltration in the adrenal cortex were observed)	45[h)]	4.2.3.2-12
Male and female dogs (beagle)	Oral	9 months (once daily) + 3 months of recovery	0, 10, 25, 50	Death or moribund sacrifice: 50 (1 of 7 females) Decreased activity; staggering gait; vocalization; bradypnea; incomplete eyelid opening; low body weight and food consumption; high serum AST, ALT, CK, ALP, GGT, and bilirubin; congestion in the small intestine; focal necrosis in the gastric pylorus mucosa; and hepatocyte hypertrophy, centrilobular congestion, vacuolation, pigmentation of sinusoidal macrophages, chronic inflammation focus, and extramedullary hematopoiesis focus in the liver ≥10: Mononuclear cell infiltration and hypertrophic cells (mononuclear and multinuclear cells) in the adrenal cortex[i)] Reversibility: Yes	50 (males) 25 (females)	4.2.3.2-13

a) These findings are changes related to the pharmacological action and slight or mild in severity, and these were considered to be of low toxicological significance.
b) One male in the 120 mg/kg/day group died on Day 43, and the dose was decreased from 80 to 70 mg/kg/day and from 120 to 90 mg/kg/day on Day 47.
c) All the findings at ≤40 mg/kg/day were changes attributable to the pharmacological action or slight in severity, and these were considered to be of low toxicological significance.
d) The preceding 14-day repeated oral dose toxicity study in dogs showed low serum iron values in the 60 mg/kg/day group, and this study additionally included the iron-supplement group in which iron was orally administered at 65 mg/kg/day every other day from 4 days before the first dose of vadadustat to Day 28.
e) Findings in the adrenal gland in the 30 and 60 mg/kg/day groups were slight in severity, and these were considered to be of low toxicological significance.
f) The hematocrit value reached ≥65% on Day 39, and the dose was reduced from 90 to 65 mg/kg/day on Day 43.

g) Findings in the adrenal gland in the 25 and 45 mg/kg/day groups were slight in severity, and these were considered to be of low toxicological significance.
h) Judgment was made based on excessively high erythrocyte count and histopathological findings in the adrenal gland in the 90/65 mg/kg/day group on up to Day 42.
i) Hypertrophic cells were identified as adrenal cortex cells based on results obtained by light microscopy and transmission electron microscopy. Changes such as abnormal serum electrolyte suggestive of decreased adrenal function were not observed, and it was considered to be of low toxicological significance.

5.3 Genotoxicity

Genotoxicity of vadadustat was investigated in *in vitro* studies including the bacterial reverse mutation test and chromosomal aberration test in Chinese hamster ovary (CHO) cells as well as *in vivo* studies including the peripheral blood lymphocyte chromosomal aberration test in rats and hepatic comet assay in rats (Table 15). The applicant explained about the reason for omission of the bone marrow micronucleus assay that stimulation to EPO production induced bone marrow micronucleus (*Mutagenesis.* 1993;8:221-9, *Mutation Res.* 2007;627:78-91), and the change related to the pharmacological action of vadadustat might affect the clastogenicity evaluation, thus the peripheral blood lymphocyte chromosomal aberration test was conducted as an *in vivo* study instead.

Although in the chromosomal aberration test in CHO cells, cells with structurally altered chromosomes were highly frequently observed in the absence of S9 mix with 20 hours of treatment, both the peripheral blood lymphocyte chromosomal aberration test in rats and hepatic comet assay in rats presented negative results, and thus vadadustat was considered unlikely to have genotoxicity.

Table 15. Genotoxicity

Type of study		Test system	S9 (treatment)	Concentration (μg/plate or μg/mL) Dose (mg/kg/day)	Test result	Attached document CTD
In vitro	Bacterial reverse mutation test (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	-/+	0,[a] 50, 150, 500, 1,500, 5,000	Negative	4.2.3.3.1-1
	Mammalian cell chromosomal aberration test	CHO cells	- (4 hours)	0,[a] 100, 150, 250	Negative	4.2.3.3.1-2
			- (20 hours)	0 [a], 25, 75, 150	Positive (≥75)	
			+ (4 hours)	0,[a] 25, 150, 250	Negative	
In vivo	Rodent chromosomal aberration test	Male rats (SD) Peripheral blood lymphocyte		0, 60, 120, 360[b] (oral, 5 days, once daily)	Negative	4.2.3.3.2-1
	Comet assay	Male rats (SD) Hepatocytes		0, 500, 1,000, 2,000 (single dose/oral)	Negative	4.2.3.3.2-2

a) DMSO
b) In the 120 and 360 mg/kg/day groups, drastic decreases in mean mitotic index (>95%) were observed, resulting in shortage of evaluable metaphase images, and thus clastogenicity was not evaluated in either group.

5.4 Carcinogenicity

Carcinogenicity studies in mice and rats were conducted (Table 16). Vadadustat was considered to have no carcinogenicity.

Table 16. Carcinogenicity

Test system	Route of administration	Treatment period	Major lesions	Sex	Dose (mg/kg)[a]					No-carcinogenic dose (mg/kg)	Attached document CTD
					0[b]	0[c]	5	15	50		
Male and female mice (rasH2)	Oral	6 months (once daily)	Tumor lesions							50	4.2.3.4.2-3
			Lung: Bronchioloalveolar adenoma[d]	Male	0	1	4	5	5		
				Female	1	1	3	3	1		
			Lung: Bronchioloalveolar adenocarcinoma	Male	0	0	0	1	0		
				Female	0	0	0	0	0		
			Spleen: Angiosarcoma[e]	Male	1	1	0	2	4		
				Female	0	2	0	4	2		
			Harderian gland: Adenoma[f]	Male	0	1	0	2	0		
				Female	0	0	1[g]	0	5		
			Harderian gland: Adenocarcinoma	Male	2	0	1	0	0		
				Female	0	0	0	0	1		
			Non-tumor lesions	Male and females	Enhanced extramedullary hematopoiesis in the spleen						

Test system	Route of administration	Treatment period	Major lesions	Sex	Dose (mg/kg)[h]					No-carcinogenic dose (mg/kg)	Attached document CTD
					0[b]	0[c]	2	7	20		
Male and female Rat (SD)	Oral	Male: 94-95 weeks Female: 87-90 weeks (once daily)	Tumor lesions							20	4.2.3.4.1-1
			Adrenal gland: Malignant phaeochromocytoma[i]	Male	6	0	4	4	4		
				Female	0	0	0	0	3		
			Liver: Hepatocyteadenoma[j]	Male	0	0	0	1	0		
				Female	0	0	0	0	2		
			Non-tumor lesions	Male Female	Enhanced extramedullary hematopoiesis, pigmented macrophage infiltration in the spleen; and erosion, submucosal linitis, and mucosa necrosis in the glandular stomach						

a) n = 25/sex/group
b) Water
c) A solution containing 0.25% hydroxypropylmethylcellulose and 0.1% Tween 80, vehicle
d) It fell within the historical data (0.0%-20.0%) at the testing facility, and it was considered unrelated to vadadustat.
e) The incidence was lower than reported ones (*Toxicol Pathol.* 2003;31:191-9, *Toxicol Pathol.* 2012;40:614-23), and the finding was considered unrelated to vadadustat.
f) The incidence of the finding in females in the 50 mg/kg/day group fell within the historical data (0.0%-23.5%) at the testing facility, and it was considered unrelated to vadadustat.
g) n = 24 tested
h) n = 70/sex/group
i) Incidences of adrenal medullary hyperplasia and benign pheochromocytoma were not high, and the finding was considered unrelated to vadadustat.
j) The incidence of the finding was lower than the reported one (*Toxicologic Histopathology.* 2017:705-24), and it was considered unrelated to vadadustat.

5.5 Reproductive and developmental toxicity

The following studies were conducted: A study of fertility and early embryonic development to implantation in rats, studies for effects on embryo-fetal development in rats and rabbits, and study for effects on pre- and post-natal development including maternal function in rats (Table 17). The study of fertility and early embryonic development to implantation in rats did not show any effect of vadadustat on the fertility and early embryonic development to implantation. The study for effects on embryo-fetal development in rats showed low body weight and immature ossification in fetuses, but no teratogenicity was observed in either rats or rabbits. The study for effects on pre- and post-natal development including maternal function in rats showed low body weight of offspring. The ratio of the exposure (C_{max} 77.81 μg/mL and AUC 1,007 μg•h/mL in rats, C_{max} 39.01 μg/mL and AUC 99.5 μg•h/mL in rabbits) at the NOAEL in rat and rabbit embryos and fetuses (80 mg/kg/day in rats and 50 mg/kg/day in rabbits) with respect to that in healthy adults who orally received multiple dose

of vadadustat at the maximum recommended clinical dose of 600 mg/day ([see Section 6.2.1] total drug concentration) was 0.9 and 1.6 times (C_{max} and AUC, respectively) in rats and 0.5 and 0.2 times in rabbits.

Table 17. Reproductive and developmental toxicity

Type of study	Test system	Route of administration	Treatment period	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rat (SD)	Oral	Male: From 28 days before mating to Day 63 or 64 (once daily) Female: From 14 days before mating to Gestation Day 7 (once daily)	0, 40, 80, 120	Male Death or moribund sacrifice: 80 (1/25 males), 120 (4/25 males) Dysfunction of both hindlimbs, crust formation, black feces, watery feces, hunchback position, emaciation, abnormal general appearance, decreased respiratory rate, respiratory distress, decreased locomotor activity, periocular black substances, red organs, black liver, and gastric black focus ≥80: Red skin 120: Low body weight and food consumption; swelling of the spleen; and red and black glandular stomach No effects on spermatic parameters and fertility Female No effects on general toxicity, fertility, or early embryonic development	Parental animal (general toxicity): 40 (males) 120 (females) Parental animals (fertility, early embryonic development): 120	4.2.3.5.1-1
Embryo-fetal development	Female rat (SD)	Oral	From Gestation Day 6 to Gestation Day 17 (once daily) Cesarean section: Day 20 of gestation	0, 40, 80, 160	Maternal animal: ≥80: Low body weight gain and food consumption Fetus: 160: Low fetal body weight; uncompleted ossification and immature ossification of the cervical spine, thoracic vertebra, lumbar spine, girdle, sacral vertebra, skull, and sternum; and small rib[a)]	Maternal animal (general toxicity): 40 Embryo-fetal development: 80	4.2.3.5.2-2
	Female rabbit (NZW)	Oral	From Day 6 to Day 18 of gestation (once daily) Cesarean section: Gestation Day 29	0, 10, 25, 50	Death or moribund sacrifice: 50 (3 of 28 females) Decreased feces and low food consumption Maternal animal: No effects Fetus: No effects	Maternal animal (general toxicity): 25 Embryo-fetal development: 50	4.2.3.5.2-4
Effects on pre- and post-natal development, including maternal function	Female rat (SD)	Oral	Maternal animal: From Gestation Day 6 to Lactation Day 20 (once daily)	0, 20, 40, 80	Maternal animal: No effects F1 off-spring: 80: Low body weight (from birth to post-weaning early phase)	Maternal animal (general toxicity, fecundity): 80 Pre- and post-natal development of F1 off-spring: 40 Functional development and reproductive function of F1 off-spring: 80	4.2.3.5.3-1

a) Judged as secondary changes related to reduced body weight gain in maternal animals

5.6 Other studies

5.6.1 Study for mechanism of toxicity

In vitro hemolysis studies using whole blood specimens from mice, rats, and dogs demonstrated that vadadustat did not induce hemolysis (Table 18).

Table 18. Study for mechanism of toxicity

Test system	Method	Major findings	Attached document CTD
In vitro hemolysis study	Whole blood specimens from mice, rats, and dogs were incubated with vadadustat at 0.98 to 1,000 µmol/L to assess hemolysis.	No hemolysis occurred in any whole blood specimen.	4.2.3.7.3-1

5.6.2 Photosafety studies

In vitro and *in vivo* phototoxicity studies were conducted (Table 19). Although positive results were obtained in the *in vitro* study, no effects were observed on the eye or skin in the *in vivo* study. Vadadustat was considered unlikely to have phototoxicity.

Table 19. Photosafety studies

Type of study	Test system	Method	Major findings	Attached document CTD
Phototoxicity	Mouse fibroblasts Balb/c 3T3	0.05, 0.2, 0.5, 2, 5, 15, 49, and 153 µg/mL UVA irradiation	Phototoxicity positive (phototoxicity index, 179.55; mean photo activity, 0.403)	4.2.3.7.7-2
	Female rat (Long-Evans)	Vadadustat was orally administered at 0, 60, 180, and 400 mg/kg for 3 days. At 42 to 46 minutes after the last dose, animals were exposed to UVA at 10.3 to 11.3 J/cm^2 and UVB at 145 to 159 mJ/cm^2 for 60 minutes (60 and 180 mg/kg groups) or 120 minutes (400 mg/kg group) followed by observation at 1, 4, 24, 48, and 72 hours after the end of light exposure.	No phototoxicity was observed on the eye or skin.	4.2.3.7.7-3

5.R Outline of the review conducted by PMDA

5.R.1 Toxicity profile of vadadustat

The applicant's explanation on toxicity profile of vadadustat:

In the repeated-dose toxicity study in rats, fibrin thrombosis in the heart, kidney, lung, stomach, ileum, and cecum; interstitial hyperplasia, cell infiltration, pigmented macrophage, and necrosis in the heart valve; and necrosis, erosion, and bleeding in the stomach were observed. Similar findings were reported in rats receiving ESAs (*Toxicol Pathol.* 2014;42:510-23). These findings were considered as changes related to vascular insufficiency due to increased blood viscosity associated with enhanced erythropoiesis, the pharmacological action of vadadustat. Because the safety margins of these findings were <1 time, their potential onset in clinical use cannot be ruled out. Vadadustat, however, is a drug of which the dose may be adjusted according to the Hb value as appropriate, and the Hb value will be periodically measured during use of vadadustat. These findings were therefore considered unlikely to lead to problems in clinical use.

In the repeated-dose toxicity study in dogs, histopathological findings such as mononuclear cell infiltration and multinuclear hypertrophic cells in the adrenal cortex were observed. The exposure

(AUC [see Section 4.1.2.2]) at 10 mg/kg/day, the lowest dose at which these findings were observed in the 9-month repeated oral dose toxicity study in dogs, was 0.01 times that in healthy adults who orally received multiple dose of vadadustat at the maximum recommended clinical dose of 600 mg/day ([see Section 6.2.1] total drug concentration). These findings, however, were considered unlikely to lead to problems in clinical use for the following reasons: The pathological changes involved a limited number of cells; no signs suggestive of adrenal insufficiency were observed; these changes were reversible; no such changes were observed in mice or rats, and no marked changes were observed in the adrenal functions in Japanese clinical studies conducted so far.

PMDA accepted the applicant's explanation but noted that events potentially attributable to the pharmacological action of vadadustat occurred and thus continuously reviews the safety in humans in Section 7.R.2.

5.R.2 Use of vadadustat in pregnant women, women of childbearing potential, and lactating women

The applicant's explanation:

(a) Use of vadadustat in pregnant women or women who may be pregnant

A dose finding study for effects on embryo-fetal development in rats (dose of vadadustat, 0-240 mg/kg/day) showed a high rate of postimplantation deaths at ≥120 mg/kg/day as well as reduced maternal body weight gain and low food consumption at 240 mg/kg/day. Because of the following points, however, the observed high rate of postimplantation deaths was considered as an incidental change, while the reduced maternal body weight gain and low food consumption were considered as changes secondary to the toxicity in maternal animals.

- The number of live offspring was not affected.

- The study for effects on embryo-fetal development in rats (dose of vadadustat, 0-160 mg/kg/day) designed based on results from the above dose finding study did not show the high rate of postimplantation deaths at up to 160 mg/kg/day.

In addition, in the study for effects on embryo-fetal development in rats, low fetal body weight and fetal immature ossification were observed at 160 mg/kg/day but reduced body weight gain and low food consumption in maternal animals were observed at ≥80 mg/kg/day. Low fetal body weight and fetal immature ossification, thus, were suggested to be effects secondary to the toxicity in maternal animals. A study for effects on embryo-fetal development in rabbits did not show any embryo-fetal toxicity or teratogenicity at up to 50 mg/kg/day.

Because the above studies showed no toxicological findings potentially attributable to the direct effects on embryos or fetuses in rats or rabbits, the applicant considers it acceptable to use vadadustat in pregnant women or women who may be pregnant if the expected therapeutic benefits outweigh the possible risks associated with treatment.

(b) Necessity of contraception in patients of childbearing potential during the treatment and a certain post-treatment period

A study of fertility and early embryonic development to implantation in rats showed no effects on the male or female reproductive organs, fertility, or early embryonic development to implantation at up to 120 mg/kg/day. In addition, repeated oral dose toxicity studies in rats and dogs showed no effects on the male or female reproductive organs. Based on the above, the applicant considers it unnecessary for patients of childbearing potential to use contraception during the treatment and a certain post-treatment period.

(c) Use of vadadustat in lactating women

Low body weight of off-spring from birth to post-weaning early phase was observed in a study for effects on pre- and post-natal development including maternal function in rats, and vadadustat was transferred into milk [see Section 4.4.3]. Based on the above findings, the applicant considers it desirable for lactating women to refrain from breast-feeding during use of vadadustat because it may affect the off-spring through milk.

PMDA's view:

At doses investigated in the repeated-dose toxicity studies and reproductive and developmental toxicity studies of vadadustat, neither histopathological findings in the male or female reproductive organs nor effects on fertility, early embryonic development, embryos, fetuses, or off-spring were observed. In addition, no critical effects on reproduction or development were suggested although the safety margin between the exposure in the toxicity studies of vadadustat and that in humans at the maximum clinical dose was not adequate [see Sections 5.2 and 5.5]. Based on the above, the applicant's explanations of the following effects are acceptable: Vadadustat may be used in pregnant women or women who may be pregnant if the expected therapeutic benefits outweigh the possible risks associated with treatment; patients of childbearing potential may not have to use contraception during the treatment with vadadustat and a certain post-treatment period; and breast-feeding is not desirable. The package insert, however, should include the information that vadadustat has been shown to be transferred into milk [see Section 4.4.3] and also into fetuses through the placenta [see Section 4.2.3]; and low fetal body weight and fetal immature ossification were observed in the study for effects on embryo-fetal development in rats.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

In Japanese clinical studies from which data were submitted in this application, [redacted] was used. [redacted] and [redacted] differ in [redacted], but their bioequivalence has been confirmed. In addition, [redacted] has been confirmed to be bioequivalent to [redacted] by [redacted]. Plasma concentrations of unchanged vadadustat and its metabolites (*O*-glucuronate conjugate and acylglucuronide conjugate), concentrations of unbound vadadustat in post-equilibrium dialysis samples, and urine concentrations of unchanged vadadustat and its metabolites (*O*-glucuronate conjugate and acylglucuronide conjugate) were determined by LC/MS/MS.

The lower limit of quantitation for each of the above concentrations was 1 to 200 ng/mL for the plasma concentration of unchanged vadadustat, 5 to 100 ng/mL for the plasma *O*-glucuronate conjugate concentration, 5 to 10 ng/mL for the plasma acylglucuronide conjugate concentration, 3 to 3.07 ng/mL for the unbound vadadustat concentration in a post-equilibrium dialysis sample, 10 ng/mL for the urine concentration of unchanged vadadustat, 200 ng/mL for the urine *O*-glucuronate conjugate concentration, and 20 ng/mL for the urine acylglucuronide conjugate concentration.

6.1.1 Bioequivalence (CTD 5.3.1.2-3, Study CI-0027 [March to May 2018], Reference data)

A randomized, open-label, 2-treatment, 2-period crossover study was conducted in 50 non-Japanese healthy adults to investigate bioequivalence of the proposed formulation of vadadustat (150 mg tablets, Formulation B) to the formulation for clinical study (150 mg tablets, Formulation A).

In this study, a single dose of 150 mg of Formulation A or Formulation B (vadadustat) was orally administered in the fasted state, with a 5-day washout period.

All of the 50 randomized subjects were included in the pharmacokinetic analysis.

The geometric mean ratios (90% confidence interval [CI]) of C_{max} and AUC_{0-t} of unchanged vadadustat in plasma after administration of Formulation B with respect to those after administration of Formulation A were 88.63% [81.98%, 95.81%] and 96.41% [92.66%, 100.31%], demonstrating bioequivalence of Formulation B to Formulation A.

6.1.2 Effects of food (CTD 5.3.1.2-4, Study CI-0028 [August to September 2018], Reference data)

A randomized, open-label, 3-treatment, 6-period crossover study was conducted in 54 non-Japanese healthy adults at a single study site in foreign country to investigate effects of food on the pharmacokinetics after a single oral administration of vadadustat at 450 mg.

In this study, a single dose of 450 mg of vadadustat was orally administered in the fasted state or after breakfast (a high-fat meal eating was started 30 minutes before the administration and completed 10 minutes before that), with a 5-day washout period. In addition, each administration used a 450 mg tablet in which the uncoated tablet had the same ingredient composition as that in the proposed formulation (150 mg tablets and 300 mg tablets) and of which bioequivalence to the proposed formulation was demonstrated.

All of the 54 randomized subjects were included in the pharmacokinetic analysis.

The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of unchanged vadadustat in plasma after administration in the fed state with respect to those after administration in the fasted state were 73.07% [67.92%, 78.61%] and 94.30% [90.30%, 98.49%]. Although C_{max} after administration in the fed state tended to be slightly lower than that after administration in the fasted state, $AUC_{0-\infty}$ did not differ between administrations in the fasted state and in the fed state. In a Japanese phase III study where administration timing of vadadustat with respect to meal time was not specified, the mean Hb

value and mean dose of vadadustat did not largely differ between the subgroup of subjects receiving vadadustat in the fed state and one of the other subjects. Based on the above, the applicant explained that the concerned decrease would not lead to any clinical problem.

6.1.3 Studies using human biomaterials

6.1.3.1 Plasma protein binding (CTD 5.3.2.1-1, 5.3.2.1-2, and 5.3.2.1-3, Studies [redacted]1137, [redacted]1159, and [redacted]7053[redacted])

When vadadustat (3-300 μg/mL) was incubated with human plasma, the mean plasma protein binding rate was 99.5% to 99.8% and thus was shown to be independent of the concentration. When *O*-glucuronate conjugate (5-100 μg/mL) was incubated with human plasma, the mean plasma protein binding rate was 86.5% to 87.8% and thus was shown to be independent of the concentration.

When vadadustat (10-100 μg/mL) was incubated with plasma specimens from Japanese healthy adults, patients with non-dialysis dependent chronic kidney disease (CKD), and patients on hemodialysis (HD) with renal anemia, the mean plasma protein binding rate was 99.7% to 99.8%, 99.4% to 99.8%, and 99.1% to 99.5%, respectively. There was no large difference between the specimens from healthy adults, patients with non-dialysis dependent CKD, and patients on HD. The high plasma protein binding rate indicates that dialysis is unlikely to have an impact on plasma concentrations of vadadustat. In addition, the applicant explained that vadadustat was considered to bind to albumin in blood mainly because of its acidic attribute.

6.1.3.2 *In vitro* investigation of metabolism (CTD 5.3.2.2-1 and 5.3.2.2-2, Studies [redacted]4105 and [redacted]0103)

Metabolism of vadadustat by CYP was investigated using human liver microsomes. Because the concentration of unchanged vadadustat did not decrease in either presence or absence of NADPH in the investigation using human liver microsomes, the applicant explained that CYP's contribution to metabolism of vadadustat was limited. In addition, metabolism of vadadustat by uridine-5'-diphospho-α-glucuronosyltransferase (UGT) was investigated using human liver, kidney, and small intestine microsomes. In human liver and kidney microsomes, the *O*-glucuronate conjugate was formed, and in human small intestine microsomes, the acylglucuronide conjugate was formed.

6.1.3.3 Investigation of UGT isoforms involved in metabolism of vadadustat (CTD 5.3.2.2-3, Study [redacted]4104)

When vadadustat was incubated with human UGT isoform expression systems (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15, and UGT2B17), the *O*-glucuronate conjugate was formed by UGT1A1, UGT1A7, UGT1A8, and UGT1A9, and the acylglucuronide conjugate was formed by UGT1A1 and UGT2B7.

6.1.3.4 Vadadustat's inhibition against human hepatic drug-metabolizing enzymes (CTD 5.3.2.2-4, 5.3.2.2-6, and 5.3.2.2-7, Studies 8275722, [redacted]5102, and [redacted]A028)

Inhibition of vadadustat (2.13-1,300 μmol/L for CYP isoforms, 1.30-1,304 μmol/L for UGT isoforms) against CYP isoforms[6)] (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) and UGT isoforms[7)] (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was investigated using human liver microsomes. IC_{50} of vadadustat against CYP2B6, CYP2C8, and CYP2C9 was 129, 42.7, and 119 μmol/L, respectively; vadadustat inhibited CYP2B6 (Ki value, 110 μmol/L), CYP2C8 (Ki value, 25.1 μmol/L), and CYP2C9 (Ki value, 48.6 μmol/L). IC_{50} of vadadustat against the other CYP and UGT isoforms exceeded 300 μmol/L. An analysis based on a static pharmacokinetic model showed that the ratio of the AUC value of a drug metabolized by any of CYP2B6, CYP2C8, and CYP2C9 with respect to that with concomitant oral administration of vadadustat at the maximum recommended clinical dose (600 mg/day) was less than 1.25. The applicant thus explained that vadadustat was unlikely to affect the pharmacokinetics of the concomitant drug by inhibiting these isoforms.

In addition, inhibition of the *O*-glucuronate conjugate (0.3-600 μmol/L) against CYP isoforms (CYP2B6, CYP2C8, and CYP2C9) and UGT isoforms (UGT1A1 and UGT1A9) was investigated using human liver microsomes. IC_{50} of vadadustat against any isoform exceeded 600 μmol/L; no inhibition of the *O*-glucuronate conjugate was observed.

6.1.3.5 Vadadustat's induction of human hepatic drug-metabolizing enzymes (CTD 5.3.2.2-5, Study 8273558)

Changes in mRNA expression levels of CYP1A2, CYP2B6, CYP3A4, and UGT1A1 during incubation of vadadustat (1.12-130 μmol/L) with human frozen hepatocytes were investigated. Vadadustat increased mRNA expression levels of CYP2B6 and UGT1A1 up to 14.6 times and 5.5 times (at the maximum concentration of 130 μmol/L). Vadadustat did not induce mRNA expression of CYP1A2 or CYP3A4. Within the concentration range investigated, increases in enzyme activities of CYP1A2, CYP3A4/5, and UGT1A1 were <2 times from baseline or <20% of that with the positive control. An increase in enzyme activity of CYP2B6 was observed but was ≤10% of that with the positive control and thus was not remarkable.

6.1.3.6 Investigation of transporter-mediated transportation (CTD 5.3.2.2-8, 5.3.2.2-9, and 5.3.2.2-10; Studies [redacted]8057, [redacted]0236, and [redacted]8101)

Using Lilly Laboratories cell-porcine kidney 1 (LLC-PK1) cells expressing P-glycoprotein (P-gp), P-gp-mediated transport of vadadustat at 0.3 to 30 μg/mL was investigated. The result indicated that vadadustat was not a substrate of P-gp.

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6) The following metabolic activities were used as indicators.
CYP1A2, Phenacetin *O*-deethylase; CYP2B6, Bupropion hydroxylase; CYP2C8, Amodiaquine *N*-deethylase; CYP2C9 Diclofenac 4'-hydroxylase; CYP2C19, *S*-Mephenytoin 4'-hydroxylase; CYP2D6, Bufuralol 1'-hydroxylase; CYP3A4/5, Testosterone 6β-hydroxylase and Midazolam 1'-hydroxylase

7) The following metabolic activities were used as indicators.
UGT1A1, 17β-Estradiol 3-glucuronidation; UGT1A4, Trifluoperazine glucuronidation; UGT1A6, 1-Naphthol glucuronidation; UGT1A9, Propofol glucuronidation; and UGT2B7, Morphine 3-glucuronidation

Using membrane vesicles expressing multidrug resistance-associated protein (MRP) 2, MRP2-mediated transport of the *O*-glucuronate conjugate (1-30 μg/mL) was investigated. The result indicated that the *O*-glucuronate conjugate was a substrate of MRP2.

Using Madin-Darby canine kidney cell II (MDCKII) cells expressing breast cancer resistance protein (BCRP), BCRP-mediated transport of vadadustat at 1 to 50 μg/mL was investigated. The result indicated that vadadustat was a substrate of BCRP.

Using human embryonic kidney cell line 293 (HEK293) cells expressing organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, multidrug and toxin extrusion (MATE) 1, and MATE2-K, transport of vadadustat (1-50 μg/mL for OATP1B1, OATP1B3, OAT1, OAT3 and OCT2; 0.3-30 μg/mL for MATE1 and MATE2-K) and the *O*-glucuronate conjugate (1-30 μg/mL) mediated by these expressed metabolic enzymes was investigated. The result indicated that vadadustat was a substrate of OATP1B1, OAT1 and OAT3, and the *O*-glucuronate conjugate was a substrate of OATP1B3 and OAT3.

6.1.3.7 Investigation of inhibition against transporters (5.3.2.2-8 and 5.3.2.2-10, Studies [redacted]8057 and [redacted]8101)

Using Caco-2 cells, effects of vadadustat (1-80 μg/mL) or the O-glucuronate conjugate (0.3-50 μg/mL) on transport of the reference substance for P-gp[8)] were investigated. Vadadustat tended to inhibit P-gp-mediated transport but by up to 50%. The *O*-glucuronate conjugate did not inhibit P-gp-mediated transport.

For inhibition against transport mediated by BCRP, bile salt export pump (BSEP), OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K, an effect of unchanged vadadustat or the *O*-glucuronate conjugate[9)] on transport of the reference substance[10)] for each of the above transporters was investigated using cells expressing the corresponding transporter. Vadadustat inhibited transport mediated by BCRP, OATP1B1, OAT1, and OAT3 with the IC_{50} values of 10.4, 4.02, 3.76, and 0.336 μg/mL, respectively. The *O*-glucuronate conjugate inhibited transport mediated by OAT1 and OAT3 with the IC_{50} values of 5.93 and 9.10 μg/mL, respectively.

6.2 Clinical pharmacology

6.2.1 Phase I study in healthy adults (CTD 5.3.3.3-1, Study CI-0020 [October 2015 to January 2016])

A placebo-controlled, randomized, double-blind study was conducted in Japanese and non-Japanese healthy adults (target sample size; 48 subjects, 24 each of Japanese and non-Japanese) to evaluate the pharmacokinetics and safety following multiple oral administration of vadadustat.

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8) Digoxin was used as the reference substance.
9) Inhibition against transport mediated by BSEP has not been investigated.
10) The following reference substances were used.
BCRP, prazosin; BSEP, ^{3}H-taurocholic acid; OATP1B1, ^{3}H-estradiol-17β-glucuronate conjugate; OATP1B3, ^{3}H-estradiol-17β-glucuronate conjugate; OAT1, ^{3}H-*p*-aminohippuric acid; OAT3, ^{3}H-estrone-3-sulfate; OCT2, ^{14}C-metformin; MATE1, ^{14}C-metformin; and MATE2-K, ^{14}C-metformin

In this study, the placebo or vadadustat at 150, 300, or 600 mg was orally administered once daily after ≥10 hours of fasting for 10 days. In addition, the subjects further fasted for 2 hours post-dose on Day 2 to Day 9 and for 4 hours post-dose on Day 1 and Day 10. All of the 48 treated subjects (12 in the placebo group, 36 in the vadadustat group) were included in the safety and pharmacokinetic analyses.

