Report on the Deliberation Results

September 4, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Evrenzo Tablets 20 mg
	Evrenzo Tablets 50 mg
	Evrenzo Tablets 100 mg
Non-proprietary Name	Roxadustat (JAN*)
Applicant	Astellas Pharma Inc.
Date of Application	September 28, 2018

Results of Deliberation

In its meeting held on August 29, 2019, 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. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Condition of Approval

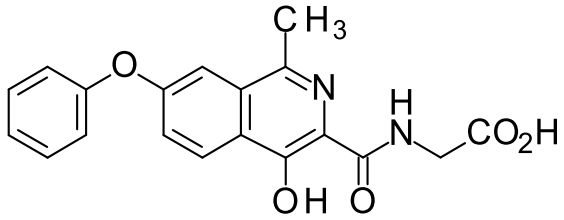
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

August 13, 2019
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	Evrenzo Tablets 20 mg Evrenzo Tablets 50 mg Evrenzo Tablets 100 mg
Non-proprietary Name	Roxadustat
Applicant	Astellas Pharma Inc.
Date of Application	September 28, 2018
Dosage Form/Strength	Film-coated tablets, each containing 20 mg, 50 mg, or 100 mg of roxadustat
Application Classification	Prescription drug, (1) Drugs with a new active ingredient
Chemical Structure	
Molecular formula:	$C_{19}H_{16}N_2O_5$
Molecular weight:	352.34
Chemical name:	*N*-[(4-Hydroxy-1-methyl-7-phenoxyisoquinolin-3-yl) carbonyl]glycine
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has promising efficacy in the treatment of renal anemia in patients on dialysis, and that the product has acceptable safety in view of its benefits (see Attachment). The safety and efficacy of the product should be further evaluated via post-marketing surveillance in patients with renal anemia on dialysis who received the product.

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 condition.

Indication

Renal anemia in patients on dialysis

Dosage and Administration

For patients naïve to erythropoiesis-stimulating agents:

The usual adult starting dosage is 50 mg of roxadustat administered orally 3 times weekly. The dose should be then adjusted according to the patient's condition. However, the maximum dose should not exceed 3.0 mg/kg.

For patients switching from an erythropoiesis-stimulating agent:

The usual adult starting dosage is 70 mg or 100 mg of roxadustat administered orally 3 times weekly. The dose should be then adjusted according to the patient's condition. However, the maximum dose should not exceed 3.0 mg/kg.

Condition of Approval

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

Attachment

Review Report (1)

July 19, 2019

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	Evrenzo Tablets 20 mg Evrenzo Tablets 50 mg Evrenzo Tablets 100 mg
Non-proprietary Name	Roxadustat
Applicant	Astellas Pharma Inc.
Date of Application	September 28, 2018
Dosage Form/Strength	Film-coated tablets, each containing 20 mg, 50 mg, or 100 mg of roxadustat
Proposed Indication	Renal anemia in patients on dialysis

Proposed Dosage and Administration

Patients on hemodialysis

The starting dosage for patients naïve to renal anemia treatment:

The usual adult dosage is 70 mg of roxadustat administered orally 3 times weekly.

The starting dosage for patients switching from another renal anemia drug (erythropoiesis-stimulating agent):

The usual adult dosage is 70 mg or 100 mg of roxadustat administered orally 3 times weekly.

Maintenance dose:

The usual adult dosage is 20 to 150 mg of roxadustat administered orally 3 times weekly.

In either dosage regimen, the dose should be adjusted according to the patient's hemoglobin concentration, etc. However, the maximum dose should not exceed the lower of 300 mg/dose or 3.0 mg/kg/dose.

Patients on peritoneal dialysis

The starting dosage for patients naïve to renal anemia treatment:

The usual adult dosage is 50 mg of roxadustat administered orally 3 times weekly.