Tables 20 to 22 show plasma pharmacokinetic parameters of unchanged vadadustat, the *O*-glucuronate conjugate, and acylglucuronide conjugate in plasma, which do not largely differ between Japanese and non-Japanese subjects. C_{max} and $AUC_{0-\tau}$ of unchanged vadadustat increased with the dose proportionally, and no accumulation was observed in subjects who orally received vadadustat at 150 to 300 mg once daily.

Table 20. Pharmacokinetic parameters of unchanged vadadustat in plasma in healthy adults who orally received multiple dose of vadadustat in the fasted state

	Dose of vadadustat		n	C_{max} (μg/mL)	t_{max}[a)] (h)	$AUC_{0-\tau}$ (μg•h/mL)	$t_{1/2}$ (h)
Day 1	150	Japanese	6	17.9 ± 5.2	1.52 (1.00, 6.12)	113 ± 38.3	-
		Non-Japanese	6	17.0 ± 0.9	2.00 (1.00, 4.03)	94.8 ± 13.6	-
	300	Japanese	6	39.6 ± 6.9	2.28 (0.97, 3.95)	241 ± 29.8	-
		Non-Japanese	6	35.1 ± 8.6	1.95 (1.00, 4.02)	199 ± 42.7	-
	600	Japanese	6	69.0 ± 11.2	2.00 (1.98, 4.02)	513 ± 101	-
		Non-Japanese	6	83.1 ± 14.9	1.98 (0.97, 5.93)	526 ± 118	-
Day 10	150	Japanese	6	24.2 ± 5.0	0.75 (0.45, 3.93)	123 ± 30.5	5.96 ± 0.91
		Non-Japanese	6	18.0 ± 1.7	2.00 (1.00, 4.03)	102 ± 22.3	6.05 ± 0.85
	300	Japanese	6	44.3 ± 10.8	1.99 (1.95, 4.00)	289 ± 75.3	6.14 ± 0.76
		Non-Japanese	6	40.4 ± 5.5	2.02 (1.95, 2.05)	226 ± 47.3	5.55 ± 0.74
	600	Japanese	6	84.8 ± 22.3	1.98 (0.98, 4.00)	624 ± 205	6.07 ± 0.42
		Non-Japanese	6	79.0 ± 14.4	1.53 (0.97, 4.02)	556 ± 154	5.64 ± 0.86

Mean ± SD; -, Not determined
a) Median (minimum, maximum)

Table 21. Pharmacokinetic parameters of *O*-glucuronate conjugate in plasma in healthy adults who orally received multiple dose of vadadustat in the fasted state

	Dose of vadadustat		n	C_{max} (μg/mL)	t_{max}[a)] (h)	$AUC_{0-\tau}$ (μg•h/mL)	$t_{1/2}$ (h)
Day 1	150	Japanese	6	2.06 ± 0.40	3.99 (2.00, 6.12)	13.6 ± 2.9	-
		Non-Japanese	6	1.78 ± 0.28	4.01 (2.00, 4.05)	11.5 ± 1.4	-
	300	Japanese	6	4.26 ± 0.79	3.95 (1.98, 4.00)	31.5 ± 4.1	-
		Non-Japanese	6	4.68 ± 1.88	4.02 (1.97, 4.03)	34.4 ± 15.9	-
	600	Japanese	6	7.73 ± 1.06	4.00 (3.98, 5.98)	69.0 ± 11.6	-
		Non-Japanese	6	7.87 ± 1.78	4.00 (3.98, 5.93)	70.1 ± 19.4	-
Day 10	150	Japanese	6	2.15 ± 0.36	2.00 (1.97, 3.95)	14.8 ± 1.4	4.65 ± 1.25
		Non-Japanese	6	1.50 ± 0.16	3.99 (2.00, 4.03)	11.0 ± 1.5	3.72 ± 0.35
	300	Japanese	6	4.14 ± 0.33	4.00 (3.98, 4.18)	33.9 ± 3.3	5.27 ± 0.78
		Non-Japanese	6	5.00 ± 1.78	4.01 (3.97, 4.05)	37.7 ± 13.4	4.62 ± 1.68
	600	Japanese	6	8.39 ± 2.16	3.98 (1.95, 4.00)	78.9 ± 24.3	5.34 ± 0.56
		Non-Japanese	6	8.00 ± 1.45	4.00 (3.97, 4.02)	71.8 ± 15.0	5.15 ± 0.81

Mean ± SD; -, Not determined
a) Median (minimum, maximum)

Table 22. Pharmacokinetic parameters of acylglucuronide conjugate in plasma in healthy adults who orally received multiple dose of vadadustat in the fasted state

	Dose of vadadustat		n	C_{max} (μg/mL)	t_{max}[a)] (h)	$AUC_{0-\tau}$ (μg•h/mL)	$t_{1/2}$ (h)
Day 1	150	Japanese	6	0.054 ± 0.039	0.50 (0.50, 6.12)	-	-
		Non-Japanese	6	0.036 ± 0.017	1.03 (0.50, 2.02)	-	-
	300	Japanese	6	0.081 ± 0.048	1.47 (0.53, 2.00)	-	-
		Non-Japanese	6	0.085 ± 0.077	1.47 (1.00, 2.03)	-	-
	600	Japanese	6	0.123 ± 0.043	0.75 (0.45, 2.00)	0.498, 0.492[b)]	-
		Non-Japanese	6	0.097 ± 0.031	0.75 (0.45, 4.03)	-	-
Day 10	150	Japanese	6	0.065 ± 0.049	0.50 (0.45, 1.00)	NC	NC
		Non-Japanese	6	0.028 ± 0.010	0.75 (0.50, 1.00)	NC	NC
	300	Japanese	6	0.067 ± 0.018	0.97 (0.47, 1.95)	NC	NC
		Non-Japanese	6	0.071 ± 0.027	0.97 (0.47, 2.03)	NC	NC
	600	Japanese	6	0.143 ± 0.020	1.01 (0.45, 2.00)	0.562 [c)]	6.37[c)]
		Non-Japanese	6	0.119 ± 0.044	1.01 (0.45, 2.02)	0.443, 0.586[b)]	6.85, 13.5[b)]

Mean ± SD; -, Not determined; NC, Not calculated
a) Median (minimum, maximum)
b) Measured values in 2 animals
c) Measured value in 1 subject

Adverse events occurred in 1 subject each in the vadadustat 300 mg group (skin irritation) and 600 mg group (dizziness), and both events were considered as adverse drug reactions. No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

6.2.2 Mass balance study (CTD 5.3.3.1-3, Study CI-0008 [July 2013], Reference data)

An open-label study was conducted in non-Japanese healthy adults (target sample size, 6 subjects) at a single study site in foreign country to investigate mass balance following a single oral administration of ^{14}C-vadadustat.

In this study, a single dose of 325 mg of ^{14}C-vadadustat (capsule) was orally administered after ≥10 hours of fasting. All of the 6 subjects enrolled in this study were included in the pharmacokinetic analysis.

Table 23 shows pharmacokinetic parameters of unchanged vadadustat, the *O*-glucuronate conjugate, and acylglucuronide conjugate in plasma, of which unchanged vadadustat was found dominant in plasma.

Table 23. Plasma pharmacokinetic parameters in non-Japanese healthy adults who orally received a single dose of ^{14}C-vadadustat in the fasted state

Dose of vadadustat	n	Measured substance	C_{max} (μg/mL)	t_{max}[a)] (h)	AUC_{0-t} (μg•h/mL)	$t_{1/2}$ (h)
325 mg	6	Unchanged vadadustat	52.7 ± 12.3	2.50 (1.50, 4.00)	328 ± 80.6	6.43 ± 1.84
	6	*O*-glucuronate conjugate	8.5 ± 2.1	5.00 (3.00, 5.00)	65.3 ± 16.0	6.61 ± 1.45
	6	Acylglucuronide conjugate	0.1 ± 0.0	1.75 (0.50, 4.00)	0.2 ± 0.1	1.77 ± 0.13

Mean ± SD
a) Median (minimum, maximum)

Proportions (mean ± SD) of the administered radioactivity excreted into urine and feces until 72 hours after administration of ^{14}C-vadadustat were 58.9% ± 9.22% and 26.9% ± 14.8%. In urine, the *O*-glucuronate conjugate (65.2% of the administered radioactivity[11)]) was mainly detected, and

[11)] It was slightly higher than the proportion of the total radioactivity excreted into urine, and the potential reason was that the total radioactivity and metabolite concentrations were determined by different methods.

unchanged vadadustat and the acylglucuronide conjugate were found in trace amounts (<1% of the administered radioactivity for both). In feces, a deglycine form of vadadustat (approximately 17.5% of the administered radioactivity) and unchanged vadadustat (approximately 10% of the administered radioactivity) were mainly detected.

6.2.3 Japanese phase II study in patients with non-dialysis dependent CKD (CTD 5.3.5.1-1, Study CI-0021 [October 2016 to July 2017])

Plasma concentrations of unchanged vadadustat, the *O*-glucuronate conjugate, and acylglucuronide conjugate in patients with non-dialysis dependent CKD (target sample size; 48 subjects, 12 per group) who orally received multiple dose of vadadustat were determined.

In this study, the placebo or vadadustat at 150, 300, or 600 mg was orally administered once daily for 6 weeks [for outline of the study and results on the efficacy and safety, see Section 7.1].

For the pharmacokinetics, Table 24 shows plasma concentrations just before administration of Week 4. The plasma concentration of unchanged vadadustat increased with the dose proportionally although large variations were observed.

Table 24. Plasma concentrations (μg/mL) of unchanged vadadustat, *O*-glucuronate conjugate, and acylglucuronide conjugate in patients with non-dialysis renal anemia who orally received multiple dose of vadadustat

Dose of vadadustat	n	Measured substance		
		Unchanged vadadustat	*O*-glucuronate conjugate	Acylglucuronide conjugate
150	12	5,530.9 ± 4,168.9	3,914.7 ± 5,772.4	Below the lower limit of quantitation
300	12	12,955.8 ± 9.771.7	12,358.6 ± 7,586.7	23.4[a)]
600	13	19,291.5 ± 9,325.3	16,586.2 ± 12,363.4	29.2 ± 17.1[b)]

Mean ± SD
a), Measured value in 1 subject; b), 4 subjects

6.2.4 Japanese phase II study in patients on HD (CTD 5.3.5.1-2, Study CI-0022 [December 2016 to October 2017])

Plasma concentrations of unchanged vadadustat, the *O*-glucuronate conjugate, and acylglucuronide conjugate in patients on HD with an ESA-naïve[12] renal anemia (target sample size; 48 subjects, 12 per group) who orally received multiple dose of vadadustat were determined.

In this study, the placebo or vadadustat at 150, 300, or 600 mg was orally administered once daily for 6 weeks [for outline of the study and results on the efficacy and safety, see Section 7.2]. In this study, administration timing with respect to dialysis was not specified because a foreign phase I study in patients on HD (CI-0009),[13)] etc. demonstrated that hemodialysis did not affect the pharmacokinetics of vadadustat.

For the pharmacokinetics, Table 25 shows plasma concentrations just before administration of Week 4. The plasma concentration of unchanged vadadustat and the *O*-glucuronate conjugate increased with the dose proportionally although large variations were observed.

12) Patients who were not treated with any ESA or were withdrawn from an ESA for a certain period (≥2 weeks for rHuEPO or ≥8 weeks for DA and CERA)
13) A single dose of 450 mg of vadadustat was orally administered to non-Japanese patients on HD 4 hours before hemodialysis or 2 hours after hemodialysis.

Table 25. Plasma concentrations (μg/mL) of unchanged vadadustat, *O*-glucuronate conjugate, and acylglucuronide conjugate in patients with renal anemia on hemodialysis who orally received multiple dose of vadadustat

Dose of vadadustat	n	Measured substance		
		Unchanged vadadustat	*O*-glucuronate conjugate	Acylglucuronide conjugate
150	12	7,512.9 ± 8,675.5	10,285.0 ± 5,649.1	2.0 ± 1.4
300	13	10,660.7 ± 7,004.9	16,737.7 ± 7,411.1	12.2 ± 1.0[a)]
600	13	16,667.7 ± 8,490.3	41,792.3 ± 23,938.0	27.1 ± 18.1[b)]

Mean ± SD
a), 3 subjects; b), 6 subjects

6.2.5 Effects of hepatic function (CTD 5.3.3.3-2, Study CI-0024 [June to October 2018], Reference data)

An open-label, parallel-group study was conducted in non-Japanese subjects with normal hepatic function and subjects with moderate (Child-Pugh Class B) hepatic impairment (target sample size; 16 subjects, 8 per group) to investigate effects of hepatic impairment on the pharmacokinetics of vadadustat.

In this study, a single dose of 450 mg of vadadustat was orally administered. All of the 16 subjects (8 per group) who were enrolled in this study and received the study drug were included in the pharmacokinetic analysis.

Geometric mean ratios [90% CI] of pharmacokinetic parameters of unchanged vadadustat in plasma in subjects with moderate hepatic impairment with respect to those in subjects with normal hepatic function were 102.46% [79.28%, 132.43%] for C_{max} and 105.89% [82.47%, 135.95%] for $AUC_{0-\infty}$. Geometric mean ratios [90% CI] of pharmacokinetic parameters[14)] of unbound form of unchanged vadadustat in plasma in subjects with moderate hepatic impairment with respect to those in subjects with normal hepatic function were 120.24% [89.95%, 160.74%] for C_{max} and 124.27% [89.36%, 172.81%] for $AUC_{0-\infty}$.

In addition, the proportion of unchanged vadadustat excreted into urine was <1% irrespective of hepatic function status, but that of the *O*-glucuronate conjugate (mean ± SD) was lower in subjects with moderate hepatic impairment (66.9% ± 11.8%) than that in subjects with normal hepatic function (82.8% ± 17.7%). The renal clearance (CL_R) of vadadustat was 7.31 mL/h in subjects with normal hepatic function and 6.30 mL/h in subjects with moderate hepatic impairment.

6.2.6 Drug interactions

6.2.6.1 Drug interaction study with inhibitors against MRP2, BCRP, OATP1B1, UGT, OAT1, and OAT3 (CTD 5.3.3.4-5, Study CI-0029 [June to August 2018], Reference data)

The *in vitro* studies suggested that vadadustat was a substrate of MRP2, BCRP, OATP1B1, UGT, OAT1, and OAT3 [see Section 6.1.3.6]. An open-label study was conducted in non-Japanese healthy adults at a single study site in foreign country to investigate effects of cyclosporine (inhibitor against

14) Calculated by multiplying pharmacokinetic parameters obtained from the total plasma concentration by the proportion (mean of the values at 3, 24, and 72 hours post-dose) of the plasma-unbound form in subjects with normal hepatic function or subjects with moderate hepatic impairment

MRP2, BCRP, and OATP1B1) and probenecid (inhibitor against UGT, OAT1, and OAT3) on the pharmacokinetics of vadadustat.

For investigation of interaction with cyclosporine, a single dose of vadadustat at 300 mg was orally administered in the fasted state in Treatment Period A, and a single dose of a combination of vadadustat at 300 mg and cyclosporine at 500 mg was orally administered in the fasted state in Treatment Period B. A 7-day washout period is specified between these treatment periods. For investigation of interaction with probenecid, a single dose of vadadustat at 300 mg was orally administered in the fasted state on Day 1 and Day 5, and probenecid at 600 mg was orally administered twice daily on Days 3 to 6 (on Day 5, vadadustat and probenecid were concomitantly administered).

Table 26 shows geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of unchanged vadadustat and the *O*-glucuronate conjugate after concomitant use of vadadustat with cyclosporine with respect to those after vadadustat monotherapy. C_{max} of unchanged vadadustat was slightly decreased with concomitant cyclosporine but $AUC_{0-\infty}$ remained almost unchanged, and concomitant cyclosporine did not affect C_{max} or $AUC_{0-\infty}$ of the *O*-glucuronate conjugate. The applicant thus explained that cyclosporine would not affect the pharmacokinetics of vadadustat to a clinically relevant extent.

Table 26. Geometric mean ratio (%) of pharmacokinetic parameters of unchanged vadadustat and *O*-glucuronate conjugate in plasma after concomitant use of vadadustat with inhibitor against BCRP and OATP1B1 with respect to those after vadadustat monotherapy[a)]

Dose of vadadustat	Concomitant drug (oral)	n	Unchanged vadadustat		*O*-glucuronate conjugate	
			C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$
300 mg	Cyclosporine	20	81.76 [76.02, 87.93]	116.89 [109.32, 124.99]	86.63 [82.25, 91.26]	113.74 [108.57, 119.16]

Geometric mean ratio (%) [90% CI]
a) Administration with cyclosporine/administration without cyclosporine × 100

Table 27 shows geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of unchanged vadadustat and the *O*-glucuronate conjugate after concomitant use of vadadustat with probenecid with respect to those after vadadustat monotherapy. $AUC_{0-\infty}$ of unchanged vadadustat and the *O*-glucuronate conjugate were increased 1.8 and 2.3 times, respectively, with concomitant probenecid. In addition, the proportions of vadadustat and the *O*-glucuronate conjugate excreted into urine (mean ± SD) were decreased with concomitant probenecid (0.81% ± 0.29% [without probenecid] to 0.46% ± 0.21% [with probenecid] for unchanged vadadustat, 77.3% ± 10.1% [without probenecid] to 56.1% ± 12.7% [with probenecid] for the *O*-glucuronate conjugate). The applicant explained that the following findings suggested that the interaction between probenecid and vadadustat was barely affected by the UGT inhibition but mainly mediated by OAT1 and OAT3: $AUC_{0-\infty}$ of both unchanged vadadustat and *O*-glucuronate conjugate were increased to a similar extent with concomitant probenecid; and concomitant probenecid did not change ratios of the plasma concentration and urinary excretion proportion of the *O*-glucuronate conjugate with respect to those of unchanged vadadustat.

Table 27. Geometric mean ratios (%) of pharmacokinetic parameters of unchanged vadadustat and *O*-glucuronate conjugate in plasma after concomitant use of vadadustat with inhibitor against UGT, OAT1, and OAT3 with respect to those after vadadustat monotherapy[a)]

Dose of vadadustat	Concomitant drug (oral)	n	Unchanged vadadustat		*O*-glucuronate conjugate	
			C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$
300 mg	Probenecid	20	102.79 [94.95, 111.28]	182.13 [171.08, 193.89]	110.38 [105.06, 115.97]	226.39 [208.92, 245.33]

Geometric mean ratio (%) [90% CI]

a) Administration with probenecid/administration without probenecid × 100

6.2.6.2 Drug interaction study with substrates of BCRP and OATP1B1 (CTD 5.3.3.4-6, Study CI-0030 [May to November 2018], Reference data)

The *in vitro* studies suggested that vadadustat inhibited transport mediated by BCRP and OATP1B1 [see Section 6.1.3.7]. An open-label study was conducted in non-Japanese healthy adults at a single study side in foreign country to investigate effects of vadadustat on the pharmacokinetics of rosuvastatin (substrate of BCRP and OATP1B1), sulfasalazine (substrate of BCRP), pravastatin (substrate of OATP1B1), atorvastatin (substrate of OATP1B1), and simvastatin (substrate of OATP1B1).

In this study, for investigation of interaction with rosuvastatin, a single dose of rosuvastatin at 20 mg was orally administered on Day 1 and Day 10, and vadadustat at 600 mg was orally administered once daily on Days 7 to 14 (on Day 10, vadadustat and rosuvastatin were concomitantly administered). For investigation of interaction with sulfasalazine, a single dose of sulfasalazine at 500 mg was orally administered on Day 1 and Day 9, and vadadustat at 600 mg was orally administered once daily on Days 6 to 12 (on Day 9, vadadustat and sulfasalazine were concomitantly administered). For investigation of interaction with pravastatin, a single dose of pravastatin at 40 mg was orally administered on Day 1 and Day 6, and vadadustat at 600 mg was orally administered once daily on Days 3 to 6 (on Day 6, vadadustat and pravastatin were concomitantly administered). For investigation of interaction with atorvastatin, atorvastatin at 40 mg was orally administered once daily on Days 1 to 8, and vadadustat at 600 mg was orally administered once daily on Days 5 to 8 (on Days 5-8, vadadustat and atorvastatin were concomitantly administered). For investigation of interaction with simvastatin, a single dose of simvastatin at 40 mg was orally administered on Day 1 and Day 5, and vadadustat at 600 mg was orally administered once daily on Days 2 to 5 (on Day 5, vadadustat and simvastatin were concomitantly administered).

Table 28 shows geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of each substrate of OATP1B1 after concomitant use of the substrate with vadadustat with respect to those after administration of the substrate alone.

Table 28. Geometric mean ratio (%) of pharmacokinetic parameters of concomitant drug in plasma after concomitant use of vadadustat with drug with respect to those after monotherapy[a)]

Dose of vadadustat	Concomitant drug (oral)	n	Measured substance	C_{max}	$AUC_{0-\infty}$
600 mg	Rosuvastatin 20 mg	33	Rosuvastatin	274.80 [246.28, 306.62]	246.86 [227.08, 26836]
	Sulfasalazine 500 mg	26	Sulfasalazine	275.32 [233.07, 325.22]	457.87 [378.24, 554.28]
			Sulfapyridine[b)]	84.81 [77.51, 92.78]	98.53 [90.76, 106.97]
			5-aminosalicylic acid[b)]	119.13 [86.69, 163.71]	139.10 [110.01, 175.89]
	Pravastatin 40 mg	25	Pravastatin	82.74 [72.27, 94.73]	102.03 [90.87, 114.56]
	Atorvastatin 40 mg	24	Atorvastatin	100.45 [85.30, 118.30]	142.05 [135.42, 149.00]
			O-hydroxy atorvastatin[c)]	91.20 [80.47, 103.36]	112.01 [106.91, 117.36]
			p-hydroxy atorvastatin[c)]	230.48 [192.41, 276.08]	167.57 [155.95, 180.06]
	Simvastatin 40 mg	23	Simvastatin	123.15 [104.55, 145.05]	194.56 [169.77, 222.97]
			β-hydroxy simvastatin acid[d)]	291.84 [260.40, 327.07]	246.21 [218.73, 277.15]

Geometric mean ratio (%) [90% CI]
a) Administration with vadadustat/administration without vadadustat × 100
b) Active metabolite of sulfasalazine
c) Metabolite of atorvastatin
d) Metabolite of simvastatin

6.2.6.3 Drug interaction study with substrates of P-gp, OAT1, and OAT3 (CTD 5.3.3.4-7, Study CI-0031 [June to September 2018], Reference data)

The *in vitro* studies suggested that vadadustat inhibited transport mediated by P-gp, OAT1, and OAT3 [see Section 6.1.3.7]. An open-label study was conducted in non-Japanese healthy adults at a single study side in foreign country to investigate effects of vadadustat on the pharmacokinetics of digoxin (substrate of P-gp), adefovir (substrate of OAT1), and furosemide (substrate of OAT1 and OAT3).

In this study, for investigation of interaction with digoxin, a single dose of digoxin at 0.5 mg was orally administered on Day 1 and Day 16, and vadadustat at 600 mg was orally administered once daily on Days 13 to 19 (on Day 16, vadadustat and digoxin were concomitantly administered). For investigation of interaction with adefovir, a single dose of adefovir at 10 mg was orally administered on Day 1 and Day 7, and vadadustat at 600 mg was orally administered once daily on Days 4 to 8 (on Day 7, vadadustat and adefovir were concomitantly administered). For investigation of interaction with furosemide, a single dose of furosemide at 40 mg was orally administered on Day 1 and Day 6, and vadadustat at 600 mg was orally administered once daily on Days 3 to 6 (on Day 6, vadadustat and furosemide were concomitantly administered).

Table 29 shows geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of each concomitant drug after concomitant use of the drug with vadadustat with respect to those after monotherapy. The applicant explained that although C_{max} of digoxin was decreased by 33% with concomitant vadadustat, vadadustat would not affect the pharmacokinetics of digoxin to a clinically relevant extent because an intra-individual variability of C_{max} of digoxin orally administered was 14% to 32% (*J Clin Pharmacol.* 2018;58:202-11, etc.); and concomitant vadadustat did not change $AUC_{0-\infty}$ of digoxin. Concomitant vadadustat increased C_{max} and $AUC_{0-\infty}$ of furosemide 1.7 and 2.1 times. Because concomitant vadadustat barely changed C_{max} and $AUC_{0-\infty}$ of adefovir, the applicant explained that concomitant vadadustat might have increased C_{max} and $AUC_{0-\infty}$ of furosemide through interaction with its OAT3 inhibition.

Table 29. Geometric mean ratio (%) of pharmacokinetic parameters of concomitant drug in plasma after concomitant use of vadadustat with drug with respect to those after monotherapy[a)]

Dose of vadadustat	Concomitant drug (oral)	n	Measured substance	C_{max}	$AUC_{0-\infty}$
600 mg	Digoxin 0.5 mg	18	Digoxin	66.92 [60.52, 74.00]	91.37 [85.20, 97.99]
	Adefovir 10 mg	14	Adefovir	95.15 [86.27, 104.95]	114.70 [108.82, 120.90]
	Furosemide 40 mg	22	Furosemide	171.25 [136.63, 214.66]	209.21 [187.07, 233.97]

Geometric mean ratio (%) [90% CI]
a) Administration with vadadustat/administration without vadadustat × 100

6.2.6.4 Drug interaction studies with oral iron preparation, iron-based phosphate binder, and ferrous sulfate (CTD 5.3.3.4-1 and 5.3.3.4-3, Studies MT-6548-J05 and CI-0012 [August to September 2018 and December 2014])

Because vadadustat might be chelated with iron, drug interaction studies with oral iron preparation, iron-based phosphate binder, and ferrous sulfate were conducted.

An open-label study was conducted in Japanese healthy adults at a single study site in Japan to investigate effects of oral iron preparation or iron-based phosphate binder on the pharmacokinetics of vadadustat.

In this study, subjects in Cohort 1 orally received vadadustat at 150 mg with or without concomitant sodium ferrous citrate (200 mg of iron) or ferric citrate hydrate (2,000 mg of ferric citrate) after a meal. Subjects in Cohort 2 orally received vadadustat at 150 mg with or without concomitant sucroferric oxyhydroxide (1,000 mg of iron) just before a meal. Subjects in Cohort 3 orally received vadadustat at 150 mg with or without concomitant ferrous sulfate extended-release tablets (210 mg of iron) in the fasted state.

An open-label study was conducted in non-Japanese healthy adults to investigate effects of oral iron preparation on the pharmacokinetics of vadadustat. In this study, vadadustat at 450 mg was orally administered with or without concomitant ferrous sulfate (65 mg of iron) in the fasted state.

Table 30 shows pharmacokinetic parameters of unchanged vadadustat in plasma after administration of vadadustat with or without each concomitant oral iron preparation. The applicant has explained that vadadustat interacts with iron preparations because each concomitant iron preparation decreased C_{max} and $AUC_{0-\infty}$ of vadadustat by approximately 50% to 90%. In main clinical studies of vadadustat, administrations of vadadustat and iron-based preparations were separated by ≥2 hours.

Table 30. Pharmacokinetic parameters of unchanged vadadustat in plasma after administration of vadadustat with or without each concomitant oral iron preparation.

Dose of vadadustat	Concomitant drug (during treatment with vadadustat)	n	Unchanged vadadustat			
			C_{max}		$AUC_{0-\infty}$	
			Geometric mean (μg/mL)	Ratio of value after concomitant use to value after vadadustat monotherapy (%) [90% CI]	Geometric mean (μg•h/mL)	Ratio of value after concomitant use to value after vadadustat monotherapy (%) [90% CI]
Sodium ferrous citrate and ferric citrate hydrate						
150 mg	Without concomitant drug (vadadustat monotherapy)	21	14.30		104.22	
	With sodium ferrous citrate	20	6.96	48.7 [40.6, 58.4]	46.59	44.8 [38.1. 52.6]
	With ferric citrate hydrate	20	5.18	36.3 [30.2. 43.5]	32.35	31.1 [26.5. 36.5]
Sucroferric oxyhydroxide						
150 mg	Without concomitant drug (vadadustat monotherapy)	20	15.20		99.47	
	With sucroferric oxyhydroxide	20	8.81	58.0 [49.9, 67.3]	45.74	46.0 [40.8, 51.9]
Ferrous sulfate extended-release tablets						
150 mg	Without concomitant drug (vadadustat monotherapy)	20	26.49		128.00	
	With ferrous sulfate extended-release tablets	20	2.14	8.1 [6.2, 10.6]	13.20	10.3 [8.0, 13.3]
Ferrous sulfate						
450 mg	Without concomitant drug (vadadustat monotherapy)	10	45.3		263	
	With ferrous sulfate extended-release tablets	10	22.3	49.3 [37.8, 64.4]	122	46.3 [37.1, 57.8]

6.2.6.5 Drug interaction study with proton pump inhibitor (CTD 5.3.3.4-8, Study CI-0033 [September to November 2018])

Because solubility of vadadustat increases with pH, the drug interaction with a proton pump inhibitor was investigated. An open-label study was conducted in non-Japanese healthy adults at a single study site in foreign country to investigate an effect of a proton pump inhibitor on the pharmacokinetics of vadadustat.

In this study, a single dose of vadadustat at 300 mg was orally administered on Day 1 and Day 6 in the fasted state, and rabeprazole at 20 mg was orally administered twice daily on Days 2 to 6 (on Day 6, vadadustat and rabeprazole were concomitantly administered). On Day 6, rabeprazole was administered 2 hours before administration of vadadustat.

Table 31 shows geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of unchanged vadadustat and the *O*-glucuronate conjugate after concomitant use of vadadustat with rabeprazole with respect to those after vadadustat monotherapy. Concomitant rabeprazole did not affect C_{max} and $AUC_{0-\infty}$ of vadadustat.

Table 31. Geometric mean ratio (%) of pharmacokinetic parameters of unchanged vadadustat and *O*-glucuronate conjugate in plasma after concomitant use of vadadustat with proton pump inhibitor with respect to those after vadadustat monotherapy[a)]

Dose of vadadustat	Concomitant drug (oral)	n	Unchanged vadadustat		*O*-glucuronate conjugate	
			C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$
300 mg	Rabeprazole	19	102.66 [98.77, 106.71]	103.61 [99.95, 107.40]	108.36 [102.97, 114.04]	106.39 [102.17, 110.78]

Geometric mean ratio (%) [90% CI]
a) Administration with rabeprazole/administration without rabeprazole × 100

6.2.7 Study for evaluation of QT/QTc (5.3.4.1-1, Study CI-0010 [January to April 2014])

A placebo- and active-controlled, randomized, partial double-blind (moxifloxacin was administered in an open-label manner), 4-treatment, 4-period crossover study was conducted in non-Japanese healthy adults aged ≥18 and ≤55 years (target sample size, 52 subjects) at a single study site in foreign country to investigate an effect on QT/corrected QT interval (QTc) after a single oral administration of vadadustat.