The starting dosage for patients switching from another renal anemia drug (erythropoiesis-stimulating agent):

The usual adult dosage is 70 mg or 100 mg of roxadustat administered orally 3 times weekly.

Maintenance dose level:

The usual adult dosage is 20 to 150 mg of roxadustat administered orally 3 times weekly.

In either dosage regimen, the dose may be adjusted according to the patient's condition including hemoglobin concentration. However, the maximum dose should not exceed the lower of 300 mg or 3.0 mg/kg/dose.

Table of Contents

List of Abbreviations

See Appendix.

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

Renal anemia results from impaired ability of the kidney to produce erythropoietin (EPO), and aggravates symptoms including shortness of breath, palpitations, easy fatigability, and loss of appetite, causing cardiac strain associated with increased cardiac output.

Erythropoiesis-stimulating agents (ESAs) are used as pharmacotherapies to treat renal anemia. All ESAs are injections, and are known to cause anti-EPO antibody-positive pure red-cell aplasia ("2015 Guideline for Renal Anemia in Chronic Kidney Disease," edited by the Japanese Society for Dialysis Therapy).

Roxadustat is a low molecule compound which acts as a hypoxia-inducible factor (HIF) – prolyl-hydroxylase (PH) inhibitor. HIF is a transcription factor consisting of 2 subunits (HIF-α and HIF-β). HIF is activated under hypoxic conditions and promotes erythropoiesis, thereby inducing adaptive responses to hypoxic conditions. Under normoxic conditions, HIF-α is hydroxylated by HIF-PHs, and decomposed by the proteasome (e.g., *Mol Cell*. 2008;30:393-402, *Death Differ*. 2008;15:635-41). Roxadustat was developed with the expectation that it would exert therapeutic effect on renal anemia by inhibiting HIF-PH to activate the HIF pathway, thereby increasing EPO production and promoting erythropoiesis.

An application for marketing approval has recently been filed based on data that demonstrated the efficacy and safety of roxadustat in Japanese clinical studies in dialysis patients with renal anemia.

As of April 2019, roxadustat has been approved in China for the indication of renal anemia in patients on dialysis (approved in December 2018), and has yet to be approved in any other countries or regions.

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 yellow powder. Its description, solubility, thermal analysis, hygroscopicity, melting point, dissociation constant, and partition coefficient were determined.

The chemical structure of the drug substance was elucidated by ultraviolet-visible absorption spectroscopy (UV/VIS), infrared absorption spectrum (IR), nuclear magnetic resonance spectrum (NMR), mass spectrometry (MS), elemental analysis, and single crystal X-ray diffraction.

2.1.2 Manufacturing process

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

The following critical quality attributes (CQAs) were identified. Material properties and process parameters that may have impacts on the CQAs were evaluated, and control strategies for the drug substance were established (Table 1).

Table 1. Outline of control strategies for the drug substance

CQA	Control method
[redacted]	

[redacted] were defined as critical steps.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include the content, description, identification (high performance liquid chromatography [HPLC]/UV/VIS, IR), purity (related substances [HPLC]), water content, residue on ignition, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

Main stability studies on the drug substance are shown in Table 2. The results of the photostability studies showed that the drug substance was photolabile.

Table 2. Outline of main stability studies on the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 batches	30°C	65% RH	Polyethylene bags (double-layered) + aluminum bag	36 months
Accelerated	3 batches	40°C	75% RH		6 months

Based on the above results, a retest period of 36 months was proposed for the drug substance when placed in double-layered polyethylene bags, stored protected from light in an aluminum bag at room temperature according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E Guidelines. The long-term testing will be continued for up to [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 containing 20, 50, or 100 mg of roxadustat. The drug product contains lactose hydrate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, partially hydrolyzed polyvinyl alcohol, titanium oxide, macrogol [redacted], talc, yellow ferric oxide, and red ferric oxide as excipients.