In this study, a single dose of the placebo, vadadustat at 600 or 1,200 mg, or moxifloxacin, the positive control, at 400 mg was orally administered in the fasted state, and a 7-day washout period was specified between these treatment periods.

All of the 50 subjects who received any study drug were included in the safety analysis and QT/QTc analysis, and of these 49 subjects were included in the pharmacokinetic analysis.

Adverse events occurred in 3 of 48 subjects (6.3%) during the placebo treatment period, 12 of 49 subjects (24.5%) during the vadadustat 600 mg treatment period, 13 of 49 subjects (26.5%) during the vadadustat 1,200 mg treatment period, and 7 of 48 subjects (14.6%) during the moxifloxacin treatment period. Table 32 shows adverse events reported by ≥3 subjects during any of the treatment periods. No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

Table 32. Adverse events reported by ≥3 subjects during any of the treatment periods

	Placebo (n = 48)	Vadadustat 600 mg (n = 49)	Vadadustat 1,200 mg (n = 49)	Moxifloxacin (n = 48)
All adverse events	6.3 (3)	24.5 (12)	26.5 (13)	14.6 (7)
Nausea	0 (0)	8.2 (4)	12.2 (6)	2.1 (1)
Diarrhoea	0 (0)	8.2 (4)	12.2 (6)	2.1 (1)
Headache	4.2 (2)	8.2 (4)	10.2 (5)	2.1 (1)
Abdominal pain	0 (0)	2.0 (1)	6.1 (3)	0 (0)
Back pain	0 (0)	2.0 (1)	4.1 (2)	2.1 (1)
Dizziness	0 (0)	6.1 (3)	0 (0)	2.1 (1)

Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver.16.1
Incidence % (n)

The largest difference of change from baseline in Fridericia-corrected QT interval (QTcF) during the placebo treatment period (ΔΔQTcF) (upper limit of 90% two-sided CI) was 1.2 (3.5) ms during the vadadustat 600 mg treatment period and 3.3 (5.7) ms during the vadadustat 1,200 mg treatment period, and the upper limits of 90% two-sided CI at both doses were below 10 ms. In addition, during the moxifloxacin treatment period, all the lower limits of 90% CI of ΔΔQTcF values at predetermined 3

timepoints (2, 3, and 4 hours post-dose) exceeded 5 ms, demonstrating that the analysis was adequately sensitive.

Of the pharmacokinetic parameters of vadadustat in plasma, C_{max} and $AUC_{0\text{-last}}$ (geometric mean [geometric coefficient of variation, %] for both) were 53.7 (25.5) μg/mL and 383 (35.9) μg•h/mL at the vadadustat 600 mg and 89.3 (27.1) μg/mL and 805 (35.6) μg•h/mL at the vadadustat 1,200 mg.

6.R Outline of the review conducted by PMDA

6.R.1 Interactions with substrates of BCRP and OATP1B1

The applicant's explanation about effects of vadadustat on the pharmacokinetics of substrates of BCRP and OATP1B1:

In the foreign drug interaction study (Study CI-0030), vadadustat increased the exposures to sulfasalazine (substrate of BCRP), atorvastatin (substrate of OATP1B1), simvastatin (substrate of OATP1B1), simvastatin acid, an active metabolite of simvastatin (substrate of OATP1B1), and rosuvastatin (substrate of BCRP and OATP1B1) [see Section 6.2.6.2]. Based on results with sulfasalazine, for drug interaction between vadadustat and a substrate of BCRP, caution statements should be included in the package insert of vadadustat. In addition, because AUC of pravastatin, which is a substrate of OATP1B1 but unaffected by BCRP, was not changed by concomitant vadadustat, the pharmacokinetics of pravastatin is not affected by vadadustat's OATP1B1 inhibition. The exposures to simvastatin, simvastatin acid, and atorvastatin were considered to be increased by vadadustat's BCRP inhibition because these drugs were substances of BCRP (*Clin Pharmacol Ther.* 2009;86:197-203, *Clin Pharmacol Ther.* 2012;92:584-98, *Drugs R D.* 2016;16:93-107, etc.). For concomitant use of simvastatin, caution statements should be included in the package insert. However, for the drug interaction between vadadustat and atorvastatin, a pooled analysis[15)] of 6 studies in total including Japanese phase II studies (CI-0021 and CI-0022) and Japanese phase III studies (MT-6548-J01 to MT-6548-J04) showed that there were no differences between combination therapy with vadadustat and atorvastatin and vadadustat monotherapy in incidences of adverse events (64 of 70 subjects [91.4%] receiving combination therapy, 270 of 299 subjects [90.3%] receiving monotherapy) and adverse drug reactions (7 of 70 subjects [10.0%] receiving combination therapy, 45 of 299 subjects [15.1%] receiving monotherapy). No caution statements may be included in the package insert at present.

PMDA's view:

There is no problem with the applicant's action that caution statements for concomitant use of vadadustat with a substrate of BCRP will be included in the package insert. Of substrates of BCRP, atorvastatin should be referred to in a caution statement in the package insert of vadadustat to the effect that concomitant use with vadadustat increased the exposure in the foreign drug interaction study (Study CI-0030), although no particular safety concerns have been raised in patients receiving

15) The safety data from the following 6 studies were pooled. The pooled analyses in the subsequent evaluation also used the same data.
Safety data covering a period up to 16 weeks in the Japanese phase II studies (CI-0021 and CI-0022) in patients with non-dialysis dependent CKD or patients on HD
Safety data covering a period up to 52 weeks in the Japanese phase III studies (MT-6548-J01 and MT-6548-J03) in patients with non-dialysis dependent CKD or patients on HD
Safety data covering a period up to 26 weeks in the Japanese phase III studies (MT-6548-J02 and MT-6548-J04) in patients on peritoneal dialysis (PD) or patients on HD

vadadustat and atorvastatin concomitantly in clinical studies at present. The applicant should continue collecting information about the safety in patients receiving vadadustat and any of the above drugs concomitantly through post-marketing surveillance, etc. to evaluate the safety.

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

The applicant submitted 6 Japanese clinical studies shown in Table 33 as the evaluation data on the efficacy and safety.

Table 33. Outline of clinical studies on efficacy and safety

Phase	Study	Study population	Study design	Treatment period	Group (No. of subjects treated)
II	CI-0021	ESA-naïve patients (untreated with any ESA or withdrawn from an ESA for ≥6 weeks) with non-dialysis dependent CKD	Randomized, double-blind, placebo-controlled, parallel-group	16 weeks	Major evaluation period (first dose to Week 6) Placebo, n = 14 Vadadustat 150 mg, n = 12 Vadadustat 300 mg, n = 12 Vadadustat 600 mg n = 13 Dose adjustment period (Weeks 7 to 16) Vadadustat 150-600 mg, n = 51
	CI-0022	ESA-naïve patients (untreated with any ESA or withdrawn from an ESA for a certain period) on HD	Randomized, double-blind, placebo-controlled, parallel-group	16 weeks	Major evaluation period (first dose to Week 6) Placebo, n = 15 Vadadustat 150 mg, n = 15 Vadadustat 300 mg, n = 15 Vadadustat 600 mg, n = 15 Dose adjustment period (Weeks 7 to 16) Vadadustat 150-600 mg, n = 43
III	MT-6548-J01	Patients with non-dialysis dependent CKD	Randomized, open-label, active-controlled, parallel-group	52 weeks	Vadadustat, n = 151 DA, n = 153
	MT-6548-J02	Patients on PD	Open-label, uncontrolled	24 weeks	Vadadustat, n = 42
	MT-6548-J03	Patients on HD receiving an ESA	Randomized, double-blind, active-controlled, parallel-group	52 weeks	Vadadustat, n = 162 DA, n = 161
	MT-6548-J04	ESA-naïve patients (untreated with any ESA or withdrawn from an ESA for a certain period) on HD	Open-label, uncontrolled	24 weeks	No. of subjects treated with vadadustat, n = 24

HD, Hemodialysis; PD, peritoneal dialysis

7.1 Phase II studies

7.1.1 Japanese phase II study in patients with non-dialysis dependent CKD (dose-finding study) (CTD 5.3.5.1-1, Study CI-0021 [October 2016 to July 2017])

A multi-center, randomized, double-blind, parallel-group study was conducted in patients with non-dialysis dependent CKD who were ≥20 years old and had ESA-naïve[16)] renal anemia (Table 34) (target sample size; 48 subjects, 12 per group) at 30 study sites in Japan to investigate the efficacy, safety, and dose-response relationship of vadadustat.

16) Patients untreated with any ESA or withdrawn from an ESA for ≥6 weeks

Table 34. Major inclusion and exclusion criteria

Major inclusion criteria • Patients with CKD not scheduled to start dialysis within 3 months • Patients with Hb ≤10.5 g/dL, serum ferritin ≥50 ng/mL, and transferrin saturation (TSAT) ≥20% • Patients who have not orally taken iron preparations or have orally taken ones at the same dose for ≥28 days before screening Major exclusion criteria • Patients complicated by anemia (hemolysis anemia, etc.) other than renal anemia • Patients who have received an ESA from 6 weeks before screening to the screening period • Patients who have intravenously received iron preparations from 4 weeks before screening to the screening period • Patients who have a medical history of untreated proliferative diabetic retinopathy, diabetic macular edema, age-related macular degeneration, central retinal vein occlusion, and active retinal haemorrhage from 8 weeks before screening to the screening period • Patients in whom treatment on the eye with laser photocoagulation or anti-vascular endothelial growth factor agent is ongoing • Patients with a medical history of deep venous thrombosis or pulmonary embolism requiring treatment

This study consisted of the 6-week major evaluation period and 10-week dose adjustment period.

During the major evaluation period (first dose to Week 6), the placebo or vadadustat at 150, 300, or 600 mg was orally administered once daily. During the dose adjustment period (Weeks 7 to 16), subjects in the placebo group also switched from the placebo to vadadustat,[17] and all the subjects orally received vadadustat at a varied dose of 150 to 600 mg[18] once daily to maintain the Hb value within the target range (10.0-12.0 g/dL). All of the 51 randomized subjects (14 in the placebo group, 12 in the vadadustat 150 mg group, 12 in the vadadustat 300 mg group, 13 in the vadadustat 600 mg group) received the study drug and were included in the efficacy and safety analyses. Discontinuation occurred in no subjects during the major evaluation period (first dose to Week 6) and 5 subjects during the dose adjustment period (Weeks 7 to 16) owing to “adverse events” in 4 subjects and “aggravated symptoms” in 1 subject.

For the efficacy, Table 35 shows results on the primary endpoint, “change in the Hb value from baseline (before the first dose of the study drug)[19] to the end of 6 weeks of treatment.” The change in any vadadustat group tended to dose-dependently increase, and was different from that in the placebo group with a statistical significance ($P < 0.005$ for vadadustat 150 mg, $P < 0.001$ for vadadustat 300 mg, and $P < 0.001$ for vadadustat 600 mg, analysis of covariance [ANCOVA], two-sided significance level of 5%, and multiplicity adjustment by step-down procedure).

17) The first dose of vadadustat after the switching was 150, 300, or 600 mg based on the dose during the major evaluation period.
18) The dose increase actions should be separated by ≥4 weeks, and the dose should be adjusted according to the following criteria:
- If an increase in Hb from baseline after 6 weeks of treatment is ≤0.5 g/dL, the dose should be increased by 150 mg.
- If the Hb value is <10.0 g/dL, the dose should be increased by 150 mg.
- If the Hb value is rapidly increased or exceeds 12.0 g/dL, the dose should be decreased by 150 mg.
- If the Hb value exceeds 13.0 g/dL, the study drug should be suspended until the Hb value is decreased to ≤12.5 g/dL and then it should be resumed at a reduced dose.

19) Mean Hb value at 2 timepoints, at the screening and before the first dose

Table 35. Change (g/dL) in the Hb value from baseline to end of 6 weeks of treatment (modified intent-to-treat [MITT] population)

	Placebo (n = 14)	Vadadustat		
		150 mg (n = 12)	300 mg (n = 12)	600 mg (n = 13)
Hb value at baseline[a)]	9.89 ± 0.58	9.95 ± 0.63	9.55 ± 0.70	9.54 ± 0.78
Hb value at end of 6 weeks of treatment	9.42 ± 0.92	10.39 ± 0.73	10.68 ± 1.27	11.16 ± 1.12
Change in the Hb value from baseline to end of 6 weeks of treatment	-0.46 ± 0.56	0.44 ± 0.46	1.12 ± 0.98	1.62 ± 0.92
Difference between groups (vadadustat − placebo) [95% CI][b)]	-	0.90 [0.29, 1.51]	1.59 [0.98, 2.21]	2.09 [1.49, 2.70]
P value[b)]	-	$P < 0.005$	$P < 0.001$	$P < 0.001$

Mean ± SD, last observation carried forward (LOCF)

a) Mean Hb value at 2 timepoints, at the screening and before the first dose

b) ANCOVA using the treatment group as a factor and the Hb value at baseline as a covariate; two-sided significance level of 5%; and multiplicity of test adjusted by step-down procedure in which hierarchy was established based on the dose in a descending order.

For the safety during the major evaluation period (first dose to Week 6), adverse events occurred in 5 of 14 subjects (35.7%) in the placebo group, 4 of 12 subjects (33.3%) in the vadadustat 150 mg group, 7 of 12 subjects (58.3%) in the vadadustat 300 mg group, and 7 of 13 subjects (53.8%) in the vadadustat 600 mg group. Table 36 shows adverse events reported by ≥2 subjects in any group. Adverse drug reactions occurred in 0 of 14 subjects (0%) in the placebo group, 1 of 12 subjects (8.3%) in the vadadustat 150 mg group, 3 of 12 subjects (25.0%) in the vadadustat 300 mg group, and 3 of 13 subjects (23.1%) in the vadadustat 600 mg group. Table 37 shows adverse drug reactions reported by ≥2 subjects in any group.

No deaths, serious adverse events, or adverse events leading to discontinuation of the study drug occurred.

Table 36. Adverse events reported by ≥2 subjects in any group during the major evaluation period (first dose to Week 6) (safety analysis set)

	Placebo (n = 14)	Vadadustat		
		150 mg (n = 12)	300 mg (n = 12)	600 mg (n = 13)
All adverse events	35.7 (5)	33.3 (4)	58.3 (7)	53.8 (57)
Hypertension	0 (0)	0 (0)	25.0 (3)	15.4 (2)
Nausea	0 (0)	0 (0)	16.7 (2)	7.7 (1)

MedDRA/J ver.20.0
Incidence % (n)

Table 37. Adverse drug reactions reported by ≥2 subjects in any group during the major evaluation period (first dose to Week 6) (safety analysis set)

	Placebo (n = 14)	Vadadustat		
		150 mg (n = 12)	300 mg (n = 12)	600 mg (n = 13)
All adverse drug reactions	0 (0)	8.3 (1)	25.0 (3)	23.1 (3)
Hypertension	0 (0)	0 (0)	16.7 (2)	15.4 (2)
Nausea	0 (0)	0 (0)	16.7 (2)	0 (0)

MedDRA/J ver.20.0
Incidence % (n)

For the safety in all of the 51 subjects who entered the dose adjustment period (Weeks 7 to 16), incidences of adverse events and adverse drug reactions were 66.7% (34 of 51) of subjects and 7.8% (4 of 51) of subjects. Adverse events reported by ≥2 subjects were viral upper respiratory tract infection and arteriovenous shunt operation in 3 subjects each, and constipation, diarrhoea, contusion,

hyperkalaemia, back pain, and delirium in 2 subjects each. There were no adverse drug reactions reported by ≥2 subjects.

No deaths occurred. Serious adverse events occurred in 11 subjects (arteriovenous shunt operation [3 subjects], hepatic function abnormal, end stage renal disease, lung infection, acute kidney injury, interstitial lung disease, spinal compression fracture, influenza, duodenal ulcer haemorrhage, renal dysfunction, and asthma [1 subject each]; some subjects experienced multiple events). Hepatic function abnormal was assessed as a serious adverse drug reaction but resolved after discontinuation of the study drug. Adverse events leading to treatment discontinuation occurred in 4 subjects (renal dysfunction, hepatic function abnormal, end stage renal disease, acute kidney injury, and lung infection [1 subject each]; some subjects experienced multiple events), but a causal relationship to the study drug were ruled out for all the adverse events except for hepatic function abnormal. The outcome of renal dysfunction was resolving, and the other events resolved.

7.1.2 Japanese phase II study in patients on HD (dose-finding study) (CTD 5.3.5.1-2, Study CI-0022 [December 2016 to October 2017])

A multi-center, randomized, double-blind, parallel-group study was conducted in patients on HD who were ≥20 years old and had ESA-naïve[20] renal anemia (Table 38) (target sample size; 48 subjects, 12 per group) at 31 study sites in Japan to investigate the efficacy, safety, and dose-response relationship of vadadustat.

Table 38. Major inclusion and exclusion criteria

Major inclusion criteria
• Patients with CKD who have started HD ≥8 weeks before screening
• Patients who have been untreated with any ESA or withdrawn from an ESA for at least a certain period specified below and in whom the mean Hb value at 2 timepoints during the screening period is <10.0 g/dL
  • rHuEPO, 2 weeks
  • DA, 4 weeks
  • CERA, 8 weeks
• Patients in whom the serum ferritin value during the screening period is ≥50 ng/mL, and TSAT is ≥20%
• Patients who have not received supplementary iron preparations (oral or intravenous) or have received ones (oral or intravenous) at the same dose for ≥28 days before screening
 	
Major exclusion criteria
• Patients complicated by anemia (hemolysis anemia, etc.) other than renal anemia
• Patients who have a medical history of untreated proliferative diabetic retinopathy, diabetic macular edema, age-related macular degeneration, central retinal vein occlusion, and active retinal haemorrhage from ≥8 weeks before screening to the screening period
• Patients in whom treatment on the eye with laser photocoagulation or anti-vascular endothelial growth factor agent is ongoing
• Patients with a medical history of deep venous thrombosis or pulmonary embolism requiring treatment

This study consisted of the 6-week major evaluation period and 10-week dose adjustment period.

During the major evaluation period (first dose to Week 6), the placebo or vadadustat at 150, 300, or 600 mg was orally administered once daily. During the dose adjustment period (Weeks 7 to 16), subjects in the placebo group also switched from the placebo to vadadustat,[21] and all the subjects

[20] Patients who were not treated with any ESA or were withdrawn from an ESA for a certain period (≥2 weeks for rHuEPO or ≥4 weeks for DA and CERA)

[21] The first dose of vadadustat after the switching was 150, 300, or 600 mg based on the dose during the major evaluation period.

orally received vadadustat at a varied dose of 150 to 600 mg[22] once daily to maintain the Hb value within the target range (10.0-12.0 g/dL).

All of the 60 randomized subjects (15 in the placebo group, 15 in the vadadustat 150 mg group, 15 in the vadadustat 300 mg group, 15 in the vadadustat 600 mg group) received the study drug and were included in the safety analysis. Of 60 subjects who received the study drug, 58 subjects (14 in the placebo group, 15 in the vadadustat 150 mg group, 15 in the vadadustat 300 mg group, 14 in the vadadustat 600 mg group) were included in the efficacy analysis, and the remaining 2 subjects (1 subject each in the placebo group and vadadustat 600 mg group) were excluded from the analysis because measured values after baseline except for those at the discontinuation and during the follow-up period were missing, and the efficacy data at Week 6 were not available.

A total of 20 subjects resulted in discontinuation (17 subjects during a period from the first dose to Week 6 [9 subjects in the placebo group, 4 subjects in the vadadustat 150 mg group, 2 subjects in the vadadustat 300 mg group, 2 subjects in the vadadustat 600 mg group]; 3 subjects during a period from Weeks 7 to 16). The reasons for discontinuation were "aggravated anemia requiring rescue treatment with an ESA or blood transfusion" in 18 subjects (16 subjects during a period from the first dose to Week 6 [9 subjects, 4 subjects, 2 subjects, 1 subjects]; and 2 subjects during a period from Weeks 7 to 16), "consent withdrawal" in 1 subject (1 subject in the vadadustat 600 mg group during a period from the first dose to Week 6), and "others" in 1 subject (1 subject during a period from Weeks 7 to 16).

For the efficacy, Table 39 shows "change in the Hb value from baseline (before the first dose of the study drug)[23] to the end of 6 weeks of treatment," the primary endpoint. The change in any vadadustat group tended to dose-dependently increase, and was different from that in the placebo group with a statistical significance ($P < 0.001$ for vadadustat 150 mg, $P < 0.001$ for vadadustat 300 mg, and $P < 0.001$ for vadadustat 600 mg, ANCOVA, two-sided significance level of 5%, and multiplicity adjustment by step-down procedure).

Table 39. Change (g/dL) in the Hb value from baseline to end of 6 weeks of treatment (MITT population)

	Placebo (n = 14)	Vadadustat		
		150 mg (n = 15)	300 mg (n = 15)	600 mg (n = 14)
Hb value at baseline[a)]	8.97 ± 0.64	9.00 ± 0.52	8.79 ± 0.53	9.32 ± 0.62
Hb value at end of 6 weeks of treatment	7.49 ± 1.13	8.71 ± 1.17	8.83 ± 1.09	9.79 ± 0.96
Change in the Hb value from baseline to end of 6 weeks of treatment	-1.49 ± 0.82	-0.29 ± 0.83	0.03 ± 0.85	0.48 ± 0.89
Difference between groups (vadadustat − placebo) [95% CI][b)]	-	1.19 [0.56, 1.82]	1.56 [0.93, 2.19]	1.89 [1.23, 2.54]
P value[b)]	-	*P* < 0.001	*P* < 0.001	*P* < 0.001

Mean ± SD, LOCF

a) Mean Hb value at 3 timepoints, including 2 timepoints during the screening and 1 before the first dose

b) ANCOVA using the treatment group as a factor and the Hb value at baseline as a covariate; two-sided significance level of 5%; and multiplicity of test adjusted by step-down procedure in which hierarchy was established based on the dose in a descending order.

[22] The dose increase actions should be separated by ≥4 weeks, and the dose should be adjusted according to the following criteria:
- If an increase in Hb from baseline after 6 weeks of treatment is ≤0.5 g/dL, the dose should be increased by 150 mg.
- If the Hb value is <10.0 g/dL, the dose should be increased by 150 mg.
- If the Hb value is rapidly increased or exceeds 12.0 g/dL, the dose should be decreased by 150 mg.
- If the Hb value exceeds 13.0 g/dL, the study drug should be suspended until the Hb value is decreased to ≤12.5 g/dL and then it should be resumed at a reduced dose.

[23] Mean Hb value at 3 timepoints, including 2 timepoints during the screening and 1 before the first dose.

For the safety during the major evaluation period (first dose to Week 6), adverse events occurred in 6 of 15 subjects (40.0%) in the placebo group, 8 of 15 subjects (53.3%) in the vadadustat 150 mg group, 11 of 15 subjects (73.3%) in the vadadustat 300 mg group, and 6 of 15 subjects (40.0%) in the vadadustat 600 mg group. Table 40 shows adverse events reported by ≥2 subjects in any group. Adverse drug reactions occurred in 0 of 15 subjects (0%) in the placebo group, 0 of 15 subjects (0%) in the vadadustat 150 mg group, 3 of 15 subjects (20.0%) in the vadadustat 300 mg group, and 1 of 15 subjects (6.7%) in the vadadustat 600 mg group. Adverse drug reactions reported by ≥2 subjects in any group was only diarrhoea in 3 subjects (2 subjects in the vadadustat 300 mg group, 1 subject in the vadadustat 600 mg group).

No deaths occurred. Serious adverse events occurred in 1 of 15 subjects (6.7%) in the placebo group (arteriovenous fistula site complication) and 3 of 15 subjects (20.0%) in the vadadustat 600 mg group (pericarditis, cholecystitis acute, enteritis infectious, shunt stenosis, and toxic encephalopathy in 1 subject each; some subjects experienced multiple events). A causal relationship to the study drug was ruled out for any of the events, and all resolved. An adverse event leading to treatment discontinuation occurred in 1 subject in the vadadustat 600 mg group (cholecystitis acute). A causal relationship to the study drug was ruled out for the event, and it resolved.

Table 40. Adverse events reported by ≥2 subjects in any group during the major evaluation period (first dose to Week 6) (safety analysis set)

	Placebo (n = 15)	Vadadustat		
		150 mg (n = 15)	300 mg (n = 15)	600 mg (n = 15)
All adverse events	40.0 (6)	53.3 (8)	73.3 (11)	40.0 (6)
Diarrhoea	6.7 (1)	0 (0)	13.3 (2)	13.3 (2)
Shunt stenosis	0 (0)	6.7 (1)	0 (0)	13.3 (2)
Nasopharyngitis	0 (0)	6.7 (1)	33.3 (5)	6.7 (1)

MedDRA/J ver.20.0
Incidence % (n)

For the safety in all of the 60 subjects who entered the dose adjustment period (Weeks 7 to 16), incidences of adverse events and adverse drug reactions were 51.7% (31 of 60) of subjects and 3.3% (2 of 60) of subjects. Adverse events reported by ≥2 subjects were nasopharyngitis in 7 subjects, headache in 5 subjects, diarrhoea in 3 subjects, and contusion, shunt stenosis, muscle spasms, cough, and insomnia in 2 subjects each. Adverse drug reactions reported by ≥2 subjects were gastrointestinal disorder and diarrhoea in 3 subjects each.

No deaths occurred. Serious adverse events occurred in 3 subjects (gastric ulcer haemorrhage, cerebral haemorrhage, shunt stenosis, and anxiety in 1 subject each; some subjects experienced multiple events). A causal relationship to the study drug was ruled out for any of the events. For their outcome, that of gastric ulcer haemorrhage remained unclear; cerebral haemorrhage did not resolve; and shunt stenosis and anxiety resolved. Adverse events leading to treatment discontinuation occurred in 2 subjects (gastric ulcer haemorrhage and anxiety in 1 subject each). A causal relationship to the study drug was ruled out for both events, and for their outcome, that of gastric ulcer haemorrhage remained unclear, and anxiety resolved.

7.2 Phase III studies

7.2.1 Japanese phase III study in patients with non-dialysis dependent CKD (CTD 5.3.5.1-6 and 5.3.5.1-8, Study MT-6548-J01 [October 2017 to August 2019])

A multi-center, randomized, open-label, active-controlled, parallel-group study was conducted in patients with non-dialysis dependent CKD who were ≥20 years old and had renal anemia being treated or untreated[24] with any ESA (Table 41) (target sample size; 300 subjects, 150 per group) at 86 study sites in Japan to investigate the efficacy and safety of vadadustat.

Table 41. Major inclusion and exclusion criteria

Major inclusion criteria
- Patients with CKD who have not undergone dialysis for ≥8 weeks before screening and are not scheduled to start dialysis during the study period
- Patients who meet either (a) or (b) below
  - (a) Patients being treated with an ESA: Patients who are not receiving an ESA or who withdrew from an ESA ≥8 weeks ago, with a mean Hb level of ≥8.0 g/dL and <11.0 g/dL measured at 2 timepoints during the screening period.
    - rHuEPO, ≤12,000 IU per 2 weeks
    - DA, ≤120 μg per 2 weeks
    - CERA, ≤250 μg per 4 weeks
  - (b) ESA-naïve patients: Patients who have not received an ESA for 8 weeks before screening and during the screening period, or patients who withdrew from an ESA ≥8 weeks ago, with a mean Hb level of ≥8.0 g/dL and <11.0 g/dL measured at 2 timepoints during the screening period.
- Patients in whom the serum ferritin value during the screening period is ≥100 ng/mL, or TSAT is ≥20%
- Patients in whom the estimated glomerular filtration rate (eGFR) during the screening period is <60 mL/min/1.73 m^2

Major exclusion criteria
- Patients complicated by anemia (hemolysis anemia, etc.) other than renal anemia
- Patients in whom fundus photographs are not available during the screening period or who have active fundal diseases
- Patients who have experienced new onset or recurrent of cerebrovascular disorder, acute coronary syndrome, deep vein thrombosis or pulmonary embolism within 12 weeks before screening.

The dosage regimen was adjusted to maintain the Hb value within the target range (11.0-13.0 g/dL) in accordance with Table 42 until the end of 52 weeks of treatment. In December 2017 after start of this study, the maximum daily dose in the vadadustat group was changed from 750 mg to 600 mg[25] based on non-clinical toxicity study results.[26]

[24] Patients untreated with any ESA or withdrawn from an ESA for ≥8 weeks

[25] Dose at which the safety and tolerability in subjects were confirmed in clinical studies of vadadustat completed by December 2017

[26] Concerning death or moribund necropsy cases at the high dose in the 7-day toxicity study in rats (4.2.3.2-1 and 4.2.3.2-2), the non-clinical advisory board of Akebia Therapeutics, Inc., a foreign development company, had a discussion and concluded that the most likely cause of the death was hemoglobinuric nephropathy resulted from intravascular hemolysis. Based on the above conclusion, the highest dose of vadadustat in clinical studies was changed to 600 mg, but the later conducted *in vitro* hemolysis study showed that vadadustat did not cause hemolysis [see Section 5.6.1], and thus the deaths in the 7-day toxicity study in rats were concluded to have been caused by complex factors.

Table 42. Dose adjustment method

<table>
<tr><th></th><th>Vadadustat</th><th>DA</th></tr>
<tr><td>Regimen</td><td>Oral administration, once daily</td><td>Subcutaneous administration, once every 1, 2, or 4 weeks</td></tr>
<tr><td>Initial dose</td><td>300 mg/day</td><td>ESA-naïve patients: Dose of 30 µg once every 2 weeks
Patients being treated with an ESA: Dose to be determined according to the pre-switch ESA as described below
<table>
<tr><th colspan="2">Pre-switch ESA</th><th rowspan="2">Initial dose of DA</th></tr>
<tr><th>rHuEPO</th><th>DA</th></tr>
<tr><td>≤3,000 IU/2 weeks</td><td>15 µg</td><td>15 µg</td></tr>
<tr><td>4,500 IU/2 weeks</td><td>20 µg</td><td>20 µg</td></tr>
<tr><td>6,000 IU/2 weeks</td><td>30 µg</td><td>30 µg</td></tr>
<tr><td>9,000 IU/2 weeks</td><td>40 µg</td><td>40 µg</td></tr>
<tr><td>12,000 IU/2 weeks</td><td>60 µg</td><td>60 µg</td></tr>
</table></td></tr>
<tr><td>Dose adjustment range</td><td>150-600 mg/day
(changed from 150-750 mg/day in December 2017)
<table>
<tr><th>Level</th><th>Dose</th></tr>
<tr><td>1</td><td>150 mg</td></tr>
<tr><td>2</td><td>300 mg</td></tr>
<tr><td>3</td><td>450 mg</td></tr>
<tr><td>4</td><td>600 mg</td></tr>
</table></td><td>15-180 µg/dose
<table>
<tr><th>Level</th><th>Dose</th></tr>
<tr><td>1</td><td>15 µg</td></tr>
<tr><td>2</td><td>30 µg</td></tr>
<tr><td>3</td><td>60 µg</td></tr>
<tr><td>4</td><td>90 µg</td></tr>
<tr><td>5</td><td>120 µg</td></tr>
<tr><td>6</td><td>180 µg</td></tr>
</table></td></tr>
<tr><td>Dose adjustment criteria</td><td>• Interval between dose increase actions should be ≥4 weeks in principle.
• No rules are specified for intervals between dose reduction actions.
• If the Hb value is rapidly increased (a change during the last 4 weeks >2.0 g/dL), the dose should be reduced by 1 level.
• If the Hb value is rapidly increased to >13.0 g/dL (a change during the last 4 weeks >2.0 g/dL), treatment should be suspended, and after the Hb value is decreased to ≤13.0 g/dL, it should be resumed at a dose 1 level lower.
• If the Hb value is not rapidly increased, the dose should be adjusted based on the Hb value as specified in the table below.</td><td>• Interval between dose increase actions should be ≥2 weeks in principle.
• No rules are specified for intervals between dose reduction actions.
• If the Hb value is maintained within the target range (11.0-12.5 g/dL), the dosing interval may be extended from once a week to once every 2 weeks or from once every 2 weeks to once every 4 weeks with the dose increased twice.
• If the Hb value does not reach the target even at a dose of 180 µg, the interval may be shortened from once every 4 weeks to once every 2 weeks or once every 2 weeks to once a week with the dose reduced by half.
• If the Hb value is rapidly increased (a change during the last 4 weeks >2.0 g/dL), the dose should be reduced by 1 level.
• If the Hb value is rapidly increased to >13.0 g/dL (a change during the last 4 weeks >2.0 g/dL), treatment should be suspended, and after the Hb value is decreased to ≤13.0 g/dL, it should be resumed at a dose 1 level lower.
• If the Hb value is not rapidly increased, the dose should be adjusted based on the Hb value as specified in the table below.</td></tr>
<tr><td colspan="2"></td><td>Table for dose adjustment based on the Hb value
<table>
<tr><th>Hb value</th><th>Dose of the study drug</th></tr>
<tr><td><11.0 g/dL</td><td>Increase by 1 level</td></tr>
<tr><td>≥11.0 g/dL and ≤12.5 g/dL</td><td>No change</td></tr>
<tr><td>>12.5 g/dL and ≤13.5 g/dL</td><td>Reduce by 1 level</td></tr>
<tr><td>>13.5 g/dL</td><td>Suspend the treatment, and after decrease the Hb value to ≤13.0 g/dL, resume at a dose 1 level lower.</td></tr>
</table></td></tr>
</table>

All of the 304 randomized subjects (151 in the vadadustat group, 153 in the DA group) received the study drug and were included in the full analysis set (FAS) and the safety analysis. The FAS served as the primary efficacy analysis population. Of these, 162 subjects (80 in the vadadustat group, 82 in the DA group) were patients being treated with an ESA, and 142 subjects (71 in the vadadustat group, 71 in the DA group) were ESA-naïve patients.

A total of 70 subjects resulted in discontinuation (40 subjects in the vadadustat group, 30 subjects in the DA group). The reasons for discontinuation were "initiation of continuous dialysis or implementation of kidney transplantation" in 28 subjects (13 subjects, 15 subjects), "consent withdrawal" in 14 subjects (11 subjects, 3 subjects), "adverse events" in 15 subjects (10 subjects, 5 subjects), "hyperviscosity syndrome or difficulty in controlling Hb" in 5 subjects (2 subjects, 3 subjects), "(sub-)investigator's decision" in 4 subjects (2 subjects, 2 subjects), "rescue treatment before the end of scheduled examination at Week 24" in 3 subjects (2 subjects, 1 subject), and "hepatic dysfunction" in 1 subject (1 subject in the DA group).

For the efficacy, Table 43 shows "mean Hb value at Weeks 20 and 24," the primary endpoint. The lower limit of 95% CI of a difference in this value between the vadadustat group and DA group (vadadustat group − DA group) exceeded the predetermined noninferiority limit (−0.75 g/dL),[27] demonstrating noninferiority of vadadustat to DA. The same analysis was performed on data in the per protocol set (PPS) (146 subjects in the vadadustat group, 152 subjects in the DA group).[28] A difference in "mean Hb value at Weeks 20 and 24" [95% CI] between the groups (vadadustat group − DA group) was −0.28 [−0.52, −0.04] (g/dL), demonstrating robustness of the primary analysis in the FAS.

Table 43. Mean Hb value (g/dL) at Weeks 20 and 24 (FAS)

	Vadadustat (n = 151)	DA (n = 153)
Baseline Hb value (mean ± SD)	10.44 ± 0.91	10.52 ± 0.88
Mean Hb value at Weeks 20 and 24[a] (least squares mean ± standard error [SE])	11.66 ± 0.09	11.93 ± 0.09
Difference between groups (vadadustat − DA)[a] [95% CI]	−0.26 [−0.50, −0.02]	

a) Mixed effect model repeated measures (MMRM) on the assumption of intra-subject unstructured covariance using the Hb value at the start date of treatment as a covariate, and the dose group, timepoint, ESA-naïve/ESA ongoing status, interaction between timepoint and dose group, and interaction between timepoint and ESA-naïve/ESA ongoing status as the fixed effects

For the safety up to Week 52 (entire period), adverse events occurred in 136 of 151 subjects (90.1%) in the vadadustat group and 141 of 153 subjects (92.2%) in the DA group, and adverse drug reactions occurred in 20 of 151 subjects (13.2%) and 7 of 153 subjects (4.6%) in the DA group. Table 44 shows adverse events reported by ≥5.0% of the subjects in any group. There were no adverse drug reactions reported by ≥5.0% of the subjects in any group.

Table 44. Adverse events reported by ≥5.0% of the subjects in any group (safety analysis set)

	Vadadustat (n = 151)	DA (n = 153)		Vadadustat (n = 151)	DA (n = 153)
All adverse events	90.1 (136)	92.2 (141)	Chronic kidney disease	6.0 (9)	9.2 (14)
Nasopharyngitis	24.5 (37)	28.1 (43)	Renal dysfunction	5.3 (8)	5.2 (8)
Diarrhoea	11.9 (18)	5.2 (8)	Pyrexia	5.3 (8)	0.7 (1)
Constipation	9.3 (14)	7.2 (11)	Pruritus	4.6 (7)	5.2 (8)
Contusion	7.3 (11)	4.6 (7)	Cystitis	4.0 (6)	5.9 (9)
Oedema peripheral	7.3 (11)	3.3 (5)	Eczema	3.3 (5)	5.2 (8)
Vomiting	6.6 (10)	2.0 (3)	Hypertension	1.3 (2)	7.2 (11)

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Incidence % (n)

[27] Determined based on intra-individual variability in patients with CKD on dialysis and situations of drugs in the same class.
[28] From the FAS, 6 subjects were removed owing to "<80% adherence to treatment with the study drug" in 3 subjects (3 subjects in the vadadustat group), "violation against rules for prohibited concomitant drugs" in 2 subjects (1 subject in the vadadustat group, 1 subject in the DA group), and "deviation from the inclusion criteria" in 1 subject (1 subject in the vadadustat group).

Deaths occurred in 1 subject in the DA group (acute myocardial infarction)[29], but the causal relationship to the study drug was ruled out. Serious adverse events occurred in 42 of 151 subjects (27.8%) in the vadadustat group and 49 of 153 subjects (32.0%) in the DA group (Table 45), but, a causal relationship to the study drug was ruled out for any event.

Table 45. Serious adverse events (safety analysis set)

Treatment	Event terms
Vadadustat	Chronic kidney disease (7 subjects); renal dysfunction (6 subjects); cataract and end stage renal disease (3 subjects each); pneumonia, cardiac failure congestive, renal failure, and spinal compression fracture (2 subjects each); and diverticulitis, renal cyst infection, cellulitis, mediastinal abscess, osteomyelitis, periodontitis, pneumonia chlamydial, pyelonephritis acute, urinary tract infection, abscess limb, hyponatraemia, fluid retention, hypoglycaemic coma, intracranial aneurysm, presyncope, cardiac failure, cardiac failure chronic, myocardial ischaemia, ventricular tachycardia, vascular rupture, large intestine polyp, abdominal pain, oesophageal achalasia, bile duct stone, cholecystitis, cholelithiasis, dermatomyositis, lumbar spinal stenosis, rotator cuff syndrome, oedema peripheral, chest pain, femoral neck fracture, seroma, subarachnoid haemorrhage, and shunt stenosis (1 subject each)
DA	Chronic kidney disease (11 subjects); renal dysfunction (6 subjects), pneumonia (3 subjects); dehydration, cardiac failure acute, inguinal hernia, and oedema peripheral (2 subjects each); and diverticulitis, renal cyst infection, cystitis, basal cell carcinoma, gastric cancer, keratoacanthoma, renal cancer, renal cancer metastatic, hyponatraemia, hypermagnesaemia, metabolic acidosis, acute myocardial infarction, peripheral artery aneurysm, large intestine polyp, diverticulum intestinal haemorrhagic, gastric ulcer haemorrhage, ischaemic enteritis, hepatic function abnormal, lumbar spinal stenosis, osteoarthritis, end stage renal disease, renal failure, diabetic nephropathy, acute kidney injury, blood creatinine increased, femoral neck fracture, femur fracture, hip fracture, radius fracture, shunt occlusion, wrist fracture, and bone contusion (1 subject each)

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Adverse events leading to treatment discontinuation occurred in 10 of 151 subjects (6.6%) in the vadadustat group (retinal haemorrhage, cardiac failure chronic, vascular rupture, abdominal discomfort, diarrhoea, gastritis, gastrointestinal polyp haemorrhage, dermatomyositis, chronic kidney disease, renal dysfunction, malaise, haemoglobin decreased, and spinal compression fracture [1 subject each]; some subjects experienced multiple events) and 6 of 153 subjects (3.9%) in the DA group (pneumonia, dementia Alzheimer's type, cognitive disorder, hepatic function abnormal, chronic kidney disease, and azotaemia [1 subject each]). Abdominal discomfort, retinal haemorrhage, diarrhoea, gastritis, and malaise in the vadadustat group were assessed as adverse drug reactions. For outcome, abdominal discomfort was resolving, and all the other adverse drug reactions resolved.

7.2.2 Japanese phase III study in patients on PD (CTD 5.3.5.2-1, Study MT-6548-J02 [January to December 2018])

A multi-center, uncontrolled, open-label study was conducted in patients on peritoneal dialysis (PD) who were ≥20 years old and had renal anemia being treated or untreated[30] with any ESA (Table 46) (target sample size, 40 subjects) at 25 study sites in Japan to investigate the efficacy and safety of vadadustat.

[29] A 56-year old man, On Day 58 of vadadustat treatment, he was transferred to an emergency department. He received a diagnosis of acute myocardial infarction at the hospital and discontinued the study drug on the same day. He died on Day 60. Because the Hb value was not increased in association with the study drug, and he was at a high risk of myocardial infarction owing to comorbid diabetes mellitus and hypertension, the causal relationship to the study drug was ruled out.

[30] Patients untreated with any ESA or withdrawn from an ESA for ≥8 weeks

Table 46. Major inclusion and exclusion criteria

Major inclusion criteria
- Patients with CKD who have started PD ≥4 weeks before screening
- Patients who meet either (a) or (b) below
  - (a) Patients being treated with an ESA: Patients who are not receiving an ESA or who withdrew from an ESA ≥8 weeks ago, with a mean Hb level of ≥8.0 g/dL and <11.0 g/dL measured at 2 timepoints during the screening period.
    - rHuEPO, ≤12,000 IU per 2 weeks
    - DA, ≤120 μg per 2 weeks
    - CERA, ≤250 μg per 4 weeks
  - (b) ESA-naïve patients: Patients who have not received an ESA for 8 weeks before screening and during the screening period, or patients who withdrew from an ESA ≥8 weeks ago, with a mean Hb level of ≥8.0 g/dL and <11.0 g/dL measured at 2 timepoints during the screening period.
- Patients in whom the serum ferritin value during the screening period is ≥100 ng/mL, or TSAT is ≥20%

Major exclusion criteria
- Patients complicated by anemia (hemolysis anemia, etc.) other than renal anemia
- Patients in whom fundus photographs are not available during the screening period or who have active fundal diseases
- Patients who have experienced new onset or recurrent of cerebrovascular disorder, acute coronary syndrome, deep vein thrombosis or pulmonary embolism within 12 weeks before screening.

The dosage regimen was adjusted to maintain the Hb value within the target range (11.0-13.0 g/dL) in accordance with Table 47 until the end of 24 weeks of treatment. Regarding the dose adjustment range of vadadustat, the initial protocol allowed the daily dose of 750 mg for patients in whom the Hb value was expected to be increased and the safety was considered acceptable, but the maximum daily dose was changed to 600 mg in December 2017, just before start of this study [for background of the change, see Section 7.2.1].

Table 47. Dose adjustment method

<table>
<tr><td>Regimen</td><td>Oral administration, once daily</td></tr>
<tr><td>Initial dose</td><td>300 mg/day</td></tr>
<tr><td>Dose adjustment range</td><td>150-600 mg/day
<table><tr><th>Level</th><th>Dose</th></tr><tr><td>1</td><td>150 mg</td></tr><tr><td>2</td><td>300 mg</td></tr><tr><td>3</td><td>450 mg</td></tr><tr><td>4</td><td>600 mg</td></tr></table></td></tr>
<tr><td>Dose adjustment criteria</td><td>• Interval between dose increase actions should be ≥4 weeks in principle.
• No rules are specified for intervals between dose reduction actions.
• If the Hb value is rapidly increased (a change during the last 4 weeks >2.0 g/dL), the dose should be reduced by 1 level.
• If the Hb value is rapidly increased to >13.0 g/dL (a change during the last 4 weeks >2.0 g/dL), treatment should be suspended, and after the Hb value is decreased to ≤13.0 g/dL, it should be resumed at a dose 1 level lower.
• If the Hb value is not rapidly increased, the dose should be adjusted based on the Hb value as specified in the table below.

Table for dose adjustment based on the Hb value
<table><tr><th>Hb value</th><th>Dose of the study drug</th></tr><tr><td><11.0 g/dL</td><td>Increase by 1 level</td></tr><tr><td>≥11.0 g/dL and ≤12.5 g/dL</td><td>No change</td></tr><tr><td>>12.5 g/dL and ≤13.5 g/dL</td><td>Reduce by 1 level</td></tr><tr><td>>13.5 g/dL</td><td>Suspend the treatment, and after decrease the Hb value to ≤13.0 g/dL, resume at a dose 1 level lower.</td></tr></table></td></tr>
</table>

All of the 42 subjects who received any study drug were included in the FAS and the safety analysis, and the FAS served as the primary efficacy analysis population. Of these 40 subjects were patients being treated with an ESA, and 2 subjects were ESA-naïve patients.

A total of 6 subjects resulted in discontinuation owing to "adverse events" in 3 subjects, "hyperviscosity syndrome or difficulty in controlling Hb" in 2 subjects, and "others, (sub-)investigator's decision" (inability to visit owing to long-term hospitalization at the other hospital) in 1 subject.

For the efficacy, Table 48 shows "mean Hb value at Weeks 20 and 24."

Table 48. Mean Hb value at Weeks 20 and 24 (g/dL) (FAS[a])

	Subjects treated with vadadustat (n = 41)[a]
Baseline Hb value (mean ± SD)	10.89 ± 1.12
Mean Hb value at Weeks 20 and 24[b] (least squares mean ± SE)	11.35 ± 0.17

a) Although the FAS comprised 42 subjects, 41 subjects were included in the analysis, excluding 1 subject in whom data on Hb value on the start date of treatment and thereafter were not available.
b) MMRM on the assumption of intra-subject unstructured covariance using the Hb value at the start date of treatment as a covariate and the timepoint as the fixed effect

For the safety,[31] adverse events occurred in 38 of 42 subjects (90.5%), and adverse drug reactions occurred in 5 of 42 subjects (11.9%). Table 49 shows adverse events reported by ≥2 subjects. Adverse drug reactions reported by ≥2 subjects were only diarrhoea in 2 subjects.

Death occurred in 1 subject (myocardial ischaemia[32]) which was assessed as an adverse drug reaction. Serious adverse events occurred in 12 of 42 subjects (28.6%) (peritonitis in 3 subjects; peripheral arterial occlusive disease in 2 subjects; and myocardial ischaemia, sepsis, catheter site infection, anaemia, cerebral infarction, cardiac failure chronic, gastric polyps, inguinal hernia, shunt occlusion, peritoneal dialysis complication, and traumatic haemothorax in 1 subject each; some subjects experienced multiple events). A causal relationship to the study drug was ruled out for all the events except for fatal myocardial ischaemia.

Adverse events leading to treatment discontinuation occurred in 3 of 41 subjects (7.1%) (cerebral infarction, traumatic haemothorax, and myocardial ischaemia in 1 subject each) and only fatal myocardial ischaemia was assessed as an adverse drug reaction.

31) The safety evaluation covered the 24-week treatment period and subsequent 14-day follow-up period.
32) A 70-year old man. The dose of vadadustat was increased to 450 mg on Day 28 after treatment with the study drug and he died on Day 38. He had a history of myocardial infarction, the autopsy imaging revealed no specific changes potentially causing death other than remarkable coronary artery calcification, and thus the death was considered attributable to myocardial ischaemia. Because no clear cause of the death was identified; autopsy for identification of the cause of the death was not performed; and the concerned event occurred during treatment with the study drug, the investigator judged that a causal relationship of the death to the study drug could not be completely ruled out.

Table 49. Adverse events reported by ≥2 subjects (safety analysis set)

	Subjects treated with vadadustat (n = 42)		Subjects treated with vadadustat (n = 42)
All adverse events	90.5 (38)	Retinal haemorrhage	4.8 (2)
Catheter site infection	23.8 (10)	Arteriosclerosis	4.8 (2)
Diarrhoea	19.0 (8)	Peripheral arterial occlusive disease	4.8 (2)
Nasopharyngitis	14.3 (6)	Cough	4.8 (2)
Peritonitis	11.9 (5)	Abdominal discomfort	4.8 (2)
Vomiting	9.5 (4)	Enterocolitis	4.8 (2)
Decreased appetite	7.1 (3)	Gastric polyps	4.8 (2)
Abdominal pain upper	7.1 (3)	Dermatitis contact	4.8 (2)
Nausea	7.1 (3)	Back pain	4.8 (2)
Upper respiratory tract infection	4.8 (2)	Pyrexia	4.8 (2)
Insomnia	4.8 (2)		

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Incidence % (n)

7.2.3 Japanese phase III study in patients on HD (CTD 5.3.5.1-7 and 5.3.5.1-9, Study MT-6548-J03 [February 2018 to July 2019])

A multi-center, randomized, double-blind, active-controlled, parallel-group study was conducted in patients on HD who were ≥20 years old and being treated with an ESA for renal anemia (Table 50) (target sample size; 300 subjects, 150 per group) at 115 study sites in Japan to investigate the efficacy and safety of vadadustat.

Table 50. Major inclusion and exclusion criteria

Major inclusion criteria
- Patients with CKD who have started 3-time weekly HD or hemodiafiltration (HDF) ≥12 weeks before screening
- Patients in whom an ESA has been administered by the same route of administration in the same dosage regimen described below for ≥8 weeks before screening, and the mean Hb value at 2 timepoints during the screening period is ≥9.5 g/dL and ≤12.0 g/dL
- rHuEPO, ≤9,000 IU per week
- DA, ≤60 μg per week
- CERA, ≤250 μg per 4 weeks
- Patients in whom the serum ferritin value during the screening period is ≥100 ng/mL, or TSAT is ≥20%

Major exclusion criteria
- Patients complicated by anemia (hemolysis anemia, etc.) other than renal anemia
- Patients in whom fundus photographs are not available during the screening period or who have active fundal diseases
- Patients who have experienced new onset or recurrent of cerebrovascular disorder, acute coronary syndrome, deep vein thrombosis, or pulmonary embolism within 12 weeks before screening

The dosage regimen was adjusted to maintain the Hb value within the target range (10.0-12.0 g/dL) in accordance with Table 51 until the end of 52 weeks of treatment.

Table 51. Dose adjustment method

<table>
<tr><th></th><th>Vadadustat</th><th>DA</th></tr>
<tr><td>Regimen</td><td>Oral administration, once daily</td><td>Intravenous administration, once every 1, 2, or 4 weeks</td></tr>
<tr><td>Initial dose</td><td>300 mg/day</td><td>Dose to be determined according to the pre-switch ESA as described below
<table>
<tr><th colspan="4">Pre-switch ESA</th><th rowspan="3">Initial dose of DA</th></tr>
<tr><th colspan="2">rHuEPO</th><th>DA</th><th></th></tr>
<tr><th>Pre-switch Total in 1 week</th><th>Pre-switch Total in 2 weeks</th><th></th><th></th></tr>
<tr><td>≤3,000 IU</td><td>≤3,000 IU</td><td>15 μg</td><td></td><td>15 μg</td></tr>
<tr><td>4,500 IU</td><td>4,500 IU</td><td>20 μg</td><td></td><td>20 μg</td></tr>
<tr><td>6,000 IU</td><td>6,000 IU</td><td>30 μg</td><td></td><td>30 μg</td></tr>
<tr><td>9,000 IU</td><td>9,000 IU</td><td>40 μg</td><td></td><td>40 μg</td></tr>
<tr><td>-</td><td>12,000 IU</td><td>60 μg</td><td></td><td>60 μg</td></tr>
</table></td></tr>
<tr><td>Dose adjustment range</td><td>150-600 mg/day
<table>
<tr><th>Level</th><th>Dose</th></tr>
<tr><td>1</td><td>150 mg</td></tr>
<tr><td>2</td><td>300 mg</td></tr>
<tr><td>3</td><td>450 mg</td></tr>
<tr><td>4</td><td>600 mg</td></tr>
</table></td><td>5-180 μg/dose
<table>
<tr><th>Level</th><th>Dose</th><th>Level</th><th>Dose</th></tr>
<tr><td>1</td><td>5 μg</td><td>8</td><td>60 μg</td></tr>
<tr><td>2</td><td>10 μg</td><td>9</td><td>80 μg</td></tr>
<tr><td>3</td><td>15 μg</td><td>10</td><td>100 μg</td></tr>
<tr><td>4</td><td>20 μg</td><td>11</td><td>120 μg</td></tr>
<tr><td>5</td><td>30 μg</td><td>12</td><td>140 μg</td></tr>
<tr><td>6</td><td>40 μg</td><td>13</td><td>160 μg</td></tr>
<tr><td>7</td><td>50 μg</td><td>14</td><td>180 μg</td></tr>
</table></td></tr>
<tr><td>Dose adjustment criteria</td><td>• Interval between dose increase actions should be ≥4 weeks in principle.
• Interval between dose reduction actions should be ≥2 weeks in principle.
• If the Hb value is rapidly increased (a change during the last 4 weeks >2.0 g/dL), the dose should be reduced by 1 level.
• If the Hb value is rapidly increased to >12.0 g/dL (a change during the last 4 weeks >2.0 g/dL), treatment should be suspended, and after the Hb value is decreased to ≤12.0 g/dL, it should be resumed at a dose 1 level lower.
• If the Hb value is not rapidly increased, the dose should be adjusted based on the Hb value as specified in the table below.</td><td>• Interval between dose increase actions should be ≥2 weeks in principle.
• Interval between dose reduction actions should be ≥2 weeks in principle.
• If the Hb value is maintained within a range from 10.0 to 11.5 g/dL, the dosing interval may be extended from once a week to once every 2 weeks or from once every 2 weeks to once every 4 weeks with the dose increased twice.
• If the Hb value does not reach the target range (10.0-12.0 g/dL) even at a dose of 180 μg, the interval may be shortened from once every 4 weeks to once every 2 weeks or once every 2 weeks to once a week with the dose reduced to 80 or 100 μg.
• If the Hb value is rapidly increased (a change during the last 4 weeks >2.0 g/dL), the dose should be reduced by 1 level.
• If the Hb value is rapidly increased to >13.0 g/dL (a change during the last 4 weeks >2.0 g/dL), treatment should be suspended until the Hb value is decreased to ≤13.0 g/dL.
• If the Hb value is not rapidly increased, the dose should be adjusted based on the Hb value as specified in the table below.</td></tr>
<tr><td colspan="2">Table for dose adjustment based on the Hb value
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<tr><th>Hb value</th><th>Dose of the study drug</th></tr>
<tr><td><10.0 g/dL</td><td>Increase by 1 level</td></tr>
<tr><td>≥10.0 g/dL and ≤11.5 g/dL</td><td>No change</td></tr>
<tr><td>>11.5 g/dL and ≤13.0 g/dL</td><td>Reduce by 1 level</td></tr>
<tr><td>>13.0 g/dL</td><td>Suspend the treatment, and after decrease the Hb value to ≤12.0 g/dL, resume at a dose 1 level lower.</td></tr>
</table></td></tr>
</table>

All of the 323 randomized subjects (162 in the vadadustat group and 161 in the DA group) received the study drug and were included in the FAS and the safety analysis. The FAS served as the primary efficacy analysis population.

A total of 68 subjects resulted in discontinuation (42 subjects in the vadadustat group, 26 subjects in the DA group). The reasons for discontinuation were “adverse events” in 28 subjects (16 subjects, 12

subjects), “request of subjects” in 18 subjects (14 subjects, 4 subjects), “hyperviscosity syndrome or difficulty in controlling Hb” in 12 subjects (10 subjects, 2 subjects), “others, (sub-)investigator’s decision” in 5 subjects (0 subjects, 5 subjects), “rescue treatment before end of scheduled examination at Week 24” in 3 subjects (2 subjects and 1 subject) and “implementation of kidney transplantation” in 2 subjects (0 subjects, 2 subjects).

For the efficacy, Table 52 shows “mean Hb value at Weeks 20 and 24,” the primary endpoint. The lower limit of 95% CI of a difference in this value between the vadadustat group and DA group (vadadustat group − DA group) exceeded the predetermined noninferiority limit (−0.75 g/dL),[33] demonstrating noninferiority of vadadustat to DA. The same analysis was performed on data in the PPS (153 subjects in the vadadustat group, 152 subjects in the DA group).[34] A difference in “mean Hb value at Weeks 20 and 24” [95% CI] between the groups (vadadustat group − DA group) was −0.05 [−0.26, −0.17] (g/dL), demonstrating robustness of the primary analysis in the FAS.

Table 52. Mean Hb value at Weeks 20 and 24 (g/dL) (FAS[a])

	Vadadustat (n = 160)[a]	DA (n = 160)[a]
Baseline Hb value (mean ± SD)	10.74 ± 0.72	10.74 ± 0.72
Mean Hb value at Weeks 20 and 24[b] (least squares mean ± SE)	10.61 ± 0.08	10.65 ± 0.08
Difference between groups (vadadustat − DA)[b] [95% CI]	-0.05 [-0.26, 0.17]	

a) Although the FAS comprised 323 subjects, 320 were included in the analysis, excluding 3 subjects in whom measured data at baseline and thereafter were not available.
b) MMRM on the assumption of intra-subject unstructured covariance using the Hb value at the start date of treatment as a covariate, and the dose group, timepoint, and interaction between timepoint and dose group as the fixed effects

For the safety up to Week 52 (entire period), adverse events occurred in 154 of 162 subjects (95.1%) in the vadadustat group and 158 of 161 subjects (98.1%) in the DA group, and adverse drug reactions occurred in 18 of 162 subjects (11.1%) and 6 of 161 subjects (3.7%) in the DA group. Table 53 shows adverse events reported by ≥5.0% of the subjects in any group. There were no adverse drug reactions reported by ≥5.0% of the subjects in any group.

Table 53. Adverse events reported by ≥5.0% of the subjects in any group (safety analysis set)

	Vadadustat (n = 162)	DA (n = 161)		Vadadustat (n = 162)	DA (n = 161)
All adverse events	95.1 (154)	98.1 (158)	Vomiting	6.2 (10)	10.6 (17)
Nasopharyngitis	45.7 (74)	45.3 (73)	Arthralgia	6.2 (10)	6.8 (11)
Diarrhoea	15.4 (25)	14.9 (24)	Eczema	6.2 (10)	5.0 (8)
Shunt stenosis	14.2 (23)	16.1 (26)	Wound	6.2 (10)	4.3 (7)
Contusion	13.0 (21)	11.8 (19)	Nausea	6.2 (10)	1.2 (2)
Retinal haemorrhage	9.9 (16)	6.2 (10)	Skin abrasion	5.6 (9)	9.3 (15)
Back pain	9.3 (15)	6.8 (11)	Influenza	5.6 (9)	7.5 (12)
Headache	8.0 (13)	3.1 (5)	Myalgia	5.6 (9)	3.1 (5)
Pain in extremity	8.0 (13)	2.5 (4)	Decreased appetite	5.6 (9)	2.5 (4)
Pruritus	7.4 (12)	5.6 (9)	Constipation	4.3 (7)	7.5 (12)
Gastroenteritis	7.4 (12)	0.6 (1)	Seasonal allergy	2.5 (4)	7.5 (12)
Conjunctivitis	6.8 (11)	2.5 (4)			

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Incidence % (n)

[33] Determined based on intra-individual variability in patients with CKD on dialysis and situations of drugs in the same class.
[34] From the FAS, 18 subjects were removed owing to “violation against rules for prohibited concomitant drugs and therapies” in 8 subjects (4 subjects in the vadadustat group, 4 subjects in the DA group), “deviation from the inclusion criteria” in 7 subjects (4 subjects, 3 subjects), “<80% adherence to treatment with the study drug” in 2 subjects (1 subject, 1 subject), and “Others” in 1 subject (0 subject, 1 subject).

Deaths occurred in 2 subjects in the vadadustat group (pneumonia[35)] and chronic kidney disease[36)] in 1 subject each) and 1 subject in the DA group (peripheral artery aneurysm rupture[37)]), but a causal relationship to the study drug was ruled out for any death. Serious adverse events occurred in 41 of 162 subjects (25.3%) in the vadadustat group and 44 of 161 subjects (27.3%) in the DA group (Table 54), but a causal relationship to the study drug was ruled out for any event.