2.2.2 Manufacturing process

The drug product is produced through a manufacturing process comprising [redacted], tableting, mixing of film-coating components, film-coating, filling, packaging/labeling, and storage.

The following CQAs have been identified. Material properties and process parameters that may have impacts on the CQAs have been evaluated, and control strategies for the drug product were established (Table 3).

Table 3. Outline of control strategies for the drug product

CQA	Control method
[redacted]	

[redacted] was defined as a critical step.

2.2.3 Control of drug product

The proposed specifications for the drug product include the strength, description, identification (UV/VIS), uniformity of dosage units (content uniformity test [HPLC]), dissolution (HPLC), microbial limit test, and assay (HPLC).

2.2.4 Stability of drug product

Main stability studies on the drug product are shown in Table 4. A bracketing approach was used for the long-term and accelerated studies. The results of the photostability studies showed that the drug product was photostable.

Table 4. Main stability studies on the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 batches	25°C	60% RH	Blister pack	36 months
Accelerated	3 batches	40°C	75% RH		6 months

Based on the above results, a shelf life of 48 months was proposed when the drug product is blister-packed (polyvinyl chloride film, aluminum) and stored at room temperature according to the ICH Q1E Guidelines. The long-term testing will be continued for up to 48 months.

2.R Outline of the review conducted by PMDA

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

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

Studies of primary pharmacodynamics include the investigation of HIF-PH inhibition, induction of EPO production, and anemia improvement in a rat model of inflammatory anemia and in partially nephrectomized rats. In secondary pharmacology studies, the action of roxadustat on enzymes and others except for HIF-PH was investigated. Safety pharmacology studies were conducted on the central nervous system, cardiovascular system, respiratory system, and renal/urinary system were investigated. In *in vivo* studies, a solution containing 0.5% carboxymethyl cellulose sodium and 0.1% polysorbate 80 was used as a vehicle.

3.1 Primary pharmacodynamics

3.1.1 HIF-PH inhibition

3.1.1.1 *In vitro* inhibition of human HIF-PH (CTD 4.2.1.1-1, Study 301_05_3010_056AMNDII)

The inhibitory activity of roxadustat against recombinant human prolyl hydroxylase domain enzyme (PHD) 1, PHD2, and PHD3 was investigated. The half maximal inhibitory concentration (IC_{50}) values of roxadustat in the presence of 1 μmol/L Fe^{2+} were 1.7 μmol/L in PHD1, 2.4 μmol/L in PHD 2, and 0.22 μmol/L in PHD3, demonstrating its inhibitory effect on human PHD1, PHD2, and PHD3.

3.1.2 Induction of EPO production

3.1.2.1 Induction of EPO production *in vitro* (CTD 4.2.1.1-2, Study 301_05_3040_057)

After adding 3 to 30 μmol/L of roxadustat to human hepatocellular carcinoma cell line Hep3B, the amount of intranuclear HIF-2α and the concentrations of EPO in the supernatant were measured. Roxadustat increased the amount of intranuclear HIF-2α and EPO concentration in the supernatant in a concentration-dependent manner. Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β are reported to suppress EPO production (*Blood*. 1992;79:1987-94). In the presence of TNF-α (0.4 ng/mL), and IL-1β (10 ng/mL), however, EPO concentrations in the supernatant increased when 30 μmol/L of roxadustat was added to Hep3B cell line.

3.1.2.2 Induction of EPO production in mice (CTD 4.2.1.1-3, Study 301_05_3510_048)

A single oral dose of roxadustat 2, 6, 20, or 60 mg/kg or vehicle was administered to male mice, and plasma EPO concentrations were measured 6 hours later. The plasma EPO concentrations (mean ± standard deviation) at 6 hours post-dose in the vehicle group and roxadustat 2, 6, 20, and 60 mg/kg groups were 107 ± 28, 109 ± 12, 160 ± 84, 190 ± 62, and 2511 ± 1031 pg/mL, respectively, indicating that roxadustat tends to increase plasma EPO concentration in a dose-dependent manner.

3.1.3 Improvement of anemia in rat models of inflammatory anemia or renal anemia

3.1.3.1 Improvement of anemia in rats with inflammatory anemia (CTD 4.2.1.1-6 and 7, Studies 301_07_3510_121_A01 and 301_05_3510_047_A01)

Oral roxadustat 40 mg/kg or vehicle was administered to rats with inflammatory anemia[1)] 3 times weekly for 2 weeks, and hemoglobin (Hb), hematocrit (Hct), and red blood cell count were measured 2 weeks after start of treatment,.

Hb and Hct levels and red blood cell count significantly increased in the roxadustat 40 mg/kg group as compared with the vehicle control group 2 weeks after the start of treatment (Table 5).

Table 5. Hb, Hct and red blood cell count 2 weeks after start of treatment in rats with inflammatory anemia

Treatment group	Hb (g/dL)		Hct (%)		Red blood cell count (10^6/μL)	
	Pre-dose	2 weeks after start of treatment	Pre-dose	2 weeks after start of treatment	Pre-dose	2 weeks after start of treatment
Vehicle control	11.2 ± 0.6	11.6 ± 0.3	32.5 ± 1.4	33.5 ± 0.6	7.4 ± 0.3	7.9 ± 0.1
Roxadustat 40 mg/kg group	10.9 ± 0.4	15.0 ± 0.3*	31.9v1.2	42.2 ± 0.8*	7.4 ± 0.2	9.1 ± 0.1*

n = 7 or 8, mean ± standard error
* p <0.05 (vs. vehicle control, Student-Newman-Keuls test)

Oral roxadustat 30 mg/kg or vehicle was administered to rats with inflammatory anemia[1)] 3 times weekly for 4 weeks, and Hb, Hct, and red blood cell count were measured 4 weeks after the start of treatment.

Hb, Hct, and red blood cell count significantly increased in the roxadustat 30 mg/kg group as compared with the vehicle control group 4 weeks after the start of treatment (Table 6).

Table 6. Hb, Hct, and red blood cell count 4 weeks after start of treatment in rats with inflammatory anemia

Treatment group	Hb (g/dL)		Hct (%)		Red blood cell count (10^6/μL)	
	Pre-dose	4 weeks after start of treatment	Pre-dose	4 weeks after start of treatment	Pre-dose	4 weeks after start of treatment
Vehicle control	9.2 ± 0.3	9.5 ± 0.4	27.3 ± 0.9	28.8 ± 1.1	6.4 ± 0.2	7.3 ± 0.3
Roxadustat 30 mg/kg	9.2 ± 0.3	13.6 ± 0.3*	27.6 ±1.2	38.5 ± 1.0*	6.5 ± 0.3	8.6 ± 0.2*

n = 7 or 8, mean ± standard error
* p <0.05 (vs. vehicle control, Student-Newman-Keuls test)

3.1.3.2 Improvement of anemia in partially nephrectomized rats with CKD (CTD 4.2.1.1-8, Study 301_06_3510_071_A01)

Oral roxadustat 20 or 40 mg/kg or vehicle was administered to 5/6 nephrectomized rats with CKD[2)] for 2 weeks, 3 times weekly at Week 1 and twice weekly at Week 2. Hb, Hct, and red blood cell count were measured 2 weeks after the start of treatment.

1) Peptidoglycan-polysaccharide (PG-PS) polymer was intraperitoneally injected into female rats to induce arthritis and associated anemia over 4 weeks.
2) Male rats underwent infarction of 2/3 of the left kidney and nephrectomy of the right kidney to induce kidney failure and associated anemia over 5 weeks.

At ≥20 mg/kg, Hb, Hct and red blood cell count significantly increased as compared with the vehicle control (Table 7).