Table 54. Serious adverse events (safety analysis set)

Treatment	Event terms
Vadadustat	Shunt stenosis and shunt occlusion (4 subjects each); pneumonia (3 subjects); gastroenteritis, decreased appetite, cardiac failure congestive, and peripheral arterial occlusive disease (2 subjects each); and hydrocele male infected, influenza, hepatic cyst infection, shunt infection, bacterial infection, device related infection, breast cancer, gastric cancer, laryngeal papilloma, squamous cell carcinoma of skin, lymphadenitis, hyperkalaemia, cerebral infarction, facial paralysis, intracranial aneurysm, arteriovenous fistula site haemorrhage, myelopathy, thrombotic cerebral infarction, sudden hearing loss, angina pectoris, coronary artery stenosis, myocardial ischaemia, arteriosclerosis coronary artery, cardiac failure, aorta polyp, gastrooesophageal reflux disease, rectal ulcer, cholangitis, lumbar spinal stenosis, rotator cuff syndrome, chronic kidney disease, femoral neck fracture, scrotal haematoma, spinal compression fracture, subdural haematoma, cervical bone fracture, and shunt blood flow excessive (1 subject each)
DA	Shunt stenosis (4 subjects); shunt occlusion, cerebral infarction, and angina pectoris (3 subjects each); peripheral arterial occlusive disease, large intestine polyp, and renal transplant (2 subjects each); and pneumonia, diverticulitis, herpes zoster, catheter site infection, staphylococcal infection, pneumonia bacterial, mycotic endophthalmitis, breast cancer, gastric cancer, prostate cancer, urethral neoplasm, renal cell carcinoma, aplastic anaemia, cerebellar infarction, retinal detachment, coronary artery stenosis, myocardial ischaemia, aortic valve stenosis, atrial fibrillation, pericarditis, coronary artery perforation, cardiac valve disease, supraventricular tachyarrhythmia, peripheral artery occlusion, peripheral artery aneurysm rupture, mediastinal mass, abdominal pain, gastritis, inguinal hernia, synovial cyst, femoral neck fracture, arteriovenous fistula thrombosis, radius fracture, rib fracture, subarachnoid haemorrhage, coronary artery restenosis, upper limb fracture, procedural hypotension, and haemodialysis complication (1 subject each)

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Adverse events leading to treatment discontinuation occurred in 16 of 162 subjects (9.9%) in the vadadustat group (drug eruption in 2 subjects; and pneumonia, breast cancer, gastric cancer, anaemia, nephrogenic anaemia, decreased appetite, cerebral infarction, cardiac failure congestive, cardiac dysfunction, peripheral arterial occlusive disease, cold sweat, chronic kidney disease, chest discomfort, haemoglobin decreased, and femoral neck fracture in 1 subject each; some subjects experienced multiple events), and in 14 of 161 subjects (8.7%) in the DA group (cerebral infarction, hepatic function abnormal, and renal transplant in 2 subjects each; and urethral neoplasm, age-related macular degeneration, aortic valve stenosis, pericarditis, peripheral artery aneurysm rupture, haemoglobin decreased, blood pressure increased, and femoral neck fracture in 1 subject each). Drug eruption, cold sweat, and chest discomfort in the vadadustat group were assessed as adverse drug reactions but all resolved.

35) An 81-year old man. He experienced cold symptoms from Day 127 of treatment with the study drug and received a diagnosis of pneumonia on Day 134. He received treatment for pneumonia, continuously taking the study drug, but died on Day 147. Pneumonia occurred incidentally, and in view of the mechanism of action of the study drug, the event was assessed as causally unrelated to the study drug.

36) A 75-year old man. He experienced cardiac arrest on Day 184 after treatment with the study drug. He visited the hospital for dialysis the day before without remarkable findings. The death was considered attributable to chronic renal failure, and the event was assessed as causally unrelated to the study drug.

37) A 77-year old man. He was hospitalized with complaints of vomiting and decreased appetite on Day 50 after treatment with the study drug. On Day 56, threatened common iliac artery rupture was suspected, and emergent blood vessel prosthesis implantation was performed on the abdominal aorta. Postoperative ileus and cerebral infarction followed, and he died on Day 82. Aneurysm was likely to have formed before the study, and the death was considered as a consequence of complications such as renal failure and hypertension. The event was assessed as causally unrelated to the study drug.

7.2.4 Japanese phase III study in patients on HD (CTD 5.3.5.2-2, Study MT-6548-J04 [March to December 2018])

A multi-center, uncontrolled, open-label study was conducted in patients on HD who were ≥20 years old and had ESA-naïve[38] renal anemia (Table 55) (target sample size, 20 subjects) at 25 study sites in Japan to investigate the efficacy and safety of vadadustat.

Table 55. Major inclusion and exclusion criteria

Major inclusion criteria • Patients with CKD who are on 3-time weekly HD or HDF • Patients in whom any ESA has not been administered ever or for a certain period as described below, and the mean Hb value at 2 timepoints during the screening period is ≥8.0 g/dL and <10.0 g/dL. • rHuEPO, 1 week • DA, 2 weeks • CERA, 4 weeks • Patients in whom the serum ferritin value during the screening period is ≥100 ng/mL, or TSAT is ≥20% Major exclusion criteria • Patients complicated by conditions causing anemia (hemolysis anemia, etc.) other than renal anemia • Patients in whom fundus photographs are not available during the screening period or who have active fundal diseases • Patients who have experienced new onset or recurrent of cerebrovascular disorder, acute coronary syndrome, deep vein thrombosis or pulmonary embolism within 12 weeks before screening

The dosage regimen was adjusted to maintain the Hb value within the target range (10.0-12.0 g/dL) in accordance with Table 56 until the end of 24 weeks of treatment.

Table 56. Dose adjustment method

<table>
<tr><td>Regimen</td><td>Oral administration, once daily</td></tr>
<tr><td>Initial dose</td><td>300 mg/day</td></tr>
<tr><td>Dose adjustment range</td><td>150-600 mg/day
<table>
<tr><th>Level</th><th>Dose</th></tr>
<tr><td>1</td><td>150 mg</td></tr>
<tr><td>2</td><td>300 mg</td></tr>
<tr><td>3</td><td>450 mg</td></tr>
<tr><td>4</td><td>600 mg</td></tr>
</table></td></tr>
<tr><td>Dose adjustment criteria</td><td>• Interval between dose increase actions should be ≥4 weeks in principle.
• Interval between dose reduction actions should be ≥2 weeks in principle.
• If the Hb value is rapidly increased (a change during the last 4 weeks >2.0 g/dL), the dose should be reduced by 1 level.
• If the Hb value is rapidly increased to >13.0 g/dL (a change during the last 4 weeks >2.0 g/dL), treatment should be suspended, and after the Hb value is decreased to ≤12.0 g/dL, it should be resumed at a dose 1 level lower.
• If the Hb value is not rapidly increased, the dose should be adjusted based on the Hb value as specified in the table below.

Table for dose adjustment based on the Hb value
<table>
<tr><th>Hb value</th><th>Dose of the study drug</th></tr>
<tr><td><10.0 g/dL</td><td>Increase by 1 level</td></tr>
<tr><td>≥10.0 g/dL and ≤11.5 g/dL</td><td>No change</td></tr>
<tr><td>>11.5 g/dL and ≤13.0 g/dL</td><td>Reduce by 1 level</td></tr>
<tr><td>>13.0 g/dL</td><td>Suspend the treatment, and after decrease the Hb value to ≤12.0 g/dL, resume at a dose 1 level lower.</td></tr>
</table></td></tr>
</table>

All of the 24 subjects who received any study drug were included in the FAS and the safety analysis, and the FAS served as the primary efficacy analysis population.

[38] Patients who were not treated with any ESA or were withdrawn from an ESA for a certain period (≥1 week for rHuEPO, ≥2 weeks for DA, and ≥4 weeks for CERA)

A total of 3 subjects resulted in discontinuation owing to "adverse events" in 2 subjects and "others, based on (sub-)investigator's decision" in 1 subject.

For the efficacy, Table 57 shows "mean Hb value at Weeks 20 and 24."

Table 57. Mean Hb value at Weeks 20 and 24 (g/dL) (FAS[a])

	Subjects treated with vadadustat (n = 23)[a]
Baseline Hb value (mean ± SD)	9.30±0.67
Mean Hb value at Weeks 20 and 24[b] (least squares mean ± SE)	10.75±0.19

a) Although the FAS comprised 24 subjects, 23 subjects were included in the analysis, excluding 1 subject in whom data on the Hb value at the start date of treatment and thereafter were not available.
b) MMRM on the assumption of intra-subject unstructured covariance using the Hb value at the start date of treatment as a covariate and the timepoint as the fixed effect

For the safety,[39] adverse events occurred in 23 of 24 subjects (95.8%), and adverse drug reactions occurred in 2 of 24 subjects (8.3%). Adverse events reported by ≥2 subjects were shunt stenosis in 6 of 24 subjects (25.0%), nasopharyngitis in 5 of 24 subjects (20.8%), diarrhoea in 4 of 24 subjects (16.7%), skin abrasion in 3 of 24 subjects (12.5%), and vomiting in 2 of 24 subjects (8.3%). There were no adverse drug reactions reported by ≥2 subjects.

No deaths occurred. Serious adverse events occurred in 7 of 24 subjects (29.2%) (pneumonia, aneurysm, peripheral arterial occlusive disease, duodenal ulcer haemorrhage, clavicle fracture, arteriovenous fistula occlusion, shunt stenosis, pelvic fracture, and vascular access malfunction in 1 subject each), but a causal relationship to the study drug was ruled out for any event.

Adverse events leading to treatment discontinuation occurred in 2 of 24 subjects (8.3%) (duodenal ulcer haemorrhage and haemoglobin decreased in 1 subject each), but a causal relationship to the study drug was ruled out for any event. For their outcome, these resolved or were resolving.

7.R. Outline of the review conducted by PMDA

7.R.1 Efficacy

The efficacy of vadadustat was separately reviewed in patients on HD [see Section 7.R.1.1], patients with non-dialysis dependent CKD [see Section 7.R.1.2], and patients on PD [see Section 7.R.1.3].

Based on the review in Sections 7.R.1.1 to 7.R.1.3, PMDA has concluded that the efficacy of vadadustat in treating renal anemia was demonstrated.

7.R.1.1 Patients on HD

Based on the review in Sections 7.R.1.1.1 and 7.R.1.1.2, PMDA has concluded that the efficacy of vadadustat in patients on HD was demonstrated.

[39] The safety evaluation covered the 24-week treatment period and subsequent 14-day follow-up period.

7.R.1.1.1 Efficacy (post-switch maintenance effect) in patients on HD being treated with an ESA for renal anemia

7.R.1.1.1.1 Results on primary endpoint, etc.

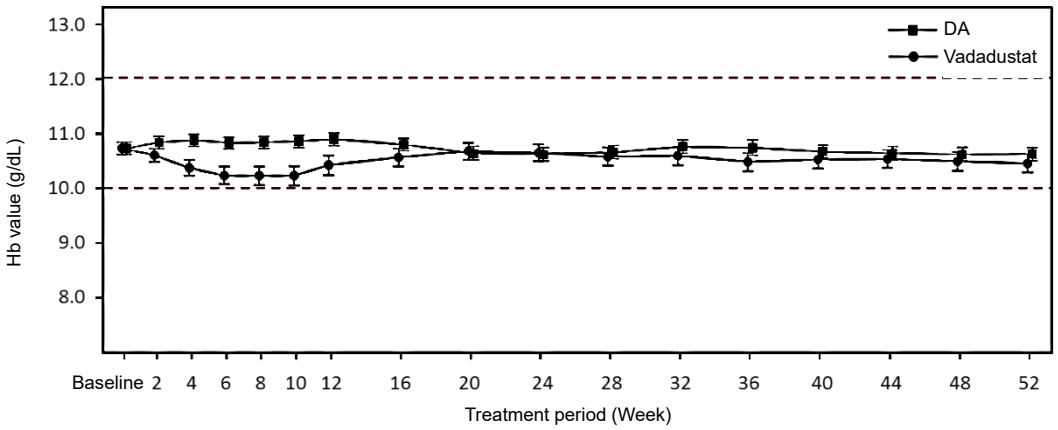
The applicant's explanation on the rationale for establishing the design and results on the primary endpoint in the Japanese phase III study (MT-6548-J03):

The Japanese phase III study (MT-6548-J03) was conducted in patients on HD being treated with an ESA for renal anemia to examine whether vadadustat used in place of an ESA could maintain the blood condition (post-switch maintenance effect).

For the primary endpoint, the Hb value was selected as an indicator in accordance with "Guideline on Clinical Evaluation of Renal Anemia Drugs" (PFSB/ELD Notification No. 0930-1 dated September 30, 2011), and the evaluation period was specified as 24 weeks to confirm that the Hb value would be maintained within the target range (10.0-12.0 g/dL). In addition, in light of variations in the Hb value, the primary endpoint was established as "mean Hb value at Weeks 20 and 24." The control drug was specified as DA, one of the standard drugs for treatment of renal anemia in patients on HD.

In the Japanese phase III study (MT-6548-J03), a difference in "mean Hb value at Weeks 20 and 24" [95% CI] between the vadadustat group and DA group (vadadustat group − DA group) was −0.05 [−0.26, 0.17] (g/dL), and the lower limit of the 95% CI exceeded the predetermined noninferiority limit (−0.75 g/dL), demonstrating noninferiority of vadadustat to DA (Table 52). In addition, the least squares means of the mean Hb value at Weeks 20 and 24 in both vadadustat group and DA group fell within the target range (10.0-12.0 g/dL).

For the major secondary endpoints, Figure 1 shows "Changes in the Hb value until Week 52" and Table 58 shows "Percentage of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 52." The Hb value in the vadadustat group tended to decrease over a period from Weeks 4 to 16 but did not drastically change, and at Week 20 and thereafter, the value was almost maintained within the target range (10.0-12.0 g/dL). Of subjects in the vadadustat group, only 4 subjects required rescue treatment with an ESA by Week 24.



Timepoint (Week)		Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
n	Vadadustat	162	160	157	155	150	150	147	144	140	138	132	131	126	122	118	118	115
	DA	161	160	159	159	158	157	157	156	154	152	150	146	142	141	139	133	133

Figure 1. Changes in the Hb value (mean [95% CI]) (FAS)

Table 58. Percentage (%) of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 52 (FAS)

Timepoint (Week)	Baseline	2	4	6	8	10	12	16	20
Vadadustat	81.5 (132/162)	75.0 (120/160)	63.7 (100/157)	58.1 (90/155)	56.0 (84/150)	56.7 (85/150)	61.9 (91/147)	68.8 (99/144)	73.6 (103/140)
DA	78.9 (127/161)	81.3 (130/160)	83.0 (132/159)	84.3 (134/159)	85.4 (135/158)	81.5 (128/157)	86.6 (136/157)	84.6 (132/156)	74.0 (114/154)
Timepoint (Week)	24	28	32	36	40	44	48	52	
Vadadustat	75.4 (104/138)	70.5 (93/132)	73.3 (96/131)	67.5 (85/126)	77.0 (94/122)	74.6 (88/118)	72.9 (86/118)	75.7 (87/115)	
DA	75.7 (115/152)	77.3 (116/150)	79.5 (116/146)	78.9 (112/142)	81.6 (115/141)	85.6 (119/139)	79.7 (106/133)	86.5 (115/133)	

Percentage (%) (number of subjects with an Hb level within the target range/number of subjects with an Hb level measured at the timepoint)

PMDA's view:

There are no particular problems with evaluation of the efficacy of vadadustat in the Japanese phase III study (MT-6548-J03) in patients on HD being treated with an ESA for renal anemia in which DA was used as the control drug; the primary endpoint was specified as "mean Hb value at Weeks 20 and 24"; and the secondary endpoints were specified as "Changes in the Hb value until Week 52" and "Percentage of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 52." Because the Japanese phase III study (MT-6548-J03) demonstrated noninferiority of vadadustat to DA, vadadustat was shown to be effective in treating renal anemia in patients on HD previously receiving an ESA. The Hb value, however, decreased after switching from an ESA to vadadustat although it was almost maintained within the target range by dose adjustment at Week 20 and thereafter. PMDA considers it necessary to provide a caution that attention should be paid to a decrease in the Hb value after switching from an ESA to vadadustat.

7.R.1.1.1.2 Efficacy in subgroups by patient characteristic

The applicant's explanation on the efficacy in subgroups by patient characteristic:

Table 59 shows the "mean Hb value at Weeks 20 and 24" in subgroups sorted by each of major patient characteristics. Although it should be noted that some subgroups have a limited sample size, there

were no patient characteristics that clearly affected the post-switch maintenance effect of vadadustat in patients on HD.

Table 59. Mean Hb value at Weeks 20 and 24[a)] (g/dL) by each of major patient characteristics (FAS)

Patient characteristic	Subgroup	Vadadustat (n = 160)	DA (n = 160)
Sex	Male	10.64 ± 0.07 (104)	10.71 ± 0.07 (109)
	Female	10.53 ± 0.10 (56)	10.51 ± 0.10 (51)
Age	<65 years old	10.55 ± 0.10 (60)	10.68 ± 0.09 (68)
	≥65 years old	10.64 ± 0.08 (100)	10.60 ± 0.08 (92)
Body weight	<60 kg	10.57 ± 0.08 (98)	10.53 ± 0.08 (91)
	≥60 kg	10.65 ± 0.09 (62)	10.78 ± 0.09 (69)
Primary disease of CKD	Diabetes	10.27 ± 0.13 (29)	10.82 ± 0.11 (39)
	Hypertension	10.74 ± 0.15 (20)	10.63 ± 0.14 (22)
	Autoimmune disease/glomerulonephritis/vasculitis	10.58 ± 0.09 (62)	10.60 ± 0.09 (64)
	Polycystic kidney/hereditary/congenital disease	10.53 ± 0.24 (17)	10.76 ± 0.32 (10)
Baseline serum ferritin value	<100 ng/mL	10.60 ± 0.09 (64)	10.67 ± 0.08 (70)
	≥100 ng/mL	10.60 ± 0.08 (96)	10.61 ± 0.08 (90)
Baseline TSAT	<20%	10.93 ± 0.14 (30)	10.60 ± 0.12 (36)
	≥20%	10.53 ± 0.07 (130)	10.65 ± 0.07 (124)
Concomitant use of oral iron preparation at Week 24	Used	10.42 ± 0.30 (7)	11.09 ± 0.31 (6)
	None	10.61 ± 0.06 (153)	10.62 ± 0.06 (154)
Dose of previous rHuEPO[b)]	<4,500 IU	10.40 ± 0.18 (17)	10.33 ± 0.14 (29)
	≥4,500 IU	10.88 ± 0.15 (32)	11.17 ± 0.17 (24)
Dose of previous DA[b)]	<20 μg	10.64 ± 0.08 (54)	10.74 ± 0.08 (54)
	≥20 μg	10.31 ± 0.11 (41)	10.24 ± 0.11 (35)
Dose of previous CERA[b)]	<25 μg	10.68 ± 0.24 (10)	11.26 ± 0.24 (10)
	≥25 μg	10.93 ± 0.34 (6)	10.70 ± 0.26 (8)

Least squares mean ± SE (n)

a) MMRM on the assumption of compound symmetry for intra-subject unstructured covariance using the Hb value at the start date of treatment as a covariate, and the dose group, timepoint, subgroup, interaction between timepoint and dose group, and interaction between timepoint and subgroup as the fixed effects

b) Calculated dose per week

PMDA confirmed that the efficacy of vadadustat did not tend to be clearly low in particular subgroups.

7.R.1.1.2 Efficacy (anemia-alleviating effect) in patients with an ESA-naïve renal anemia on HD

The applicant's explanation on the rationale for establishing the design and results on the primary endpoint in the Japanese phase III study (MT-6548-J04):

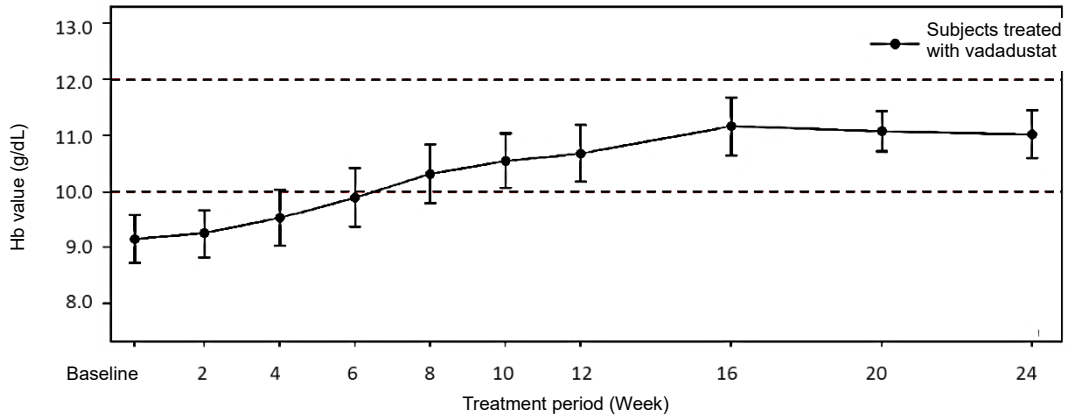
The Japanese phase III study (MT-6548-J04) was conducted in patients on HD with ESA-naïve[40)] renal anemia to examine whether vadadustat could alleviate anemia.

Because the number of ESA-naïve patients on HD was limited in Japan, this study was conducted in an open-label, uncontrolled manner in view of the feasibility.

Table 57 shows the "mean Hb value at Weeks 20 and 24" in the Japanese phase III study (MT-6548-J04). The least squares mean [95% CI] of the Hb values was 10.75 [10.35, 11.14] (g/dL), which fell within the target range (10.0-12.0 g/dL).

[40)] Patients who were not treated with any ESA or were withdrawn from an ESA for a certain period (≥1 week for rHuEPO, ≥2 weeks for DA, and ≥4 weeks for CERA)

In addition, Figure 2 shows "Changes in the Hb value until Week 24," and Table 60 shows "Percentage of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 24." The Hb value was increased in response to vadadustat and was almost maintained within the target range (10.0-12.0 g/dL) at Week 8 and thereafter.



Timepoint (Week)	Baseline	2	4	6	8	10	12	16	20	24
n	24	23	22	21	20	19	19	19	19	19

Figure 2. Changes in the Hb value (mean [95% CI]) (FAS)

Table 60. Percentage (%) of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 24 (FAS)

Timepoint (Week)	Baseline	2	4	6	8	10	12	16	20	24
Subjects treated with vadadustat	16.7 (4/24)	21.7 (5/23)	36.4 (8/22)	47.6 (10/21)	55.0 (11/20)	63.2 (12/19)	68.4 (13/19)	63.2 (12/19)	78.9 (15/19)	73.7 (14/19)

Percentage (%) (number of subjects with an Hb level within the target range/number of subjects with an Hb level measured at the timepoint)

PMDA confirmed that the Hb value increased in response to vadadustat and was maintained within the target range (10.0-12.0 g/dL) by adjusting the dose of vadadustat according to the Hb value in the Japanese phase III study (MT-6548-J04) and thus has concluded that the efficacy of vadadustat can be expected in ESA-naïve patients on HD to a certain extent.

7.R.1.2 Patients with non-dialysis dependent CKD

Based on the review in Sections 7.R.1.2.1 to 7.R.1.2.3, PMDA has concluded that the efficacy of vadadustat has been demonstrated in treating renal anemia in patients with non-dialysis dependent CKD.

7.R.1.2.1 Results on primary endpoint, etc.

The applicant's explanation on the rationale for establishing the design and results on the primary endpoint in the Japanese phase III study (MT-6548-J01):

The Japanese phase III study (MT-6548-J01) was conducted in patients with non-dialysis dependent CKD who had renal anemia being treated with an ESA or untreated with any ESA[41)] to examine the

[41)] Patients untreated with any ESA or withdrawn from an ESA for ≥8 weeks

post-switch maintenance effect of vadadustat used in place of an ESA or the anemia-alleviating effect of vadadustat introduced.

The primary endpoint was specified as the "mean Hb value at Weeks 20 and 24" as with the Japanese phase III study in patients on HD being treated with an ESA (MT-6548-J03) [see Section 7.R.1.1.1]. In this study, which enrolled both patients being treated with an ESA and ESA-naïve patients, allocation was performed in consideration of prior treatment with an ESA and the mean Hb value during the screening period (<10.0 g/dL or ≥10.0 g/dL for ESA-naïve patients; and <11.0 g/dL or ≥11.0 g/dL for ESA-treated patients). The control drug was specified as DA, one of the standard drugs for patients with non-dialysis dependent CKD, and the Hb value was targeted to fall within a range of 11.0 to 13.0 g/dL.

In the Japanese phase III study (MT-6548-J01), a difference in "mean Hb value at Weeks 20 and 24" [95% CI] between the vadadustat group and DA group (vadadustat group − DA group) was −0.26 [−0.50, 0.02] (g/dL), and the lower limit of the 95% CI exceeded the predetermined noninferiority limit (−0.75 g/dL), demonstrating noninferiority of vadadustat to DA (Table 43).

Table 61 shows the "mean Hb value at Weeks 20 and 24" in subgroups sorted by each of major patient characteristics. Although it should be noted that some subgroups have a limited sample size, there were no patient characteristics that clearly affected the efficacy of vadadustat in patients with non-dialysis dependent CKD.

Table 61. Mean Hb value at Weeks 20 and 24[a] (g/dL) by each of major patient characteristics (FAS)

Patient characteristic	Subgroup	Vadadustat (n = 151)	DA (n = 153)
Sex	Male	11.49 ± 0.09 (75)	11.93 ± 0.10 (73)
	Female	11.83 ± 0.08 (76)	11.92 ± 0.08 (80)
Age	<65 years old	11.96 ± 0.13 (33)	11.97 ± 0.14 (28)
	≥65 years old	11.57 ± 0.07 (118)	11.90 ± 0.07 (125)
Body weight	<60 kg	11.65 ± 0.08 (95)	11.92 ± 0.08 (92)
	≥60 kg	11.66 ± 0.10 (56)	11.89 ± 0.10 (61)
Primary disease of CKD	Diabetes	11.84 ± 0.12 (43)	12.01 ± 0.11 (48)
	Hypertension	11.42 ± 0.11 (52)	11.92 ± 0.10 (60)
	Autoimmune disease/glomerulonephritis/vasculitis	11.40 ± 0.17 (20)	11.83 ± 0.13 (31)
	Polycystic kidney/hereditary/congenital disease	12.04 ± 0.28 (13)	11.55 ± 0.34 (9)
	Interstitial nephritis/pyelonephritis	11.30 ± 0.35 (4)	12.18 ± 0.85 (2)
Baseline serum ferritin value	<100 ng/mL	11.60 ± 0.10 (60)	12.01 ± 0.09 (73)
	≥100 ng/mL	11.69 ± 0.08 (91)	11.82 ± 0.09 (80)
Baseline TSAT	<20%	12.11 ± 0.17 (17)	12.21 ± 0.17 (17)
	≥20%	11.60 ± 0.07 (134)	11.88 ± 0.07 (136)
Concomitant use of oral iron preparation at Week 24	Used	11.83 ± 0.10 (54)	12.15 ± 0.11 (48)
	None	11.55 ± 0.08 (97)	11.80 ± 0.07 (105)
Dose of previous DA[b]	<15 μg	11.81 ± 0.14 (20)	11.68 ± 0.16 (16)
	≥15 μg	11.37 ± 0.15 (27)	11.70 ± 0.14 (29)
Dose of previous CERA[b]	<12.5 μg	11.48 ± 0.22 (9)	11.58 ± 0.16 (16)
	≥12.5 μg	11.11 ± 0.18 (24)	12.06 ± 0.19 (21)

Least squares mean ± SE (n)

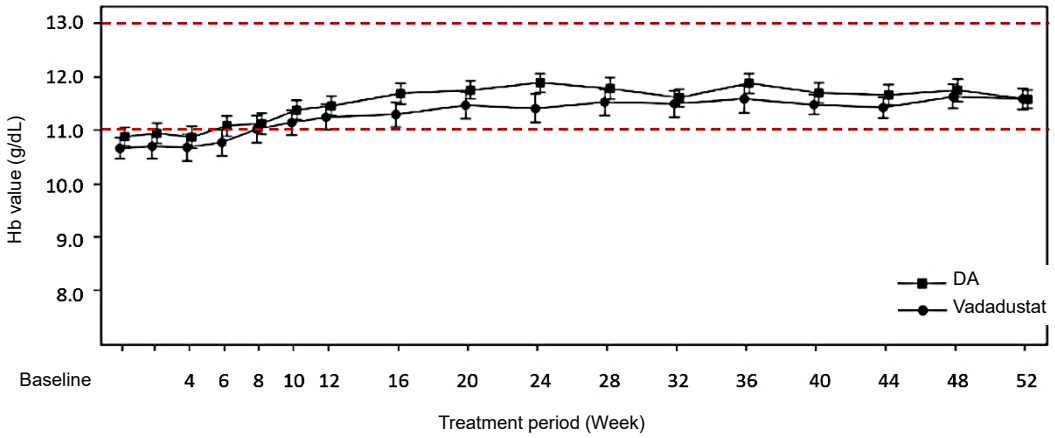
a) MMRM on the assumption of compound symmetry for intra-subject unstructured covariance using the Hb value at the start date of treatment as a covariate, and the dose group, timepoint, subgroup, interaction between timepoint and dose group, and interaction between timepoint and subgroup as the fixed effects

b) Calculated dose per week

7.R.1.2.2 Efficacy (post-switch maintenance effect) in patients with non-dialysis dependent CKD who had renal anemia being treated with an ESA

The applicant's explanation on the efficacy in patients with non-dialysis dependent CKD who had renal anemia being treated with an ESA based on results from the Japanese phase III study (MT-6548-J01):

The "mean Hb value at Weeks 20 and 24" (least squares mean ± standard error [SE]) was 11.88 ± 0.09 g/dL in the vadadustat group and 11.77 ± 0.08 g/dL in the DA group. Figure 3 shows "Changes in the Hb value until Week 52," and Table 62 shows "Percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 52." Although the Hb value was below the target value at baseline, it was increased in both vadadustat group and DA group after switching from an ESA and almost maintained within the target range (11.0-13.0 g/dL) at Week 8 and thereafter.



Timepoint (Week)		Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
n	Vadadustat	80	80	80	79	77	78	77	76	72	66	60	58	57	54	55	54	53
	DA	82	82	82	82	81	82	80	80	79	75	73	70	67	66	65	65	64

Figure 3. Changes in the Hb value (mean [95% CI]) (FAS)

Table 62. Percentage (%) of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 52 (FAS)

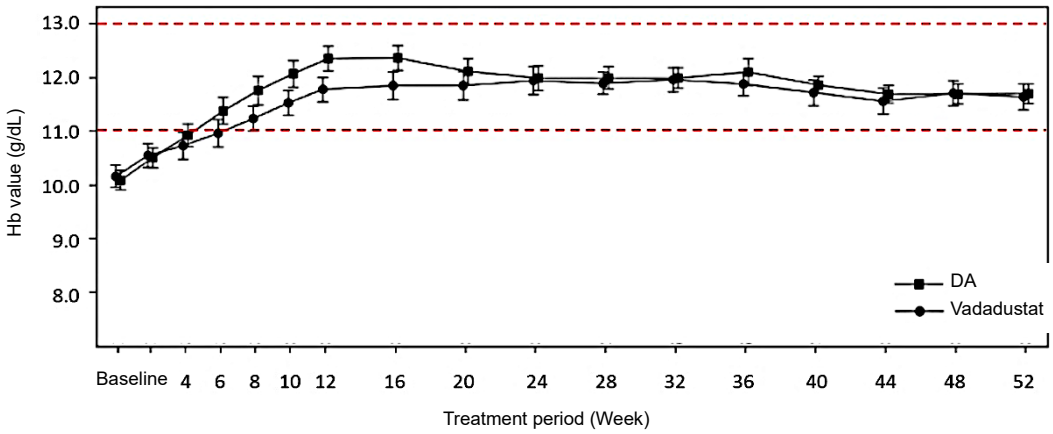
Timepoint (Week)	Baseline	2	4	6	8	10	12	16	20
Vadadustat	45.0 (36/80)	38.8 (31/80)	48.8 (39/80)	41.8 (33/79)	57.1 (44/77)	51.3 (40/78)	58.4 (45/77)	61.8 (47/76)	63.9 (46/72)
DA	52.4 (43/82)	47.6 (39/82)	50.0 (41/82)	61.0 (50/82)	55.6 (45/81)	65.9 (54/82)	70.0 (56/80)	72.5 (58/80)	75.9 (60/79)
Timepoint (Week)	24	28	32	36	40	44	48	52	
Vadadustat	66.7 (44/66)	71.7 (43/60)	72.4 (42/58)	77.2 (44/57)	77.8 (42/54)	74.5 (41/55)	70.4 (38/54)	79.2 (42/53)	
DA	82.7 (62/75)	76.7 (56/73)	77.1 (54/70)	83.6 (56/67)	83.3 (55/66)	80.0 (52/65)	78.5 (51/65)	76.6 (49/64)	

Percentage (%) (number of subjects with an Hb level within the target range/number of subjects with an Hb level measured at the timepoint)

7.R.1.2.3 Efficacy (anemia-alleviating effect) in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia

The applicant's explanation on the efficacy in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia based on results from the Japanese phase III study (MT-6548-J01):

The "mean Hb value at Weeks 20 and 24" (least squares mean ± SE) was 11.88 ± 0.09 g/dL in the vadadustat group and 12.04 ± 0.09 g/dL in the DA group. Figure 4 shows "Changes in the Hb value until Week 52," and Table 63 shows "Percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 52." The Hb value was increased in both vadadustat group and DA group and almost maintained within the target range (11.0-13.0 g/dL) at Week 8 and thereafter.