Table 7. Hb, Hct, and red blood cell count 2 weeks after the start of treatment in 5/6 nephrectomized rats with CKD

Treatment group	Hb (g/dL)		Hct (%)		Red blood cell count (10^6/μL)	
	Pre-dose	2 weeks after start of treatment	Pre-dose	2 weeks after start of treatment	Pre-dose	2 weeks after start of treatment
Vehicle control	13.2 ± 0.4	12.7 ± 0.5	38.0 ± 0.8	37.3 ± 1.4	7.4 ± 0.2	7.0 ± 0.4
Roxadustat 20 mg/kg	13.3 ± 0.3	15.8 ± 0.3*	38.4 ± 0.7	45.5 ± 0.8*	7.4 ± 0.2	8.2 ± 0.3*
Roxadustat 40 mg/kg	13.1 ± 0.4	17.9 ± 0.7*	38.6 ± 1.0	51.1 ± 1.7*	7.4 ± 0.2	9.0 ± 0.3*

n = 8 or 9, mean ± standard error
* p <0.05 (vs. vehicle control, Student-Newman-Keuls test)

3.2 Secondary pharmacodynamics

3.2.1 Studies on selectivity (CTD 4.2.1.2-1 and 2, Studies 301_13_3010_009A2 and 301_04_3010_010)

Actions of roxadustat 10 μmol/L on 67 receptors and 16 enzymes were investigated. Roxadustat 10 μmol/L inhibited ligand binding to the human cholecystokinin A (CCK_A) receptor, human norepinephrine (NE) transporter, human dopamine transporter, and human dopamine receptor D4.4 by ≥35%.

The IC_{50} of roxadustat for ligand binding was investigated. The IC_{50} values were 9.9 μmol/L for human CCK_A receptor, 15 μmol/L for human NE transporter, 18 μmol/L for human dopamine transporter, and >100 μmol/L for human dopamine receptor D4.4, corresponding to 23-times, 35-times, 42-times, and >234-times, respectively, the estimated C_{max} (427 nmol/L) at the clinical maximum dose of roxadustat (300 mg 3 times weekly).

The applicant explained that the results suggest roxadustat is unlikely to inhibit ligand binding to the receptors and transporters in clinical use.

3.3 Safety pharmacology

Table 8 shows the main safety pharmacology studies submitted.

Table 8. Summary of results of safety pharmacology studies

Item	Species/strain	Test parameter/method	Dose of roxadustat	Route of administration	Findings[a)]	CTD (Study No.)
Central nervous system	Rat (n = 5/sex/group)	Irwin test	30, 100, 300 mg/kg	Single dose; oral	No effects up to the maximum dose of 300 mg/kg. The no-observed effect level (NOEL) for the central nervous system in rats was determined to be >300 mg/kg (margin of safety, 41-fold).	4.2.1.3-10 (301_05_ 3510_022)
Cardiovascular system	Human embryonic kidney cell line 293 (HEK293) cells (n = 3 or 4/group)	hERG current	93, 178, 291 μmol/L	*in vitro*	Addition of 93, 178, and 291 μmol/L of roxadustat exhibited 16.8%, 38.2%, and 52.8% inhibition, respectively. It was not possible to calculate accurate IC_{50} values for 178 and 291 μmol/L because of the small amounts of roxadustat precipitated (IC_{50} >93 μmol/L).	4.2.1.3-1 (301_05_ 3510_038)
	Monkey (n = 4 males/group)	Heart rate, blood pressure (systolic, diastolic, and mean), electrocardiography	3, 30, 100 mg/kg	Single dose; oral	Heart rate increased at 100 mg/kg. The NOEL for the cardiovascular system in monkeys was determined to be 30 mg/kg (margin of safety, 6.6-fold).	4.2.1.3-2 (301_05_ 3510_025)
	Rat (n = 6 males/group)	Heart rate, blood pressure (systolic, diastolic, and mean)	20, 40 mg/kg	3 times weekly for 4 weeks; oral	Heart rate increased at ≥20 mg/kg, and decreased blood pressure at 40 mg/kg were observed. The NOEL for the cardiovascular system in rats was determined to be <20 mg/kg (margin of safety, <8.5-fold).	4.2.1.3-9 (352016002)
Respiratory system	Rat (anesthesia; n = 4/sex/group)	Whole body plethysmography (WBP; e.g., respiratory rate, tidal volume, minute ventilation)	10, 30, 100 mg/kg	Single dose; intra-venous	Respiratory rate and minute ventilation increased at ≥30 mg/kg, and tidal volume increased at 100 mg/kg. The NOEL for the respiratory system in rats was determined to be 10 mg/kg (margin of safety, 10-fold).	4.2.1.3-11 (301_05_ 3510_023)
Renal and urinary system	Rat (n = 5/sex/group)	Urine output, urine pH, urine electrolytes (Na^+, K^+, and Cl^-)	30, 100, 300 mg/kg	Single dose; oral	Urine output, urine pH, and excretion of Na^+, K^+, and Cl^- increased at ≥30 mg/kg. Urine K^+ concentrations increased at ≥100 mg/kg. The NOEL for the renal and urinary system in rats was determined to be <30 mg/kg (margin of safety, <24-fold).	4.2.1.3-12 (301_05_ 3510_024)

a) The safety margin was calculated by comparing with the C_{max} (427 nmol/L) at the maximum clinical dose (300 mg 3 times weekly). The C_{max} at the maximum clinical dose was estimated by the population pharmacokinetics (PPK) analysis of data from clinical studies (CL-0302, CL-0304, CL-0307, and CL-0308) conducted in Japanese patients with renal anemia on dialysis.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological actions

The applicant's explanation about the pharmacological actions of roxadustat:

Roxadustat is an inhibitor of HIF-PH, an enzyme involved in HIF degradation. HIF is a transcription factor consisting of 2 subunits, HIF-α and HIF-β, and is activated under hypoxic conditions and promotes erythropoiesis, thereby inducing adaptive responses to the hypoxic conditions. In normoxic conditions, however, HIF-α is hydroxylated by HIF-PHs, and decomposed by the proteasome (e.g., *Mol Cell.* 2008;30:393-402, *Death Differ.* 2008;15:635-41). Roxadustat inhibits HIF-PHs and suppresses HIF-α degradation, thereby activating the HIF pathway.

In the normal kidney, when local oxygen partial pressure decreases in the peritubular interstitium, EPO-producing cells in the interstitium activate the HIF pathway to produce EPO. In patients with renal failure, renal oxygen delivery is decreased due to low renal blood flow, while local oxygen consumption is also low as a result of tubular disorder and reduced glomerular filtration rate, Therefore, oxygen partial pressure is assumed to be relatively well maintained around the tubules, the site of EPO production.

Consequently, if patients with renal failure suffer decreased Hb levels and associated renal anemia, the oxygen partial pressure around the tubules does not decrease, resulting in inadequate response to hypoxia in EPO-producing cells (2015 Guideline for Renal Anemia in Chronic Kidney Disease, *Am J Kidney Dis.* 2001;38:415-25). Therefore, roxadustat is expected to exert its therapeutic effect on renal anemia by activating the HIF pathway in EPO-producing cells so as to promote EPO production regardless of the local oxygen partial pressure, accelerating erythropoiesis and elevating Hb levels.

The results of studies submitted with the present application demonstrated roxadustat's effects on human HIF-PH inhibition and induction of EPO production, as well as increases in Hb, Hct, and red blood cell count in a rat model of PG-PS-induced inflammatory anemia and in partially nephrectomized rats with CKD. These findings suggest that roxadustat improves renal anemia through the activation of the HIF pathway.