Timepoint (Week)		Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
n	Vadadustat	71	71	69	69	68	67	68	67	67	66	65	62	62	60	59	56	56
	DA	71	71	70	70	70	68	68	68	65	65	64	62	62	61	59	59	58

Figure 4. Changes in the Hb value (mean [95% CI]) (FAS)

Table 63. Percentage (%) of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 52 (FAS)

Timepoint (Week)	Baseline	2	4	6	8	10	12	16	20
Vadadustat	15.5 (11//71)	33.8 (24/71)	43.5 (30/69)	49.3 (34/69)	58.8 (40/68)	68.7 (46/67)	79.4 (54/68)	76.1 (51/67)	67.2 (45/67)
DA	9.9 (7/71)	26.8 (19/71)	57.1 (40/70)	67.1 (47/70)	77.1 (54/70)	70.6 (48/68)	64.7 (44/68)	70.6 (48/68)	70.8 (46/65)
Timepoint (Week)	24	28	32	36	40	44	48	52	
Vadadustat	69.7 (46/66)	83.1 (54/65)	77.4 (48/62)	77.4 (48/62)	75.0 (45/60)	69.5 (41/59)	78.6 (44/56)	71.4 (40/56)	
DA	72.3 (47/65)	76.6 (49/64)	80.6 (50/62)	71.0 (44/62)	91.8 (56/61)	91.5 (54/59)	81.4 (48/59)	84.5 (49/58)	

Percentage (%) (number of subjects with an Hb level within the target range/number of subjects with an Hb level measured at the timepoint)

Based on reviews in the above Sections 7.R.1.2.1 to 7.R.1.2.3, PMDA confirmed that the Japanese phase III Study (MT-6548-J01) demonstrated noninferiority of vadadustat to DA in all the patient populations, and the efficacy of vadadustat did not tend to be clearly low in any particular patient population. In addition, PMDA confirmed that in both patients being treated with an ESA and ESA-naïve patients, the Hb value increased in response to vadadustat and was maintained within the target range (11.0-13.0 g/dL) by adjusting the dose of vadadustat according to the Hb value. Therefore,

PMDA has concluded that vadadustat is shown to be effective in treating renal anemia in patients with non-dialysis dependent CKD.

7.R.1.3 Patients on PD

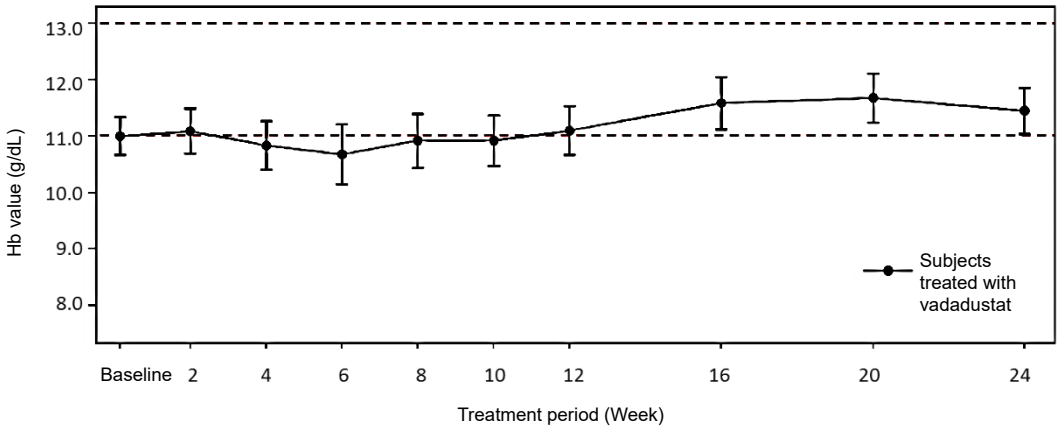
The applicant's explanation on the rationale for establishing the design and results on the primary efficacy endpoint in the Japanese phase III study (MT-6548-J02):

The Japanese phase III study (MT-6548-J02) was conducted in patients on PD who had renal anemia being treated with an ESA or untreated with any ESA[42)] to examine the post-switch maintenance effect of vadadustat used in place of an ESA or the anemia-alleviating effect of vadadustat introduced.

In this study, which enrolled both patients being treated with an ESA and ESA-naïve patients, the Hb value was targeted to fall within a range from 11.0 to 13.0 g/dL. In addition, at the time of planning of this study, the number of patients on PD was approximately 9,000 in Japan, and of these approximately 20% were concomitantly undergoing hemodialysis or hemodiafiltration ("Annual Dialysis Data Report [as of December 31, 2015]," edited by the Japanese Society for Dialysis Therapy), and the number of target patients was limited. This study was conducted in an open-label, uncontrolled manner in view of the feasibility. In the Japanese phase III study (MT-6548-J02), 40 patients switched from an ESA and 2 ESA-naïve patients were enrolled.

Table 48 shows the "mean Hb value at Weeks 20 and 24" in the Japanese phase III study (MT-6548-J02). The least squares mean [95% CI] of the Hb values was 11.35 [10.99, 11.70] (g/dL), which fell within the target range (11.0-13.0 g/dL). For the efficacy of vadadustat in patients switched from an ESA, Figure 5 shows changes in the Hb value until Week 24 and Table 64 shows "Percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 24," one of the secondary endpoints. After switching from an ESA to vadadustat, the Hb value tended to decrease until Week 10 but did not drastically change, and only 1 subject required rescue treatment with an ESA before Week 24. At Week 12 and thereafter, the value was almost maintained within the target range (11.0-13.0 g/dL).

42) Patients untreated with any ESA or withdrawn from an ESA for ≥8 weeks



Timepoint (Week)	Baseline	2	4	6	8	10	12	16	20	24
n	40	38	39	37	36	36	36	35	34	33

Figure 5. Changes in the Hb value (least squares mean [95% CI])

Table 64. Percentage (%) of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 24

Timepoint (Week)	Baseline	2	4	6	8	10	12	16	20	24
Subjects treated with vadadustat	60.0 (24/40)	63.2 (24/38)	43.6 (17/39)	37.8 (14/37)	50.0 (18/36)	44.4 (16/36)	47.2 (17/36)	34.3 (12/35)	70.6 (24/34)	66.7 (22/33)

Percentage (%) (number of subjects with an Hb level within the target range/number of subjects with an Hb level measured at the timepoint)

For the efficacy of vadadustat in the ESA-naïve patient population, the Hb value tended to increase in response to vadadustat although the enrolled sample size was limited to 2 subjects, also limiting interpretation of the results.

PMDA considers it inevitable for the applicant to have conducted the Japanese phase III study (MT-6548-J02) in patients on PD in an open-label, uncontrolled manner. PMDA confirmed that the Hb value was maintained within the target range (11.0-13.0 g/dL) by adjusting the dose of vadadustat according to the Hb value in the Japanese phase III study (MT-6548-J02) and thus has concluded that the efficacy of vadadustat can be expected in patients on PD to a certain extent.

7.R.2 Safety

Based on the review in Sections 7.R.2.1 to 7.R.2.5, PMDA has concluded that vadadustat has acceptable safety in patients with renal anemia when the dose is adjusted according to the Hb value.

7.R.2.1 Patients on HD

The applicant's explanation on the safety of vadadustat in patients on HD based on results from the Japanese phase III studies in patients on HD (MT-6548-J03 and MT-6548-J04):

Table 65 summarizes adverse events in subjects receiving vadadustat in the Japanese phase III studies (MT-6548-J03 and MT-6548-J04). In the Japanese phase III study (MT-6548-J03) in patients on HD being treated with an ESA, the incidence of adverse drug reactions tended to be higher in the vadadustat group than in the DA group, but no particular events tended to show the high incidence. No large differences were observed in incidence or content of adverse events (Table 53) between the groups. In addition, no clinically relevant differences were observed in incidence or content of adverse

events between the Japanese phase III study (MT-6548-J04) in ESA-naïve patients on HD [see Section 7.2.4] and the vadadustat group in the Japanese phase III study (MT-6548-J03).

Table 65. Summary of adverse events in clinical studies in patients on HD (MT-6548-J03 and MT-6548-J04)

	MT-6548-J03		MT-6548-J04
	Patients on HD receiving an ESA		ESA-naïve patients on HD
	Evaluation period, 52 weeks		Evaluation period, 26 weeks
	Vadadustat (n = 162)	DA (n = 161)	Subjects treated with vadadustat (n = 24)
Adverse events	95.1 (154)	98.1 (158)	95.8 (23)
Adverse drug reactions	11.1 (18)	3.7 (6)	8.3 (2)
Deaths	1.2 (2)	0.6 (1)	0 (0)
Serious adverse events	25.3 (41)	27.3 (44)	29.2 (7)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	9.9 (16)	8.7 (14)	8.3 (2)
Adverse drug reactions leading to treatment discontinuation	1.2 (2)	1.2 (2)	0 (0)

Incidence % (n)

PMDA confirmed that the safety of vadadustat in patients on HD did not show any clinically relevant trend in comparison between the vadadustat group and DA group. In addition, no clinically relevant difference was observed in safety between patients on HD being treated with an ESA and ESA-naïve patients on HD.

7.R.2.2 Patients with non-dialysis dependent CKD

The applicant's explanation on the safety of vadadustat in patients with non-dialysis dependent CKD based on results from the Japanese phase III study in patients with non-dialysis dependent CKD (MT-6548-J01):

Table 66 summarizes adverse events in subjects receiving vadadustat in the Japanese phase III study (MT-6548-J01). Although the incidence of adverse drug reactions tended to be higher in the vadadustat group than in the DA group, most of these reactions were mild or moderate, and none were deemed to be serious. No clinically relevant differences were observed in incidence or content of adverse events between patients being treated with an ESA and ESA-naïve patients.

Table 66. Summary of adverse events in clinical study in patients with non-dialysis dependent CKD (MT-6548-J01; evaluation period, 52 weeks)

	Overall		Patients with non-dialysis dependent CKD being treated with an ESA		ESA-naïve patients with non-dialysis dependent CKD	
	Vadadustat (n = 151)	DA (n = 153)	Vadadustat (n = 80)	DA (n = 82)	Vadadustat (n = 71)	DA (n = 71)
Adverse events	90.1 (136)	92.2 (141)	90.0 (72)	95.1 (78)	90.1 (64)	88.7 (63)
Adverse drug reactions	13.2 (20)	4.6 (7)	12.5 (10)	2.4 (2)	14.1 (10)	7.0 (5)
Deaths	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)	1.4 (1)
Serious adverse events	27.8 (42)	32.0 (49)	32.5 (26)	37.8 (31)	22.5 (16)	25.4 (18)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	6.6 (10)	3.9 (6)	6.3 (5)	3.7 (3)	7.0 (5)	4.2 (3)
Adverse drug reactions leading to treatment discontinuation	2.6 (4)	0 (0)	2.5 (2)	0 (0)	2.8 (2)	0 (0)

Incidence % (n)

PMDA confirmed that the safety of vadadustat in patients with non-dialysis dependent CKD did not show any clinically relevant trend in comparison between the vadadustat group and DA group. In addition, no clinically relevant difference was observed in safety between patients with non-dialysis dependent CKD being treated with an ESA and ESA-naïve patients with non-dialysis dependent CKD.

7.R.2.3 Patients on PD

The applicant's explanation on the safety of vadadustat in patients on PD based on results from the Japanese phase III study in patients on PD (MT-6548-J02):

Table 67 summarizes adverse events in subjects receiving vadadustat in the Japanese phase III study (MT-6548-J02). The incidence of adverse events in patients on PD did not tend to be higher than that in patients on HD (Table 65) or patients with non-dialysis dependent CKD (Table 66). In addition, when the reported adverse events (Table 49) were compared with those in patients on HD and patients with non-dialysis dependent CKD, none presented a higher incidence only in patients on PD than in the other patient populations, except for catheter site infection and peritonitis which were specific to patients on PD. For death in 1 subject (myocardial ischaemia), a causal relationship to the study drug could not be completely ruled out because it occurred during treatment with the study drug, and thus it was assessed as a serious adverse drug reaction [see Section 7.2.3].

Table 67. Summary of adverse events in clinical study in patients on PD (MT-6548-J02; evaluation period, 26 weeks)

	Subjects treated with vadadustat (n = 42)
Adverse events	90.5 (38)
Adverse drug reactions	11.9 (5)
Deaths	2.4 (1)
Serious adverse events	28.6 (12)
Serious adverse drug reactions	2.4 (1)
Adverse events leading to treatment discontinuation	7.1 (3)
Adverse drug reactions leading to treatment discontinuation	2.4 (1)

Incidence % (n)

PMDA confirmed that the safety of vadadustat in patients on PD did not show any clinically relevant trend.

7.R.2.4 Long-term safety

The applicant's explanation on the long-term safety of vadadustat:

For the safety in the Japanese phase III studies (MT-6548-J01 and MT-6548-J03) in which the treatment period was 52 weeks, Tables 68 and 69 show the incidence of adverse events in each phase of treatment with vadadustat. The incidence did not tend to increase with the increasing period of treatment with vadadustat. In addition, the incidence of "diarrhoea" tended to be high at the early phase of treatment with vadadustat, but the event was mild or moderate in any subject and resolved with an appropriate action such as dose reduction of vadadustat. Such a trend is therefore considered to have no clinical relevance. For the safety in the Japanese phase III studies (MT-6548-J02 and MT-6548-J04) in which the treatment period was 26 weeks, the incidence of adverse events did not tend to increase with the increasing period of treatment with vadadustat.

Table 68. Incidence of adverse events in patients with non-dialysis dependent CKD in each phase of treatment with vadadustat (MT-6548-J01)

	Weeks 0 to 12 (n = 151)	Weeks 12 to 24 (n = 144)	Weeks 24 to 36 (n = 129)	Weeks 36 to 52 (n = 119)	Entire period (n = 151)
Adverse events	53.0 (80)	50.0 (72)	55.8 (72)	54.6 (65)	90.1 (136)
Adverse drug reactions	9.3 (14)	2.8 (4)	1.6 (2)	0.8 (1)	13.2 (20)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events	3.3 (5)	11.1 (16)	10.9 (14)	13.4 (16)	27.8 (42)
Adverse events leading to treatment discontinuation	1.3 (2)	3.5 (5)	0.8 (1)	1.7 (2)	6.6 (10)
Adverse events reported by ≥10.0% of subjects in all the phases					
Nasopharyngitis	8.6 (13)	9.0 (13)	12.4 (16)	10.1 (12)	24.5 (37)
Diarrhoea	6.6 (10)	4.2 (6)	1.6 (2)	0.8 (1)	11.9 (18)

MedDRA/J ver.22.0
Incidence % (n)

Table 69. Incidence of adverse events in patients on HD in each phase of treatment with vadadustat (MT-6548-J03)

	Weeks 0 to 12 (n = 162)	Weeks 12 to 24 (n = 144)	Weeks 24 to 36 (n = 136)	Weeks 36 to 52 (n = 129)	Entire period (n = 162)
Adverse events	71.6 (116)	77.1 (111)	73.5 (100)	79.1 (102)	95.1 (154)
Adverse drug reactions	8.6 (14)	2.8 (4)	2.2 (3)	0.8 (1)	11.1 (18)
Deaths	0 (0)	0.7 (1)	0.7 (1)	0 (0)	1.2 (2)
Serious adverse events	8.0 (13)	6.3 (9)	8.8 (12)	10.1 (13)	25.3 (41)
Adverse events leading to treatment discontinuation	3.7 (6)	3.5 (5)	0.7 (1)	3.1 (4)	9.9 (16)
Adverse events reported by ≥10.0% of subjects in all the phases					
Nasopharyngitis	13.0 (21)	11.8 (17)	29.4 (40)	20.9 (27)	45.7 (74)
Diarrhoea	8.0 (13)	4.2 (6)	3.7 (5)	7.8 (10)	15.4 (25)
Shunt stenosis	6.2 (10)	3.5 (5)	3.7 (5)	6.2 (8)	14.2 (23)
Contusion	3.1 (5)	5.6 (8)	2.9 (4)	7.8 (10)	13.0 (21)

MedDRA/J ver.22.0
Incidence % (n)

Based on results on the safety in each phase of treatment with vadadustat, PMDA confirmed that adverse events did not tend to increase with the increasing period of treatment.

7.R.2.5 Important adverse events

PMDA conducted the following reviews mainly on adverse events to which special attention should be paid based on the mechanism of action of vadadustat and data from non-clinical and clinical studies as well as adverse events of special interest reported with drugs in the same class.

7.R.2.5.1 Thromboembolism

The applicant's explanation on thromboembolism:

For events related to thromboembolism in clinical studies, the incidence of events classified into Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Queries (SMQ) "Embolic and thrombotic events (narrow)" were reviewed.

Table 70 shows adverse events related to thromboembolism in the Japanese phase III studies (MT-6548-J01 and MT-6548-J03). The incidence of adverse events related to thromboembolism in the vadadustat group was comparable to that in the DA group, and none of the particular events in the vadadustat group presented a higher trend of incidence. A causal relationship to the study drug was ruled out for any of the reported events.

Table 70. Adverse events related to thromboembolism (MT-6548-J01 and MT-6548-J03; evaluation period, 52 weeks)

	MT-6548-J01		MT-6548-J03	
	Patients with non-dialysis dependent CKD		Patients on HD	
	Vadadustat (n = 151)	DA (n = 153)	Vadadustat (n = 162)	DA (n = 161)
Overall events related to thromboembolism	0.7 (1)	3.9 (6)	7.4 (12)	8.7 (14)
Shunt occlusion	0 (0)	0.7 (1)	2.5 (4)	2.5 (4)
Peripheral arterial occlusive disease	0 (0)	0 (0)	1.9 (3)	1.9 (3)
Retinal vein occlusion	0.7 (1)	0.0 (0)	0.6 (1)	0 (0)
Cerebral infarction	0 (0)	0.7 (1)	0.6 (1)	3.1 (5)
Lacunar infarction	0 (0)	1.3 (2)	0.6 (1)	0 (0)
Cerebellar infarction	0 (0)	0 (0)	0.6 (1)	0.6 (1)
Shunt thrombosis	0 (0)	0 (0)	0.6 (1)	0 (0)
Thrombotic cerebral infarction	0 (0)	0 (0)	0.6 (1)	0 (0)
Peripheral artery occlusion	0 (0)	0 (0)	0 (0)	0.6 (1)
Thrombophlebitis	0 (0)	0 (0)	0 (0)	0.6 (1)
Arteriovenous fistula thrombosis	0 (0)	0 (0)	0 (0)	0.6 (1)
Acute myocardial infarction	0 (0)	0.7 (1)	0 (0)	0 (0)
Pulmonary embolism	0 (0)	0.7 (1)	0 (0)	0 (0)

MedDRA/J ver.22.0
Incidence % (n)

In addition, Table 71 shows adverse events related to thromboembolism in subjects after the administration of vadadustat in the pooled analysis[43)] in a total of 6 studies including Japanese phase II studies (CI-0021 and CI-0022) and Japanese phase III studies (MT-6548-J01 to MT-6548-J04). A causal relationship to the study drug was ruled out for any of the reported events.

Table 71. Incidences of adverse events related to thromboembolism (pooled analysis in 6 Japanese clinical studies[a)])

	Subjects treated with vadadustat			
	Patients with non-dialysis dependent CKD[b)] (n = 202)	Patients on HD[c)] (n = 237)	Patients on PD[d)] (n = 42)	Total (n = 481)
Overall events related to thromboembolism	0.5 (1)	5.9 (14)	11.9 (5)	4.2 (20)
Peripheral arterial occlusive disease	0 (0)	1.7 (4)	4.8 (2)	1.2 (6)
Shunt occlusion	0 (0)	1.7 (4)	2.4 (1)	1.0 (5)
Retinal vein occlusion	0.5 (1)	0.4 (1)	2.4 (1)	0.6 (3)
Cerebral infarction	0 (0)	0.4 (1)	2.4 (1)	0.4 (2)
Cerebellar infarction	0 (0)	0.4 (1)	0 (0)	0.2 (1)
Lacunar infarction	0 (0)	0.4 (1)	0 (0)	0.2 (1)
Arteriovenous fistula thrombosis	0 (0)	0.4 (1)	0 (0)	0.2 (1)
Shunt thrombosis	0 (0)	0.4 (1)	0 (0)	0.2 (1)
Thrombotic cerebral infarction	0 (0)	0.4 (1)	0 (0)	0.2 (1)

MedDRA/J ver.22.0
Incidence % (n)
a) Japanese phase II studies (CI-0021 and CI-0022) and Japanese phase III studies (MT-6548-J01 to MT-6548-J04)
b) Safety data covering periods up to 16 weeks in the Japanese phase II study (CI-0021) and of 52 weeks in the Japanese phase III studies (MT-6548-J01)
c) Pooled analysis on the safety data covering periods up to 16 weeks in the Japanese phase II study (CI-0022), of 52 weeks in the Japanese phase study (MT-6548-J03), and of 26 weeks in the Japanese phase III study (MT-6548-J04)
d) Safety data covering a period of 26 weeks in the Japanese phase III study (MT-6548-J04)

[43)] The safety data from the following 6 studies were pooled. The pooled analyses in the subsequent evaluation also used the same data.
Safety data covering a period up to 16 weeks in the Japanese phase II studies (CI-0021 and CI-0022) in patients with non-dialysis dependent CKD or patients on HD
Safety data covering a period up to 52 weeks in the Japanese phase III studies (MT-6548-J01 and MT-6548-J03) in patients with non-dialysis dependent CKD or patients on HD
Safety data covering a period of 26 weeks in the Japanese phase III studies (MT-6548-J02 and MT-6548-J04) in patients on PD or patients on HD

PMDA confirmed that no clinically relevant differences were observed in safety data on the concerned events between the vadadustat group and DA group. The increased Hb value, however, is associated with a risk of thromboembolism, multiple serious adverse events related to thromboembolism occurred in both vadadustat group and DA group, and package inserts of drugs in the same class with the same mechanism of action include caution statements about thromboembolism in the Warnings section. PMDA therefore considers that the package insert of vadadustat should include caution statements about thromboembolism as with those of drugs in the same class, and information on incidence of thromboembolism should be continuously collected through post-marketing surveillances.

7.R.2.5.2 Cardiovascular events

The applicant's explanation on cardiovascular-related events:

In the Japanese phase III study (MT-6548-J01), cardiovascular-related events occurred in 3 of 151 subjects (2.0%) in the vadadustat group (myocardial ischaemia, intracranial aneurysm, and subarachnoid haemorrhage in 1 subject each) and 4 of 153 subjects (2.6%) in the DA group (lacunar infarction in 2 subjects; and intracranial aneurysm and cerebral infarction in 1 subject each). A causal relationship to the study drug was ruled out for any event.

In the Japanese phase III study (MT-6548-J03), cardiovascular-related events occurred in 9 of 162 subjects (5.6%) in the vadadustat group (cerebral infarction, cerebellar infarction, carotid artery stenosis, intracranial aneurysm, lacunar infarction, thrombotic cerebral infarction, myocardial ischaemia, angina pectoris, coronary artery stenosis, angina unstable, arteriosclerosis coronary artery, and subdural haematoma in 1 subject each; some subjects experienced multiple events) and 14 of 161 subjects (8.7%) in the DA group (cerebral infarction in 5 subjects; angina pectoris in 3 subjects; coronary artery stenosis in 2 subjects; and cerebellar infarction, carotid artery stenosis, myocardial ischaemia, and coronary artery restenosis in 1 subject each; some subjects experienced multiple events). A causal relationship to the study drug was ruled out for any event.

In the pooled analysis in a total of 6 studies including Japanese phase II studies (CI-0021 and CI-0022) and Japanese phase III studies (MT-6548-J01 to MT-6548-J04), cardiovascular-related events were found in 15 of 481 subjects (3.1%) (myocardial ischaemia in 3 subjects; intracranial aneurysm and cerebral infarction in 2 subjects each; and subarachnoid haemorrhage, carotid artery stenosis, cerebellar infarction, cerebral haemorrhage, lacunar infarction, thrombotic cerebral infarction, angina pectoris, angina unstable, arteriosclerosis coronary artery, coronary artery stenosis and subdural haematoma in 1 subject each; some subjects experienced multiple events). An adverse drug reaction was observed in 1 of 481 subjects (0.2%) (myocardial ischaemia), leading to death. The concerned death occurred in a patient on PD in the Japanese phase III study (MT-6548-J02), and a causal relationship to the study drug could not be completely ruled out for the reaction because it occurred during treatment with the study drug [see Section 7.2.3].

As described above, cardiovascular-related events are less likely to raise problems in patients receiving vadadustat than patients receiving DA at present, and thus the applicant considers it unnecessary to include caution statements in the package insert.

PMDA confirmed that the incidence of cardiovascular-related events in the vadadustat group was comparable to that in the DA group in the Japanese phase III studies, and no adverse drug reactions occurred. In addition, although the pooled analysis in 6 Japanese clinical studies presented the death in 1 patient receiving vadadustat, PMDA has accepted the applicant's view that it is unnecessary to include caution statements about cardiovascular events in the package insert of vadadustat at present because the causal relationship to vadadustat remained unclear. In consideration of the risk of thromboembolism, however, the applicant should continue collecting information about cardiovascular-related events through post-marketing surveillance, etc. as well.

7.R.2.5.3 Hepatic dysfunction

The applicant's explanation on hepatic dysfunction:

Akebia Therapeutics, Inc., a foreign development company, extracted events classified into MedDRA SMQ "Drug-related Hepatic Disorders Comprehensive" from the safety database in Japanese and foreign clinical studies[44)] (cut-off on November 18, 2019) and asked external medical experts to assess the extracted events. Of approximately 4,500 subjects who received vadadustat, 21 subjects (0.4%) were assessed to have experienced liver disorder probably or highly related to vadadustat. All of the 21 subjects were participants in foreign clinical studies, and of these 17 subjects were assessed to have experienced serious liver disorder. Table 72 shows the details in the 17 subjects. None of these resulted in death or hepatitis fulminant, and all were confirmed to have recovered.

[44)] Completed foreign phase I study and foreign phase II study (a total of 24 studies), ongoing foreign phase I study (1 study), ongoing foreign phase II study (1 study), ongoing foreign phase III study (4 studies), completed Japanese phase I study (MT-6548-J05), completed Japanese phase III studies (MT-6548-J02 and MT-6548-J04), and ongoing Japanese phase III studies (MT-6548-J01 and MT-6548-J03)

Table 72. Details of cases with serious liver disorder probably or highly related to vadadustat according to the safety database in Japanese and foreign clinical studies (cut-off on November 18, 2019)

Case	Age	Stage	Dose of vadadustat[a)]	Term of adverse drug reaction	Time from first dose to onset	Severity	Outcome	Action on study drug
1[b)]	75	Non-dialysis	150	Transaminases increased	82 days	Severe	Recovered	Suspended
				Transaminases increased	279 days	Moderate	Recovered	Discontinued
2	57	Non-dialysis	300	Drug-induced liver injury	28 days	Severe	Recovered	Discontinued
3	43	Dialysis	450	Alanine aminotransferase increased	31 days	Severe	Recovered	Discontinued
				Aspartate aminotransferase increased	31 days	Severe	Recovered	Discontinued
				Chronic hepatitis B	31 days	Moderate	Recovered	Discontinued
4[c)]	69	Non-dialysis	450	Liver function test abnormal	86 days	Moderate	Recovered	Discontinued
5	40	Non-dialysis	450	Aspartate aminotransferase increased	364 days	Moderate	Recovered	Suspended
				Alanine aminotransferase increased	364 days	Moderate	Recovered	Suspended
6	82	Non-dialysis	300	Transaminases increased	33 days	Moderate	Recovered	Suspended
7	58	Dialysis	450	Alanine aminotransferase increased	340 days	Mild	Recovered	Continued
				Alanine aminotransferase increased	345 days	Moderate	Recovered	Suspended
8	50	Non-dialysis	600	Aspartate aminotransferase increased	85 days	Moderate	Recovered	Continued
9	68	Non-dialysis	150	Alanine aminotransferase increased	93 days	Moderate	Recovered	Not applicable[d)]
				Aspartate aminotransferase increased	93 days	Moderate	Recovered	Not applicable[d)]
10	74	Dialysis	300	Hepatic enzyme increased	89 days	Mild	Recovered	Suspended
11	56	Dialysis	450	Alanine aminotransferase increased	35 days	Mild	Recovered	Suspended
12	36	Dialysis	600	Liver injury	253 days	Mild	Recovered	Discontinued
13	54	Dialysis	300	Alanine aminotransferase increased	34 days	Mild	Recovered	Suspended
14	69	Non-dialysis	600	Drug-induced liver injury	112 days	Mild	Recovered	Discontinued
15	80	Non-dialysis	450	Transaminases increased	85 days	Mild	Recovered	Discontinued
16	50	Dialysis	450	Liver function test increased	169 days	Mild	Recovered	Suspended
17	33	Dialysis	450	Alanine aminotransferase increased	168 days	Mild	Recovered	Not applicable[e)]
				Aspartate aminotransferase increased	168 days	Mild	Recovered	Not applicable[e)]

MedDRA ver.22.1

a) Dose at a timepoint closest to day of onset
b) Positive for rechallenge
c) Applicable to Hy's law
d) Because the medication was discontinued owing to the rescue treatment with an ESA, the action on the study drug was reported as "Not applicable."
e) Because the study drug was not administered at the time of onset of the event, the action on the study drug was reported as "Not applicable."

In the Japanese and foreign clinical studies in patients with CKD, exclusion criteria for hepatic functions[45)] had been applied, and on February 27, 2019, clinical study discontinuation criteria[46)] and

[45)] The following exclusion criteria were specified:
Japanese phase II studies: Patients in whom the aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin value during screening is >2.0 times the upper limit of the standard value.
Japanese phase III studies: Patients in whom the AST, ALT or total bilirubin value during screening is >2.5 times the upper limit of the standard value.
Foreign phase II and phase III studies: Patients in whom the AST, ALT or total bilirubin value during screening is >2.0 times the upper limit of the standard value.