PMDA's view:
Based on the data from the studies of primary pharmacodynamics submitted for the present application and the discussion of the applicant, roxadustat has an inhibitory effect on HIF-PH, increases Hb via the activation of the HIF pathway, and exerts its effect on renal anemia.

3.R.2 Safety pharmacology

The applicant's explanation about the findings of safety pharmacology studies:
Changes noted in the cardiovascular system were an increase in heart rate in monkeys[3)] and an increase in heart rate and a decrease in blood pressure in rats. The decrease in blood pressure was likely attributable to vasodilatation due to elevated HIF concentration in tissue, and the increase in heart rate was likely a reflex response to the decreased blood pressure, based on the facts below. However, the safety margin of roxadustat for the cardiovascular system in monkeys was <6.6-fold, and that in rats was <8.5-fold. The NOEL for heart rate and blood pressure in a rat single oral dose study conducted under non-GLP conditions was 10 mg/kg, with a safety margin of 4.3-fold. Given these findings, roxadustat is unlikely to affect the cardiovascular system in clinical use.

- Vasodilatation is induced in tissue as a result of activation of the HIF pathway (*Cell.* 1997;89:9-12, *Mol Cell Biol.* 2003;23:9361-74).
- In a study using isolated perfused heart specimens from the rat,[4)] roxadustat did not exhibit direct effect on the heart rate or heart contractility, whereas it decreased coronary pressure and coronary resistance that were consistent with the vasodilatation effect on coronary vascular beds.

3) Unlike in rats, blood pressure did not decrease in monkeys. The applicant explained that an increase in respiration rate caused by roxadustat's hypotensive action is a reaction that stimulates the recovery of blood pressure to a physiological level via baroreceptorl. However, in monkeys, blood pressure may have been maintained at a normal level because of sufficient compensation, and thus no decreased blood pressure was observed.

4) Under non-GLP conditions, using isolated perfused heart specimens from the rat, heart rate, left ventricular developed pressure, left ventricular end-diastolic pressure, coronary perfusion pressure, coronary resistance, etc. at roxadustat 1, 3, and 10 μg/mL were measured. The results indicated no effects of roxadustat on heart rate, left ventricular developed pressure, or left ventricular end-diastolic pressure. In contrast, coronary perfusion pressure and coronary resistance decreased in a roxadustat concentration-dependent manner.

Changes noted in the respiratory system were increases in respiratory rate, minute ventilation, and tidal volume in rats. These changes may be attributable to accelerated respiration by roxadustat acting on the CCK_A receptor, NE transporter, and dopamine transporter based on the observations below. Nevertheless, in its clinical use, roxadustat is unlikely to affect the respiratory system because of its low possibility of inhibiting ligand binding to these receptors [see Section 3.2], and the 10-fold safety margin of roxadustat for the respiratory system in rats.

- Roxadustat is known to inhibit ligand binding to the human CCK_A receptor, human NE transporter, and human dopamine transporter [see Section 3.2].
- An association of these receptors and transporters with the respiratory control function has been reported (e.g., *Neuropeptides.* 2015;54:29-34, *Circulation.* 2004;110:1191-6).

The changes noted in the rat renal/urinary system were increases in urine output, urine pH, excretion of Na^+, K^+, and Cl^-, and urine K^+ concentration. It has been reported that the inhibition of PHD causes the accumulation of HIF-1α in the renal medulla, increasing urine output and urinary Na^+ excretion (*Am J Physiol Renal Physiol*. 2007;292:F207-16). Therefore, the changes in the renal/urinary system are attributable to the HIF pathway in the renal medulla activated by roxadustat. The safety margin of the renal/urinary system in rats could not be calculated. Nevertheless, given that the C_{max} in the rats which presented with the changes in the renal/urinary system is 24 times the C_{max} for the maximum clinical dose of roxadustat, and that no particular problems have been reported in the occurrence of renal/urinary system-related adverse events in clinical studies, roxadustat is unlikely to affect the renal/urinary system when used clinically.