[46)] The following discontinuation criteria were specified:
Patients in whom values on hepatic function parameters during the treatment period are found to be abnormal meeting any of the following cases should discontinue the study:
- "The ALT or AST value >3 times the upper limit of the standard value" and "the total bilirubin value >2 times the upper limit of the standard value"
- "The ALT or AST value >3 times the upper limit of the standard value" and "the PT-INR value >1.5"
- "The ALT or AST value >8 times the upper limit of the standard value"
- "The ALT or AST value >5 times the upper limit of the standard value" continued for ≥2 weeks
- "The ALT or AST value >3 times the upper limit of the standard value" associated with a symptom (for example, fatigue, nausea, vomiting, right abdominal pain upper, pyrexia, rash) or eosinophilia

treatment suspension criteria[47] for laboratory values on hepatic function parameters were additionally specified. On that day, phase III studies (MT-6548-J01 and MT-6548-J03) were ongoing in Japan, and all the clinical studies except for these 2 studies were completed.

In the Japanese phase III study (MT-6548-J01), no subjects met the clinical study discontinuation criteria or treatment suspension criteria for abnormal laboratory values on hepatic function parameters in the vadadustat group after these criteria had been additionally specified on February 27, 2019. In the vadadustat group, no large changes in hepatic function parameters occurred either. Adverse events related to hepatic dysfunction occurred in 6 of 151 subjects (4.0%) in the vadadustat group (hepatic function abnormal in 3 subjects; and hypoalbuminaemia, hepatic cirrhosis, drug-induced liver injury, and blood alkaline phosphatase (ALP) increased in 1 subject each; some subjects experienced multiple events) and in 4 of 153 subjects (2.6%) in the DA group (hepatic function abnormal in 2 subjects; and hepatic steatosis, liver disorder, and γ-glutamyltransferase (γ-GTP) increased in 1 subject each; some subjects experienced multiple events). Hepatic function abnormal observed in 1 subject in the vadadustat group was assessed as an adverse drug reaction but was non-serious and mild.

In the Japanese phase III study (MT-6548-J03), no subjects met the clinical study discontinuation criteria or treatment suspension criteria for abnormal laboratory values on hepatic function parameters in the vadadustat group after these criteria had been additionally specified on February 27, 2019. In the vadadustat group, no large changes in hepatic function parameters occurred either. Adverse events related to hepatic dysfunction occurred in 3 of 163 subjects (1.9%) in the vadadustat group (hypoalbuminaemia, hepatic function abnormal, and aspartate aminotransferase (AST) increased in 1 subject each) and 6 of 161 subjects (3.7%) in the DA group (hepatic function abnormal and gamma-GTP in 2 subjects each; and hypoalbuminaemia, blood ALP increased, and liver function test increased in 1 subject each; some subjects experienced multiple events). AST increased observed in 1 subject in the vadadustat group was assessed as an adverse drug reaction but was non-serious and mild.

In the pooled analysis in a total of 6 studies including Japanese phase II studies (CI-0021 and CI-0022) and Japanese phase III studies (MT-6548-J01 to MT-6548-J04), adverse events related to hepatic dysfunction were found in 12 of 481 subjects (2.5%) (hepatic function abnormal in 5 subjects; hypoalbuminaemia in 3 subjects; AST increased in 2 subjects; and hepatic cirrhosis, drug-induced liver injury, and blood ALP increased in 1 subject each; some subjects experienced multiple events), and adverse drug reactions were found in 4 of 481 subjects (0.8%) (hepatic function abnormal and AST increased in 2 subjects each). Of these 1 adverse drug reaction (hepatic function abnormal) was deemed to be serious but resolved after treatment discontinuation.

As described above, adverse drug reactions related to hepatic dysfunction occurred in the Japanese and foreign clinical studies, and the applicant considers it necessary to include caution statements about hepatic dysfunction in the package insert.

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[47] The following suspension criteria were specified:
- "The ALT or AST value >3 times the upper limit of the standard value" during the treatment period but without "the total bilirubin value >2 times the upper limit of the standard value"

PMDA confirmed that adverse events and adverse drug reactions related to hepatic dysfunction in the vadadustat group were comparable to those in the DA group in the Japanese phase III studies and that no clinically relevant difference was observed. In the Japanese and foreign clinical studies, however, serious adverse drug reactions related to hepatic dysfunction occurred, and thus PMDA considers it necessary to include caution statements about hepatic dysfunction in the package insert of vadadustat. In addition, hepatic functions should be periodically monitored, and if any abnormalities are observed, appropriate measures such as drug suspension and treatment discontinuation should be taken. Then, the applicant should continue collecting information about adverse events related to hepatic dysfunction through post-marketing surveillance, etc.

7.R.2.5.4 Retinal haemorrhage

The applicant's explanation on retinal haemorrhage:

HIF induces expression of vascular endothelial growth factor (VEGF) and thereby enhances angiogenesis (*Cardiovasc Res.* 2010;86:236-42). In addition, patients with renal anemia have underlying diabetes mellitus and hypertension and thus poses a high risk of retinal disorder. In clinical studies of vadadustat, the exclusion criteria were specified to exclude patients at a high risk of retinal haemorrhage, and fundoscopy (before, during, and after treatment with vadadustat) and VEGF assay were performed.

In the Japanese phase III study (MT-6548-J01), adverse events of retinal haemorrhage occurred in 2 of 151 subjects (1.3%) in the vadadustat group and 5 of 153 subjects (3.3%) in the DA group, and the adverse drug reactions occurred in 1 of 151 subjects (0.7%) in the vadadustat group and 0 of 153 subjects (0%) in the DA group. The incidences of the adverse events and adverse drug reactions in the vadadustat group were comparable to those in the DA group. The adverse drug reaction in 1 subject in the vadadustat group led to discontinuation of vadadustat but was mild and non-serious. Of the other adverse events related to retinal disorder, the incidence in the vadadustat group was comparable to that in the DA group, and none of the particular events in the vadadustat group presented a higher trend of the incidence.

In the Japanese phase III study (MT-6548-J03), adverse events of retinal haemorrhage occurred in 16 of 162 subjects (9.9%) in the vadadustat group and 10 of 161 subjects (6.2%) in the DA group, and no adverse drug reactions occurred in either group. Of the other adverse events related to retinal disorder, the incidence in the vadadustat group was comparable to that in the DA group, and none of the particular events in the vadadustat group presented a higher trend of the incidence.

In addition, in the pooled analysis in a total of 6 studies including Japanese phase II studies (CI-0021 and CI-0022) and Japanese phase III studies (MT-6548-J01 to MT-6548-J04), adverse events of retinal haemorrhage associated with vadadustat were found in 20 of 481 subjects (4.2%) and adverse drug reactions were found in 2 of 481 subjects (0.4%). Of the adverse drug reactions in 2 subjects, the reaction in 1 subject was in Study MT-6548-J01 as described above, and the other reaction in 1 subject was mild and non-serious without discontinuation or suspension of vadadustat. In any of the subjects in whom retinal haemorrhage occurred, no large changes in VEGF level were observed.

Based on the above, vadadustat is considered less likely to raise a problem with retinal haemorrhage than DA when used in clinical settings.

PMDA has confirmed that vadadustat does not tend to increase the risk of retinal haemorrhage clearly compared with DA at present. In clinical studies, however, adverse events of retinal haemorrhage occurred, and vadadustat may enhance neovascularisation through activation of the HIF pathway. PMDA therefore considers that the package insert of vadadustat should include caution statements to the effect that special attention should be paid to patients at a high risk of retinal haemorrhage (patients complicated by proliferative diabetic retinopathy, macular oedema, exudative age-related macular degeneration, and retinal vein occlusion) and information about incidence of retinal haemorrhage should be continuously collected through post-marketing surveillances.

7.R.2.5.5 Hypertension

The applicant's explanation on hypertension:
Akebia Therapeutics, Inc., a foreign development company, extracted serious adverse events related to hypertension occurring between August 19, 2017 and August 18, 2018 from the safety database in Japanese and foreign clinical studies. In subjects receiving vadadustat, 44 serious adverse events were found, and of these 1 event was assessed as an adverse drug reaction.

In the Japanese phase III study (MT-6548-J01), adverse events related to hypertension occurred in 4 of 151 subjects (2.6%) in the vadadustat group (hypertension and blood pressure increased in 2 subjects each) and 12 of 153 subjects (7.8%) in the DA group (hypertension in 11 subjects and blood pressure increased in 1 subject), and the adverse drug reactions occurred in 1 of 151 subjects (0.7%) in the vadadustat group (hypertension) and 2 of 153 subjects (1.3%) in the DA group (hypertension in 2 subjects). Incidences of the adverse events and adverse drug reactions in the vadadustat group were comparable to those in the DA group.

In the Japanese phase III study (MT-6548-J03), adverse events related to hypertension occurred in 10 of 162 subjects (6.2%) in the vadadustat group (hypertension in 6 subjects, blood pressure increased in 3 subjects, and procedural hypertension in 2 subjects; some subjects experienced multiple events) and 12 of 161 subjects (7.5%) in the DA group (hypertension and blood pressure increased in 6 subjects each), and the events in 2 subjects in the vadadustat group (hypertension) were assessed as adverse drug reactions. Incidences of the adverse events and adverse drug reactions in the vadadustat group were comparable to those in the DA group. The adverse drug reactions in 2 subjects in the vadadustat group were mild and non-serious.

In addition, in the pooled analysis in a total of 6 studies including Japanese phase II studies (CI-0021 and CI-0022) and Japanese phase III studies (MT-6548-J01 to MT-6548-J04), adverse events related to hypertension associated with vadadustat were found in 21 of 481 subjects (4.4%) and adverse drug reactions were found in 7 of 481 subjects (1.5%).

Based on the above, vadadustat is considered unlikely to raise a problem with hypertension when used in clinical settings.

PMDA confirmed that adverse events and adverse drug reactions related to hypertension in the vadadustat group were comparable to those in the DA group in the Japanese phase III studies and that no any clinically relevant difference was observed. The package inserts of ESAs, however, include caution statements to the effect that blood pressure increased may occur, and thus the drug should be administered by paying attention to changes in blood pressure. PMDA therefore considers that the package insert of vadadustat should also include caution statements as done for ESAs, and information about incidence of events related to hypertension should be continuously collected through post-marketing surveillances.

7.R.2.5.6 Malignant tumors

The applicant's explanation on malignant tumors:

HIF targets genes coding proteins involved in neovascularisation, energy metabolism, cell proliferation, vascular remodeling, and immune response (*J Appl Physiol.* 2000;88:1474-80 and *Nat Rev Nephrol.* 2016;12:157-68). At present, it remains unclear whether HIF-PH inhibitors' activation on HIF pathway stimulates development of malignant tumors.

In the Japanese phase III study (MT-6548-J01), malignant tumors were observed in 2 of 151 subjects (1.3%) in the vadadustat group (colon adenoma and oral papilloma in 1 subject each) and 6 of 153 subjects (3.9%) in the DA group (basal cell carcinoma, gastric cancer, keratoacanthoma, renal cancer, seborrhoeic keratosis, skin papilloma, renal cancer metastatic, and kidney angiomyolipoma in 1 subject each; some subjects experienced multiple events). A causal relationship to the study drug was ruled out for any finding.

In the Japanese phase III study (MT-6548-J03), malignant tumors were found in 7 of 162 subjects (4.3%) in the vadadustat group (breast cancer, gastric cancer, seborrhoeic keratosis, cholesteatoma, laryngeal papilloma, squamous cell carcinoma of skin, and uterine leiomyoma in 1 subject each) and 9 of 161 subjects (5.6%) in the DA group (breast cancer, gastric cancer, seborrhoeic keratosis, pyogenic granuloma, thymoma, prostate cancer, pancreatic neoplasm, urethral neoplasm, renal cell carcinoma, and gastrointestinal submucosal tumour in 1 subject each; some subjects experienced multiple events). A causal relationship to the study drug was ruled out for any finding.

In addition, in the pooled analysis in a total of 6 studies including Japanese phase II studies (CI-0021 and CI-0022) and Japanese phase III studies (MT-6548-J01 to MT-6548-J04), adverse events related to malignant tumors associated with vadadustat were found in 10 of 481 subjects (2.1%), and a causal relationship to vadadustat was ruled out for any event.

Based on the above, vadadustat is considered unlikely to raise a problem with malignant tumors when used in clinical settings.

PMDA has confirmed that incidences of malignant tumors in the vadadustat group do not raise any particular problem. In clinical studies, however, patients with coexisting malignant tumors were excluded, and it cannot be excluded that vadadustat may promote tumor growth by enhancing

neovascularization. PMDA therefore considers that the package insert of vadadustat should include caution statements, and information about incidence of malignant tumors should be continuously collected through post-marketing surveillances.

7.R.3 Clinical positioning of vadadustat

The applicant's explanation on clinical positioning of vadadustat:

At present, ESAs (intravenous or subcutaneous preparations) are mainly used in treatment of renal anemia in Japan. Vadadustat is an oral preparation with a mechanism of action different from that of ESAs. Based on results from the Japanese phase III studies (MT-6548-J01 to MT-6548-J04), the efficacy of vadadustat in the treatment of renal anemia was demonstrated [see Section 7.R.1] and considered to have acceptable safety [see Section 7.R.2]. In addition, while ESAs are intravenous or subcutaneous preparations, vadadustat is an oral preparation of which administration is expected to be at a low risk of infection and less invasive. Especially, it can reduce physical burden on patients with non-dialysis dependent CKD and patients on PD. In view of the above advantages, vadadustat is considered to offer a new option in treatment of renal anemia. Vadadustat is not planned to be concomitantly used with an ESA or the other HIF-PH inhibitor.

The Japanese phase III studies (MT-6548-J01 to MT-6548-J04) demonstrated the efficacy of vadadustat [see Section 7.R.1] and indicated the acceptable safety [see Section 7.R.2]. PMDA has concluded that vadadustat is shown to be useful in treating renal anemia. Vadadustat is an oral preparation with a mechanism of action different from that of ESAs, and it is considered to offer a new option in treatment of renal anemia.

7.R.4 Indication

The applicant's explanation on the indication of vadadustat:

In the Japanese phase III studies (MT-6548-J01 to MT-6548-J04) in patients on HD, patients with non-dialysis dependent CKD, and patients on PD, vadadustat was shown to maintain the blood condition after switching from an ESA and alleviate anemia in patients on HD and patients with non-dialysis dependent CKD and suggested to be effective in treating anemia in patients on PD [see Section 7.R.1]. In addition, in the Japanese phase III studies (MT-6548-J01 to MT-6548-J04), the safety was acceptable [see Section 7.R.2]. The applicant considers it appropriate to propose "renal anemia" as the indication of vadadustat.

In the Japanese phase III studies (MT-6548-J01 to MT-6548-J04) in patients on HD, patients with non-dialysis dependent CKD, and patients on PD, vadadustat was shown to be effective in treating renal anemia in both patients being treated with an ESA and ESA-naïve patients [see Section 7.R.1], and the safety was acceptable [see Section 7.R.2]. PMDA has concluded that the indication of vadadustat may be established as "renal anemia."

7.R.5 Dosage and administration

7.R.5.1 Dosage regimens of vadadustat in patients being treated with an ESA

7.R.5.1.1 Dose of vadadustat in place of an ESA in patients on HD being treated with an ESA for renal anemia and dose adjustment method

The applicant's explanation on dose of vadadustat in place of an ESA in patients on HD being treated with an ESA for renal anemia and dose adjustment method:

(a) Dose of vadadustat in place of an ESA

In the foreign phase II study in patients on HD being treated with an ESA for renal anemia (CI-0011),[48)] no large changes in the Hb value were observed after switching from an ESA to vadadustat at either 300 or 450 mg. In the Japanese phase III study (MT-6548-J03) in patients on HD being treated with an ESA for renal anemia, the dose of vadadustat in place of an ESA was specified at 300 mg because a rapid increase in the Hb value is suggested to entail a risk of adverse events in the cardiovascular system.

Figure 1 shows changes in the Hb value and Table 58 shows percentage of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 52, in the Japanese phase III study (MT-6548-J03). The Hb value in the vadadustat group tended to decrease until Week 16 but did not rapidly decrease, and no subjects required blood transfusion.

Based on the above, it was considered appropriate to specify 300 mg as the dose of vadadustat in place of an ESA in patients on HD being treated with an ESA for renal anemia. The response to vadadustat, on the other hand, is presumed to vary depending on many and various factors. It was therefore considered difficult to establish the post-switch dose appropriate for any patient uniformly. In addition, the Japanese phase II studies (CI-0021 and CI-0022) indicated that a risk of the rapid increase in the Hb value was acceptable even at the post-switch dose of 600 mg. Based on the above, the applicant considered that the post-switch dose should be 300 mg in principle but be adjusted as appropriate according to the course and severity of anemia before the administration of vadadustat as well as the dose of the prior ESA.

(b) Dose adjustment method of vadadustat

Vadadustat is a drug for which the dose should be adjusted as appropriate to maintain the Hb value within the target range (10.0-12.0 g/dL), and the dose adjustment method in the Japanese phase III study (MT-6548-J03) was specified as shown in Table 51, and the dose of vadadustat was adjusted within the range from 150 to 600 mg.

Figure 1 shows changes in the Hb value and Table 58 shows percentage of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 52, in the Japanese phase III study (MT-6548-J03). The Hb value was almost maintained within the target range (10.0-12.0 g/dL) between Weeks 20 and 52 by adjusting the dose of vadadustat within the range from 150 to 600 mg in accordance with the dose adjustment method based on the Hb value.

[48)] In non-Japanese patients on HD being treated with an ESA, vadadustat was started at either 300 mg or 450 mg (post-switch dose) in place of an ESA, and then it was orally administered once daily within the range from 150 to 600 mg according to the Hb value for 16 weeks.

Figure 6 shows changes in dose of vadadustat, and the doses used at each timepoint were widely distributed in the range from 150 to 600 mg.

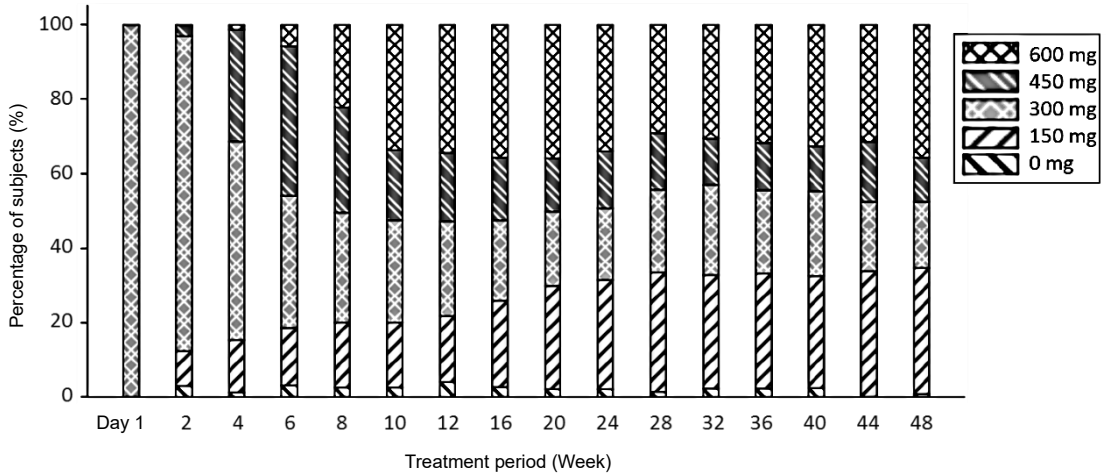

Figure 6. Changes in dose of vadadustat (FAS)

Throughout the treatment period, the Hb value did not increase at >0.5 g/dL/week in any subject in either vadadustat group or DA group. In addition, the Hb value at the upper limit of the target range (12.0 g/dL) or higher was found in 41 of 162 subjects (25.3%) in the vadadustat group and 48 of 161 subjects (29.8%) in the DA group. Furthermore, the value ≥13.0 g/dL was found only in 6 of 162 subjects (3.7%) in the vadadustat group and 5 of 161 subjects (3.5%) in the DA group, and no large differences were observed between the groups.

Based on the above, as the dose adjustment method of vadadustat in patients on HD being treated with an ESA for renal anemia, it was considered appropriate to adjust the dose of vadadustat within the range from 150 to 600 mg as specified in Table 51 for the Japanese phase III study (MT-6548-J03).

PMDA's view:
In the Japanese phase III study (MT-6548-J03), the Hb value decreased after switching from an ESA to vadadustat, but by adjusting the dose of vadadustat according to the Hb value, the value was almost maintained within the target range at Week 20 and thereafter, and the acceptable safety was confirmed. Vadadustat in place of an ESA should be administered in accordance with the dosage regimen in the Japanese phase III study (MT-6548-J03).

Based on results from the Japanese phase II studies (CI-0021 and CI-0022), the applicant claimed that vadadustat in place of an ESA might be started at 600 mg. In the Japanese phase III study (MT-6548-J03), however, the applicant specified that vadadustat in place of an ESA should be started only at 300 mg based on results from the foreign phase II study (CI-0011) which evaluated the safety of vadadustat used in place of an ESA in patients on HD being treated with an ESA, because the concerned dose would protect patients from a rapid increase in the Hb value irrespective of their condition, allowing the drug switch while keeping the Hb value stable. PMDA therefore cannot accept the applicant's claim that vadadustat in place of an ESA may be started at up to 600 mg, which was not investigated as the post-switch dose in the Japanese phase III study (MT-6548-J03). Because the

efficacy and safety were demonstrated in the Japanese phase III study (MT-6548-J03) in which vadadustat was started at 300 mg, and then the dose was adjusted within the range from 150 to 600 mg by monitoring the Hb value, vadadustat (used in place of an ESA) should be started at 300 mg.

7.R.5.1.2 Dose of vadadustat in place of an ESA in patients with non-dialysis dependent CKD being treated with an ESA for renal anemia and dose adjustment method

The applicant's explanation on dose of vadadustat in place of an ESA in patients with non-dialysis dependent CKD being treated with an ESA for renal anemia and dose adjustment method:

(a) Dose of vadadustat in place of an ESA

In the Japanese phase III study (MT-6548-J01), the dose of vadadustat in place of an ESA was specified at 300 mg based on results from the foreign phase II study (CI-0007)[49] in patients with non-dialysis dependent CKD being treated with an ESA for renal anemia, in which after vadadustat was started at 450 mg in place of an ESA, no large changes in the Hb value were observed, and from the foreign phase II study (CI-0011) in patients on HD being treated with an ESA for renal anemia [see Section 7.R.5.1.1].

Figure 3 shows changes in the Hb value and Table 62 shows percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 52, in the Japanese phase III study (MT-6548-J01) in patients with non-dialysis dependent CKD being treated with an ESA for renal anemia. Although the Hb value in the vadadustat group was below the target value at baseline, the value was increased after switching from an ESA, and then reached within the target range (11.0-13.0 g/dL). No rapid increases in the Hb value were observed.

Based on the above, it was considered appropriate to specify 300 mg as the dose of vadadustat in place of an ESA in patients with non-dialysis dependent CKD being treated with an ESA for renal anemia. The response to vadadustat, on the other hand, is presumed to vary depending on many and various factors. It was therefore considered difficult to establish the post-switch initial dose appropriate for any patient uniformly. In addition, the Japanese phase II studies (CI-0021 and CI-0022) indicated that a risk of the rapid increase in the Hb value was acceptable even at the post-switch dose of 600 mg. Based on the above, the applicant considered that the post-switch dose should be 300 mg in principle but be adjusted as appropriate according to the course and severity of anemia before the administration of MT-6548 as well as the dose of the prior ESA.

(b) Dose adjustment method of vadadustat

Vadadustat is a drug for which the dose should be adjusted as appropriate to maintain the Hb value within the target range (11.0-13.0 g/dL), the dose adjustment method in the Japanese phase III study (MT-6548-J01) was specified as shown in Table 42, and the dose of vadadustat was adjusted within the range from 150 to 600 mg.[50]

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[49] In non-Japanese patients with non-dialysis dependent CKD being treated with an ESA for renal anemia, vadadustat was started at 450 mg (post-switch dose) in place of an ESA, and then it was orally administered once daily within the range from 150 to 600 mg according to the Hb value for 20 weeks.

[50] In December 2017 after start of this study, the maximum dose of vadadustat was changed from 750 mg to 600 mg, taking into account of the data in the non-clinical toxicity studies [see Section 7.2.1].

Figure 3 shows changes in the Hb value and Table 62 shows percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 52 in the patients with non-dialysis dependent CKD being treated with an ESA for renal anemia, in the Japanese phase III study (MT-6548-J01). The Hb value was almost maintained within the target range (11.0-13.0 g/dL) at Week 8 and thereafter by adjusting the dose of vadadustat within the range from 150 to 600 mg in accordance with the dose adjustment method based on the Hb value.

Figure 7 shows changes in dose of vadadustat, and the doses used at each timepoint were widely distributed in the range from 150 to 600 mg.

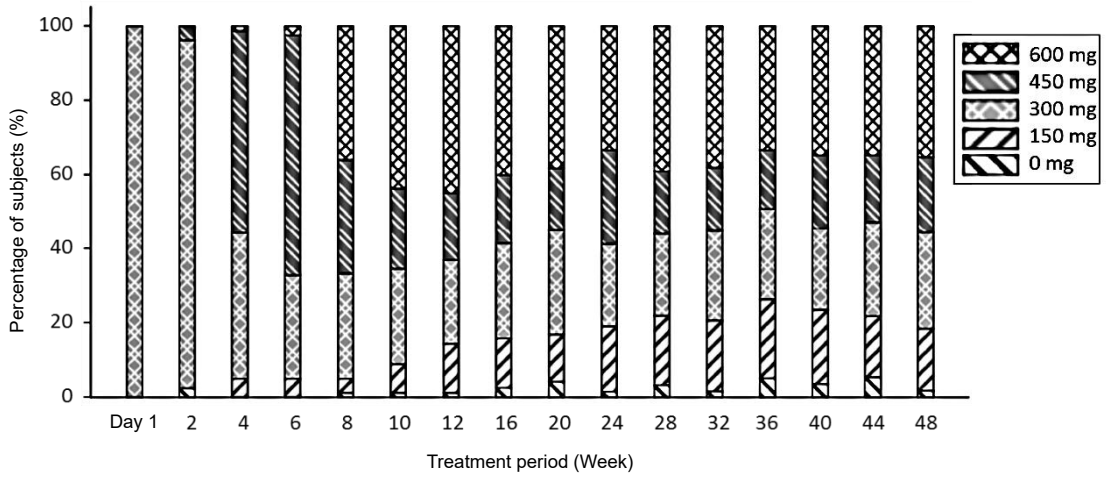

Figure 7. Changes in dose of vadadustat (FAS)

Throughout the treatment period, the Hb value did not increase at >0.5 g/dL/week in any subject in either vadadustat group or DA group. In addition, the Hb value at the upper limit of the target range (13.0 g/dL) or higher was found in 13 of 80 subjects (16.3%) in the vadadustat group and 29 of 82 subjects (35.4%) in the DA group. Furthermore, the value ≥14.0 g/dL was found only in 1 of 80 subjects (1.3%) in the vadadustat group and 6 of 82 subjects (7.3%) in the DA group.

Based on the above, as the dose adjustment method of vadadustat in patients with non-dialysis dependent CKD being treated with an ESA for renal anemia, it was considered appropriate to adjust the dose of vadadustat within the range from 150 to 600 mg as specified in Table 42 for the Japanese phase III study (MT-6548-J01).

PMDA's view:
In the Japanese phase III study (MT-6548-J01), the Hb value was almost maintained within the target range (11.0-13.0 g/dL) at Week 8 and thereafter by adjusting the dose of vadadustat according to the Hb value, and the acceptable safety was confirmed. Vadadustat in place of an ESA should be administered in accordance with the dosage regimen in the Japanese phase III study (MT-6548-J01).

PMDA, however, cannot accept the applicant's claim that vadadustat in place of an ESA may be started at up to 600 mg, which was not investigated in the Japanese phase III study (MT-6548-J01), as with the dose in patients on HD being treated with an ESA for renal anemia [see Section 7.R.5.1.1].

Because the efficacy and safety were demonstrated in the Japanese phase III study (MT-6548-J01) in which vadadustat was started at 300 mg, and then the dose was adjusted within the range from 150 to 600 mg by monitoring the Hb value, vadadustat (used in place of an ESA) should be started at 300 mg.

7.R.5.1.3 Dose of vadadustat in place of an ESA in patients on PD being treated with an ESA for renal anemia and dose adjustment method

The applicant's explanation on dose of vadadustat in place of an ESA in patients on PD being treated with an ESA for renal anemia and dose adjustment method:

(a) Dose of vadadustat in place of an ESA

In the Japanese phase III study (MT-6548-J02), the dose of vadadustat in place of an ESA in patients on PD being treated with an ESA for renal anemia was specified at 300 mg as with that for renal anemia being treated with an ESA in Japanese phase III study (MT-6548-J01) in patients with non-dialysis dependent CKD.

Figure 5 shows changes in the Hb value and Table 64 shows percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 24, in the Japanese phase III study (MT-6548-J02). After switching from an ESA to vadadustat, the Hb value tended to decrease until Week 10, but only 1 subject required rescue treatment with an ESA before Week 24.

Based on the above, it was considered appropriate to specify 300 mg as the dose of vadadustat in place of an ESA in patients on PD being treated with an ESA for renal anemia. The response to vadadustat, on the other hand, is presumed to vary depending on many and various factors. It was therefore considered difficult to establish the post-switch initial dose appropriate for any patient uniformly. In addition, the Japanese phase II studies (CI-0021 and CI-0022) indicated that a risk of the rapid increase in the Hb value was acceptable even at the post-switch dose of 600 mg. Based on the above, the applicant considered that the post-switch dose should be 300 mg in principle but be adjusted as appropriate according to the course and severity of anemia before the administration of MT-6548 as well as the dose of the prior ESA.

(b) Dose adjustment method of vadadustat

Vadadustat is a drug for which the dose should be adjusted as appropriate to maintain the Hb value within the target range (11.0-13.0 g/dL), the dose adjustment method in patients on PD being treated with an ESA for renal anemia in the Japanese phase III study (MT-6548-J02) was specified as shown in Table 47, and the dose of vadadustat was adjusted within the range from 150 to 600 mg.

Figure 5 shows changes in the Hb value and Table 64 shows percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 24 in the patients on PD being treated with an ESA for renal anemia, in the Japanese phase III study (MT-6548-J02). The Hb value was almost maintained within the target range (11.0-13.0 g/dL) at Week 12 and thereafter by adjusting the dose of vadadustat within the range from 150 to 600 mg in accordance with the dose adjustment method based on the Hb value.

Figure 8 shows changes in dose of vadadustat, and the doses used at each timepoint were widely distributed in the range from 150 to 600 mg.

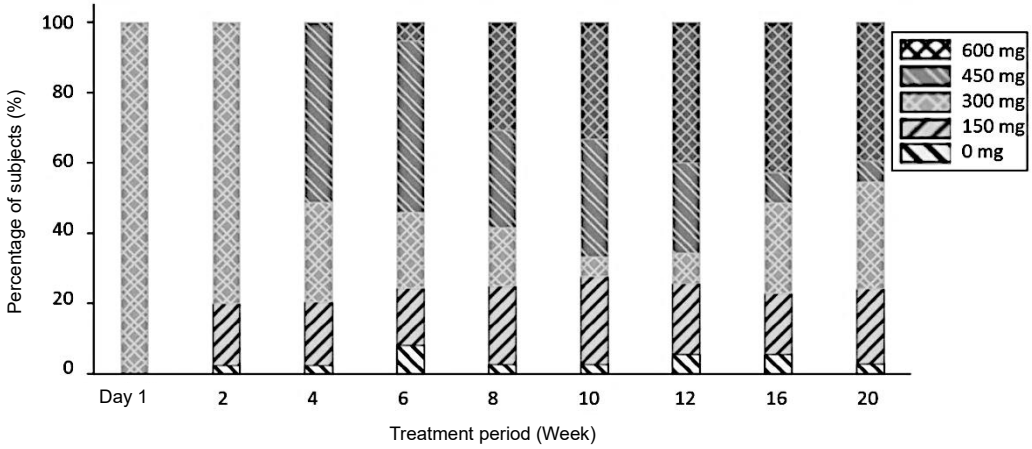

Figure 8. Changes in dose of vadadustat (FAS)

Throughout the treatment period, the Hb value increased at >0.5 g/dL/week only in 1 of 39 subjects (2.6%). In addition, the Hb value at the upper limit of the target range (13.0 g/dL) or higher was found in 12 of 40 subjects (30.0%), and furthermore the value ≥14.0 g/dL was found only in 2 of 40 subjects (5.0%).

Based on the above, as the dose adjustment method of vadadustat in patients on PD being treated with an ESA for renal anemia, it was considered appropriate to adjust the dose of vadadustat within the range from 150 to 600 mg as specified in Table 47 for the Japanese phase III study (MT-6548-J02).

PMDA's view:
In the Japanese phase III study (MT-6548-J02), the Hb value decreased after switching from an ESA to vadadustat in patients on PD being treated with an ESA for renal anemia, but by adjusting the dose of vadadustat according to the Hb value, the value was almost maintained within the target range (11.0-13.0 g/dL) at Week 8 and thereafter, and the acceptable safety was confirmed. Vadadustat in place of an ESA should be administered in accordance with the dosage regimen in the Japanese phase III study (MT-6548-J02).

PMDA, however, cannot accept the applicant's claim that vadadustat in place of an ESA may be started at up to 600 mg, which was not investigated as the post-switch dose in the Japanese phase III study (MT-6548-J02), as with the dose in patients on HD being treated with an ESA for renal anemia [see Section 7.R.5.1.1]. Because the efficacy and safety were demonstrated in the Japanese phase III study (MT-6548-J02) in which vadadustat was started at 300 mg, and then the dose was adjusted within the range from 150 to 600 mg by monitoring the Hb value, vadadustat (used in place of an ESA) should be started at 300 mg.

7.R.5.2 Dosage regimens of vadadustat in ESA-naïve patients

7.R.5.2.1 Initial dose of vadadustat in patients on HD with ESA-naïve renal anemia and dose adjustment method

The applicant's explanation on initial dose of vadadustat in patients on HD with ESA-naïve renal anemia and dose adjustment method:

(a) Initial dose of vadadustat

In the Japanese phase II study (CI-0022) in patients on HD with ESA-naïve renal anemia, the increasing rate of the Hb value until Week 4 (mean) was −0.24 g/dL/week in the placebo group, 0.02 g/dL/week in the vadadustat 150 mg group, 0.12 g/dL/week in the vadadustat 300 mg group, and 0.13 g/dL/week in the vadadustat 600 mg group, and the Hb value did not increase at >0.5 g/dL/week in any subject in any group.

In the Japanese phase III study (MT-6548-J04) in patients on HD with ESA-naïve renal anemia, the initial dose of vadadustat was specified at 300 mg, at which administration was expected to increase the Hb value moderately and protect patients from a rapid increase in the Hb value because the rapid increase in the Hb value is suggested to entail a risk of adverse events in the cardiovascular system, and results from the Japanese phase II study (CI-0022) supported such an expectation.

Figure 2 shows changes in the Hb value and Table 60 shows percentage of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 24, in the Japanese phase III study (MT-6548-J04). After the administration of vadadustat, the Hb value increased and reached within the target range at Week 8.

The increasing rate of the Hb value until Week 4 (mean ± SD) was 0.05 ± 0.24 g/dL/week, and the rate >0.5 g/dL/week was found in 1 subject between Weeks 0 and 4 without any rapid increase in the Hb value.

Based on the above, it was considered appropriate to specify 300 mg as the initial dose of vadadustat in patients on HD with ESA-naïve renal anemia. The response to vadadustat, on the other hand, is presumed to vary depending on many and various factors, and the increasing rate of the Hb value is also presumed to differ depending on course and severity of anemia in the patient. The applicant, therefore, considered that the initial dose should be specified at 300 mg in principle, and the subsequent dose should be adjusted according to the course and severity of anemia as appropriate.

(b) Dose adjustment method of vadadustat

Vadadustat is a drug for which the dose should be adjusted as appropriate to maintain the Hb value within the target range (10.0-12.0 g/dL), the dose adjustment method in the Japanese phase III study (MT-6548-J04) was specified as shown in Table 56, and the dose of vadadustat was adjusted within the range from 150 to 600 mg.

Figure 2 shows changes in the Hb value and Table 60 shows percentage of subjects with an Hb level within the target range (10.0-12.0 g/dL) at each timepoint until Week 24, in the Japanese phase III study (MT-6548-J04). The Hb value was almost maintained within the target range (10.0-12.0 g/dL)

between Weeks 8 and 24 by adjusting the dose of vadadustat within the range from 150 to 600 mg in accordance with the dose adjustment method based on the Hb value.

Figure 9 shows changes in dose of vadadustat, and the doses used at each timepoint were widely distributed in the range from 150 to 600 mg.

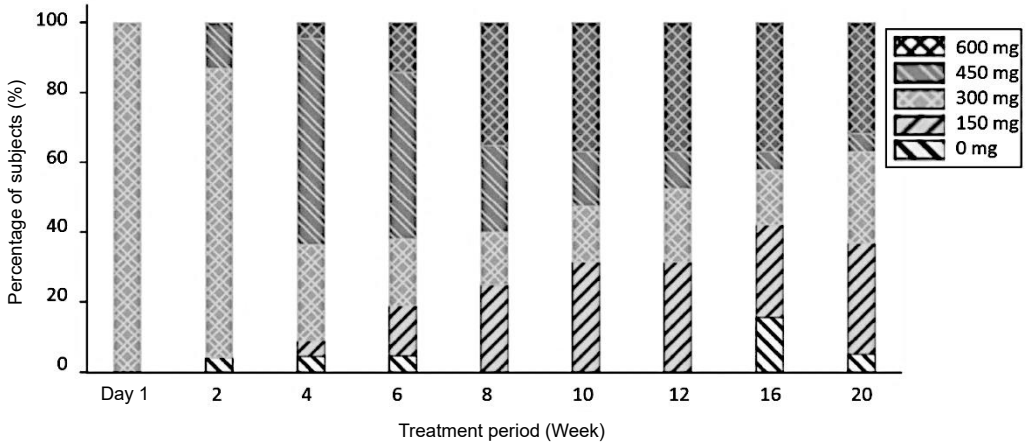

Figure 9. Changes in dose of vadadustat (FAS)

Throughout the treatment period, the Hb value increased at >0.5 g/dL/week only in 1 of 23 subjects (4.3%). In addition, the Hb value at the upper limit of the target range (12.0 g/dL) or higher was found in 7 of 24 subjects (29.2%), and furthermore the value ≥13.0 g/dL was found only in 1 of 24 subjects (4.2%). Accordingly, a risk of rapid and excessive increases in the Hb value was considered low in patients receiving vadadustat.

Based on the above, as the dose adjustment method of vadadustat in patients on HD with ESA-naïve renal anemia, it was considered appropriate to adjust the dose of vadadustat within the range from 150 to 600 mg as specified in Table 56 for the Japanese phase III study (MT-6548-J04).

PMDA's view:
In the Japanese phase III study (MT-6548-J04), the Hb value increased in response to vadadustat and then was almost maintained within the target range (10.0-12.0 g/dL) by adjusting the dose of vadadustat according to the Hb value, and the acceptable safety was confirmed. Vadadustat should be administered to ESA-naïve patients in accordance with the dosage regimen in the Japanese phase III study (MT-6548-J04).

PMDA, however, cannot accept the applicant's claim that vadadustat may be started at up to the dose that was not investigated as the post-switch dose in the Japanese phase III study (MT-6548-J04). Accordingly, because the efficacy and safety were demonstrated in the Japanese phase III study (MT-6548-J04) in which vadadustat was started at 300 mg, and then the dose was adjusted within the range from 150 to 600 mg by monitoring the Hb value, vadadustat should be started at 300 mg.

7.R.5.2.2 Initial dose of vadadustat in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia and dose adjustment method

The applicant's explanation on initial dose of vadadustat in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia and dose adjustment method:

(a) Initial dose of vadadustat

In the Japanese phase II study (CI-0021) in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia, the increasing rate of the Hb value until Week 4 (mean) was −0.13 g/dL/week in the placebo group, 0.07 g/dL/week in the vadadustat 150 mg group, 0.24 g/dL/week in the vadadustat 300 mg group, and 0.38 g/dL/week in the vadadustat 600 mg group, and the increasing rate of the Hb value calculated from values at 2 timepoints, baseline and Week 4, was found >0.5 g/dL/week in 16.7% of the subjects in the vadadustat 300 mg group and 30.8% of the subjects in the 600 mg group.

In the Japanese phase III study (MT-6548-J01), the initial dose of vadadustat in patients with non-dialysis dependent CKD and ESA-naïve renal anemia was specified at 300 mg, at which administration was expected to increase the Hb value moderately and protect patients from a rapid increase in the Hb value because the rapid increase in the Hb value is suggested to entail a risk of adverse events in the cardiovascular system, and results from the Japanese phase II study (CI-0021) supported such an expectation.

Figure 4 shows changes in the Hb value and Table 63 shows percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 52, in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia in the Japanese phase III study (MT-6548-J01). After the administration of vadadustat, the Hb value increased and reached within the target range at Week 8.

The increasing rate of the Hb value until Week 4 (mean ± SE) was 0.14 ± 0.20 g/dL/week in the vadadustat group and 0.21 ± 0.16 g/dL/week in the DA group. The rate of >0.5 g/dL/week was found in 4 of 69 subjects (5.8%) in the vadadustat group and 1 of 71 subjects (1.4%) in the DA group between Weeks 0 and 4 and in 0 of 68 subjects (0%) in the vadadustat group and 1 of 70 subjects (1.4%) in the DA group between Weeks 4 and 8 without any rapid increase in the Hb value. No large differences were observed between the groups.

Based on the above, it was considered appropriate to specify 300 mg as the initial dose of vadadustat in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia. The response to MT-6548, on the other hand, is presumed to vary depending on many and various factors, and the increasing rate of the Hb value is also presumed to differ depending on course and severity of anemia in the patient. The applicant, therefore, considered that the initial dose should be specified at 300 mg in principle, and the subsequent dose should be adjusted according to the course and severity of anemia as appropriate.

(b) Dose adjustment method of vadadustat

Vadadustat is a drug for which the dose should be adjusted as appropriate to maintain the Hb value within the target range (11.0-13.0 g/dL), the dose adjustment method in the Japanese phase III study (MT-6548-J01) was specified as shown in Table 42, and the dose of vadadustat was adjusted within the range from 150 to 600 mg.[51)]

Figure 4 shows changes in the Hb value and Table 63 shows percentage of subjects with an Hb level within the target range (11.0-13.0 g/dL) at each timepoint until Week 52, in the patients with non-dialysis dependent CKD who had ESA-naïve renal anemia in the Japanese phase III study (MT-6548-J01). The Hb value was almost maintained within the target range (11.0-13.0 g/dL) between Weeks 8 and 24 by adjusting the dose of vadadustat within the range from 150 to 600 mg in accordance with the dose adjustment method based on the Hb value.

Figure 10 shows changes in dose of vadadustat, and the doses used at each timepoint were widely distributed in the range from 150 to 600 mg.

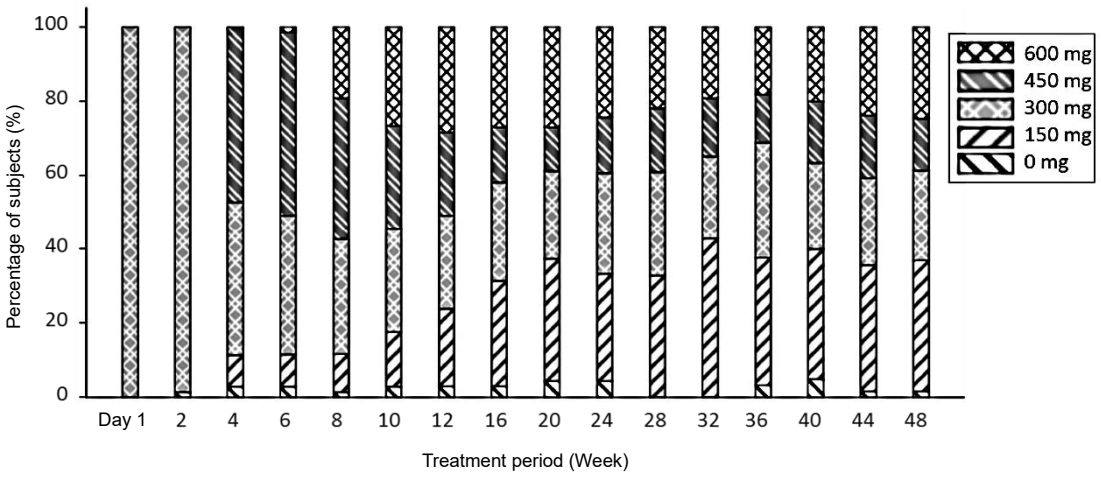

Figure 10. Changes in dose of vadadustat (FAS)

Throughout the treatment period, the Hb value increased at >0.5 g/dL/week only in 4 of 69 subjects (5.8%) in the vadadustat group and 2 of 71 subjects (2.8%) in the DA group. In addition, the Hb value at the upper limit of the target range (13.0 g/dL) or higher was found in 34 of 71 subjects (47.9%) in the vadadustat group and 46 of 71 subjects (64.8%) in the DA group. Furthermore, the value ≥14.0 g/dL was found only in 3 of 71 subjects (4.2%) in the vadadustat group and 7 of 71 subjects (9.9%) in the DA group, and no large differences were observed between the groups. Accordingly, a risk of rapid and excessive increases in the Hb value was considered low in patients receiving vadadustat.

Based on the above, as the dose adjustment method of vadadustat in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia, it was considered appropriate to adjust the dose of

[51)] In December 2017 after start of this study, the dose range of vadadustat from 150 to 750 mg was changed taking into account of the data in the non-clinical toxicity studies [see Section 7.2.1].

vadadustat within the range from 150 to 600 mg as specified in Table 42 for the Japanese phase III study (MT-6548-J01).

PMDA's view:
In the Japanese phase III study (MT-6548-J01), the Hb value in patients with non-dialysis dependent CKD who had ESA-naïve renal anemia increased in response to vadadustat and then was almost maintained within the target range (11.0-13.0 g/dL) by adjusting the dose of vadadustat according to the Hb value, and the acceptable safety was confirmed. Vadadustat should be administered to ESA-naïve patients in accordance with the dosage regimen in the Japanese phase III study (MT-6548-J01).

PMDA, however, cannot accept the applicant's claim that vadadustat may be started at up to the dose that was not investigated as the post-switch dose in the Japanese phase III study (MT-6548-J01). Accordingly, because the efficacy and safety were demonstrated in the Japanese phase III study (MT-6548-J01) in which vadadustat was started at 300 mg, and then the dose was adjusted within the range from 150 to 600 mg by monitoring the Hb value, vadadustat should be started at 300 mg.

7.R.5.2.3 Initial dose of vadadustat in patients on PD with ESA-naïve renal anemia and dose adjustment method

The applicant's explanation on initial dose of vadadustat in patients on PD with ESA-naïve renal anemia and dose adjustment method:
(a) Initial dose of vadadustat
In the Japanese phase III study (MT-6548-J02), the initial dose of vadadustat in patients on PD with ESA-naïve renal anemia was specified at 300 mg as with that for ESA-naïve renal anemia in Japanese phase III study (MT-6548-J01) in patients with non-dialysis dependent CKD.

The Japanese phase III study (MT-6548-J02) included only 2 ESA-naïve patients, and thus the limited sample size should be noted, but the Hb value tended to increase in response to vadadustat.

Based on the above, it was considered appropriate to specify 300 mg as the initial dose of vadadustat in patients on PD with ESA-naïve renal anemia. The response to MT-6548, on the other hand, is presumed to vary depending on many and various factors, and the increasing rate of the Hb value is also presumed to differ depending on the course and severity of anemia in the patient. The applicant, therefore, considered that the initial dose should be specified at 300 mg in principle, and the subsequent dose should be adjusted according to the course and severity of anemia as appropriate.

(b) Dose adjustment method of vadadustat
Vadadustat is a drug for which the dose should be adjusted as appropriate to maintain the Hb value within the target range (11.0-13.0 g/dL), the dose adjustment method in patients on PD with ESA-naïve renal anemia in the Japanese phase III study (MT-6548-J02) was specified as shown in Table 47, and the dose of vadadustat was adjusted within the range from 150 to 600 mg.

The Japanese phase III study (MT-6548-J02) included only 2 ESA-naïve patients, and thus interpretation of the results has limitations due to the limited sample size. But the Hb value would be maintained within the target range (11.0-13.0 g/dL) by adjusting the dose as done in patients on PD being treated with an ESA for renal anemia [see Section 7.R.5.1.3].

Accordingly, as the dose adjustment method of vadadustat in patients on PD with ESA-naïve renal anemia, it was considered appropriate to adjust the dose of vadadustat within the range from 150 to 600 mg as specified in Table 47 for the Japanese phase III study (MT-6548-J02).

PMDA's view:
Although in the Japanese phase III study (MT-6548-J02), the sample size of patients on PD with ESA-naïve renal anemia was limited, the dosage regimen of vadadustat in ESA-naïve patients should be specified based on that in the Japanese phase III study (MT-6548-J01) also referring to results in patients on PD being treated with an ESA for renal anemia.

PMDA, however, cannot accept the applicant's claim that vadadustat may be started at up to the dose that was not investigated as the post-switch dose in the Japanese phase III study (MT-6548-J02). Accordingly, because the efficacy and safety were demonstrated in the Japanese phase III study (MT-6548-J02) in which vadadustat was started at 300 mg, and then the dose was adjusted within the range from 150 to 600 mg by monitoring the Hb value, vadadustat should be started at 300 mg.

7.R.6 Post-marketing investigations

The applicant plans a post-marketing surveillance shown in Table 73.

Table 73. Outline of specified use-results survey plan (draft)

Objective	To investigate the long-term safety and efficacy of vadadustat in patients with renal anemia in clinical use
Survey method	Central registry system
Population	Patients with renal anemia
Planned sample size	1,400 patients (patients with non-dialysis dependent CKD and patients on PD, 700; and patients on HD, 700) (registered sample size)
Observation period	1 year
Main survey items	• Patient characteristics: Sex, age, time of onset of renal anemia, history of dialysis, prior treatment (drug name, route of administration, daily dose, and treatment duration), medical history, complications, etc. • Dialysis therapy (type, frequency, and period of dialysis) • Use of vadadustat (daily dose and frequency, and treatment duration) • Use of concomitant drugs (drug name, route of administration, daily dose, and treatment duration) • Laboratory value (Hb value) • Adverse events (day of onset, seriousness, outcome, causal relationship to vadadustat, measures, etc.) • Hepatic function

PMDA considers that for the outline of the specified use-results survey plan (draft), information on the following points should be collected for investigation, but will be finalized, taking account of comments raised in the Expert Discussion.

- Thromboembolism and cardiovascular events, retinal haemorrhage, hypertension, and malignant tumors

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 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-6, CTD 5.3.5.1-7, CTD 5.3.5.1-8, CTD 5.3.5.1-9, CTD 5.3.5.2-1, and CTD 5.3.5.2-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, which confirmed that the clinical studies were conducted in accordance with GCP overall, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The following findings were noted at some of the study sites, although these would not significantly affect the overall evaluation of the studies, and the head of the concerned study site was notified of these findings as ones requiring corrective actions.

Findings requiring corrective action

Study site

- Defect in control of study drugs (dispensing the study drug with a wrong allocation number to some of the subjects)

- Deviation from the protocol (noncompliance with rules for dosage regimen of the study drug)

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

On the basis of the data submitted, PMDA has concluded that vadadustat has efficacy in the treatment of renal anemia, and that vadadustat has acceptable safety in view of its benefits. Vadadustat offers a new treatment option for patients with renal anemia and vadadustat is of clinically significance.

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

Review Report (2)

May 15, 2020

Product Submitted for Approval

Brand Name	Vafseo Tablets 150 mg Vafseo Tablets 300 mg
Non-proprietary Name	Vadadustat
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	July 8, 2019

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

PMDA's conclusion presented in Section "7.R.1 Efficacy" in Review Report (1) was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- In the Japanese phase III studies (MT-6548-J01 to MT-6548-J04), the percentage (%) of subjects with an Hb level within the target range at each timepoint" was calculated using "the number of subjects evaluated at the timepoint" as the denominator (Tables 58, 60, and 62 to 64). However, in the Japanese phase III studies (MT-6548-J01 and MT-6548-J03), more subjects discontinued treatment in the vadadustat group than in the DA group (40 subjects in the vadadustat group and 30 in the DA group in MT-6548-J01, 42 subjects in the vadadustat group and 26 in the DA group in MT-6548-J03). Therefore, the "percentage (%) of subjects with an Hb level within the target range" should be calculated using "the total number of subjects including subjects who discontinued treatment" as the denominator, and the newly calculated data should be provided.

Taking account of the comment from the expert advisors, PMDA has reached the following conclusion:

- "Percentage (%) of subjects with an Hb level within the target range at the last timepoint" in the Japanese phase III studies (MT-6548-J01 to MT-6548-J04) should be calculated using "the total number of subjects including subjects who discontinued treatment" as the

denominator (Table 74). These new data should be provided in the "Clinical Studies" section of the package insert.

Table 74. Percentage of subjects with an Hb level within the target range at the last timepoint[a)] (MT-6548-J01 to MT-6548-J04)

MT-6548-J01				MT-6548-J02	MT-6548-J03		MT-6548-J04
Patients with non-dialysis dependent CKD being treated with an ESA		ESA-naïve patients with non-dialysis dependent CKD		Patients on PD	Patients on HD being treated with an ESA		ESA-naïve patients on HD
Vadadustat (n = 80)	DA (n = 82)	Vadadustat (n = 71)	DA (n = 71)	Vadadustat (n = 42)	Vadadustat (n = 162)	DA (n = 161)	Vadadustat (n = 24)
60.0 (48)	79.3 (65)	71.8 (51)	77.5 (55)	64.3 (27)	64.2 (104)	83.9 (135)	58.3 (14)

Percentage (%) (number of subjects with an Hb level within the target range)

a) MT-6548-J01 and MT-6548-J03: mean Hb level during the treatment period of 48 and 52 weeks
MT-6548-J02 and MT-6548-J04: mean Hb level during the treatment period of 20 and 24 weeks

1.2 Safety

PMDA's conclusion presented in Section "7.R.2 Safety" in Review Report (1) was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- In light of the mechanism of action of vadadustat, there is a concern about serious adverse events related to thromboembolism. The package insert of vadadustat should include clear caution statements for use about a risk of thromboembolism so that adequate attention will be paid to the risk, as done for roxadustat, a drug with the same mechanism of action.

Taking account of the comment from the expert advisor, PMDA has concluded that the following caution statements should be included in the "Warnings" section of the package insert:

Warnings

During use of vadadustat, serious thromboembolism such as cerebral infarction, myocardial infarction, and pulmonary embolism may occur, possibly resulting in death. Before start of vadadustat, a risk of thromboembolism should be assessed including concurrent or past history of cerebral infarction, myocardial infarction, pulmonary embolism, etc., and then carefully determine whether vadadustat should be administered to the patient. In addition, during use of vadadustat, the condition of the patient should be closely monitored for signs or symptoms suspected of thromboembolism. Patients should be instructed to visit a medical institution immediately if symptoms suspected of thromboembolism occur.

1.3 Indication and dosage and administration

PMDA's conclusion presented in Sections "7.R.4 Indication" and "7.R.5 Dosage and administration" in Review Report (1) was supported by the expert advisors at the Expert Discussion.

PMDA's conclusion:

The proposed indication of vadadustat is appropriate, and the "Precautions Concerning Indications" section should specify the hemoglobin levels that should trigger treatment with vadadustat. The "Dosage and Administration" should be as follows (modified from the proposed wording), and the "Precautions Concerning Dosage and Administration" section should include advice regarding dose

increase and resumption. In addition, because patients in clinical studies showed decreases in Hb levels after switching from an ESA to vadadustat, the "Important Precautions" section of the package insert should include a caution statement to the effect that Hb levels should be monitored approximately once every 2 weeks after start of vadadustat until the Hb level reaches a stable state within the target range.

Indication
Renal anemia

Precautions Concerning Indication
For patients naïve to erythropoiesis-stimulating agents:
Initiate vadadustat if the hemoglobin level is <11 g/dL in patients with non-dialysis dependent chronic kidney disease and patients on peritoneal dialysis and <10 g/dL in patients on hemodialysis.

Dosage and Administration
The usual starting dose for adults is 300 mg of vadadustat orally administered once daily. The subsequent dose may be adjusted according to the patient's condition. The maximum dose should not exceed 600 mg.

Precautions Concerning Dosage and Administration
- The dose may be increased but only by 150 mg increments at ≥4-week intervals.
- After suspension, the treatment should be resumed at a dose 1 level lower.

1.4 Risk management plan (draft)

PMDA's conclusion presented in Section "7.R.6 Post-marketing investigations" in Review Report (1) was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- Vadadustat may cause or aggravate malignant tumors by enhancing neovascularization through activation on the HIF pathway. Information should be collected through post-marketing surveillances, etc. with the observation period >1 year.

- HIF may affect the condition of autosomal dominant polycystic kidney disease. Information on disease progression in patients with autosomal dominant polycystic kidney disease should be collected through post-marketing surveillances, etc.

In view of the Review Report (1) and comments raised from expert advisors, PMDA has concluded that the risk management plan (draft) for vadadustat should include the safety and efficacy specifications presented in Table 75, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 76 and the use-results survey presented in Table 77.

Table 75. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Thromboembolism • Hypertension • Hepatic dysfunction	• Cardiovascular events (except for thromboembolism) • Retinal haemorrhage • Malignant tumors • Disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD)	• Not applicable
Efficacy specification		
• Not applicable		

Table 76. 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 • Specified use-results survey	• Disseminate data gathered during early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals • Preparation and distribution of materials for patients

Table 77. Outline of specified use-results survey plan (draft)

Objective	To investigate the long-term safety and efficacy of vadadustat in patients with renal anemia in clinical use
Survey method	Central registry system
Population	Patients with renal anemia
Planned sample size	2,000 patients (≥500 patients with non-dialysis dependent chronic kidney disease, ≥100 patients on peritoneal dialysis, and ≥500 patients on hemodialysis) (registered number of patients)
Observation period	2 years
Main survey items	• Patient characteristics: Sex, age, onset time of renal anemia, history of dialysis, prior treatment (drug name, route of administration, daily dose, and treatment duration), medical history, complications, etc. • Dialysis therapy (type and period of dialysis) • Use of vadadustat (daily dose and frequency, and treatment duration) • Use of concomitant drugs (drug name, route of administration, daily dose, and treatment duration) • Laboratory value (Hb level) • Adverse events (day of onset, seriousness, outcome, causal relationship to vadadustat, actions taken, etc.) • Hepatic function; incidences of thromboembolism and cardiovascular events, retinal haemorrhage, hypertension, malignant tumors; and disease progression in patients with autosomal dominant polycystic kidney disease

2. Overall Evaluation

As a result of the above review, PMDA concludes 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, and the drug product and its drug substance are both classified as powerful drugs.

Indication

Renal anemia

Dosage and Administration

The usual starting dose for adults is 300 mg of vadadustat orally administered once daily. The subsequent dose may be adjusted according to the patient's condition. The maximum dose should not exceed 600 mg.

Approval Condition

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

Appendix

List of Abbreviations

ACE	Angiotensin-converting enzyme
Adverse drug reactions	Adverse events for which a causal relationship to the study drug cannot be ruled out
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
BZD	Benzodiazepine
CAMK	Calcium/calmodulin-dependent protein kinase
CERA	Continuous Erythropoietin Receptor Activator
CHO	Chinese hamster ovary
CK	Creatine kinase
CKD	Chronic kidney disease
CL_R	Renal clearance
C_{max}	Maximum concentration
CQA	Critical quality attribute
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events
CTD	Common technical document
CYP	Cytochrome P450
DA	Darbepoetin alfa (genetical recombination)
DMSO	Dimethyl sulfoxide
EC_{50}	Half maximal effective concentration
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
ESA-naïve patients	Patients in the Japanese phase III studies (MT-6548-J01 and MT-6548-J02) who are not receiving an ESA or who withdrew from an ESA ≥8 weeks ago, with a mean Hb level of ≥8.0 g/dL and <11.0 g/dL measured at 2 timepoints during the screening period
FAS	Full analysis set
FOB	Functional observational battery
GC	Gas chromatography
GCP	Good clinical practice
GLP	Good laboratory practice
Hb	Hemoglobin
Hct	Hematocrit
HD	Hemodialysis
HDF	Hemodiafiltration
HEK293 cells	Human embryonic kidney cell line 293
hERG	Human ether-a-go-go related gene
HIF	Hypoxia inducible factor
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICP-MS	Inductively coupled plasma-mass spectrometry

IR	Infrared absorption spectroscopy
IU	International unit
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LLC-PK1 cells	Lilly Laboratories cell-porcine kidney 1 cells
LOCF	Last observation carried forward
MATE	Multidrug and toxin extrusion
MDCKII	Madin-Darby canine kidney cell II
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MITT	Modified Intent-to-Treat
MMRM	Mixed effect Model Repeated Measures
MRP	Multidrug resistance-associated protein
MS	Mass spectrometry
NADPH	Nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P_{app} A→B	The apical to basolateral permeability coefficient
Patients being treated with an ESA	Patients in the Japanese phase III studies (MT-6548-J01 and MT-6548-J02) who are receiving an ESA by the same route of administration at the prespecified dose for ≥8 weeks before screening, with a mean Hb level of ≥9.0 g/dL and <12.5 g/dL measured at 2 timepoints during the screening period
PD	Peritoneal dialysis
P-gp	P-glycoprotein
PH	Prolyl hydroxylase
PHD	Prolyl hydroxylase domain enzyme
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
QTcI	Individual-corrected QT interval
RH	Relative humidity
rHuEPO	Recombinant human erythropoietin
SD	Sprague-Dawley
SMQ	Standardised MedDRA Queries
$t_{1/2}$	Elimination half life
t_{max}	Time to reach maximum concentration
TSAT	Transferrin saturation
UGT	Uridine-5'-diphospho-α-glucuronosyltransferase
UV	Ultraviolet spectroscopy
UV/VIS	Ultraviolet-visible spectroscopy
UVA	ultraviolet A
UVB	ultraviolet B
Vafseo	Vafseo Tablets 150 mg, Vafseo Tablets 300 mg
VEGF	Vascular endothelial growth factor
γ-GTP	γ-Glutamyltransferase