Based on the above, it is unlikely that roxadustat will affect the central nervous, cardiovascular, respiratory, and renal/urinary systems in its clinical use.

PMDA accepted the applicant's explanation.

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

The pharmacokinetics of roxadustat in mice, rats, and monkeys following the administration of ^{14}C-labeled and unlabeled roxadustat was investigated. The concentration of unchanged roxadustat in plasma and in breast milk was measured by liquid chromatography tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation was 0.1 to 0.001 μg/mL (CTD 4.2.2.2-3 and 4.2.2.2-4) for plasma, and 0.0005 μg/mL (CTD 4.2.2.1-9 and 4.2.2.1-14) for breast milk. When ^{14}C-roxadustat was used, radioactivity levels were measured by liquid scintillation counting, or quantitative whole body autoradiography. Results from the main studies are presented in the following sections.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-3 and 4.2.2.2-4, Studies 1517-ME-0030 and 301_06_3510_077)

Table 9 shows pharmacokinetic parameters after a single oral or intravenous dose of roxadustat was administered to male rats, or male and female monkeys. While in rats, C_{max} and AUC_{inf} increased in a generally dose-proportional manner, a greater-than-dose-proportional increase in AUC_{inf} was observed at 30 mg/kg in monkeys administered roxadustat both orally and intravenously.

Table 9. Plasma pharmacokinetic parameters after single dose administration of roxadustat

Animal species	Route of administration	Roxadustat dose (mg/kg)	C_{max} (μg/mL)	t_{max} (h)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	Bioavailability (%)
Male rat[a)]	Oral	6	30.4 ± 7.4	0.3 ± 0.1	153 ± 50	4.1 ± 1.9	85.6 [b)]
		20	70.5 ± 20.7	2.0 ± 2.7	596 ± 72	2.7 ± 0.1	100.0 [b)]
		60	151 ± 3	2.1 ± 2.7	1,600 ± 280	5.5 ± 0.4	89.5 [b)]
	Intravenous	20	—	—	596 ± 50	3.6 ± 1.4	—
Male monkey	Oral	3	9.1 ± 2.9	0.8 ± 0.3	11.9 ± 1.2	15.6 ± 1.4	72.2 ± 9.8
		10	14.0 ± 4.0	1.3 ± 0.6	33.0 ± 8.7	15.2 ± 1.7	40.4 ± 2.8
		30	91.6 ± 47.8	2.3 ± 1.5	311.7 ± 113.2	12.2 ± 2.2	57.5 ± 11.4
	Intravenous	3	27.4 ± 1.0	0.1 ± 0.0	16.6 ± 0.7	6.9 ± 2.7	—
		10	117.0 ± 29.7	0.1 ± 0.0	81.2 ± 15.8	9.9 ± 1.2	—
		30	345.0 ± 15.0	0.1 ± 0.0	531.2 ± 86.0	10.7 ± 1.1	—
Female monkey	Oral	3	4.4 ± 1.9	0.8 ± 0.3	7.1 ± 1.2	15.0 ± 4.2	66.4 ± 4.7
		10	30.4 ± 26.6	1.3 ± 0.6	55.8 ± 44.4	13.2 ± 2.8	51.7 ± 32.2
		30	125.0 ± 25.7	2.0 ± 0.0	475.8 ± 85.8	11.5 ± 1.6	82.8 ± 12.2
	Intravenous	3	25.1 ± 2.0	0.1 ± 0.0	10.7 ± 1.4	8.6 ± 2.4	—
		10	95.4 ± 5.5	0.1 ± 0.0	100.9 ± 21.4	9.1 ± 3.1	—
		30	300.0 ± 29.1	0.1 ± 0.0	589.7 ± 166.2	10.8 ± 1.8	—

n = 3; mean value ± standard deviation
a) n = 3 or 4
b) Calculated using AUC_{inf} following intravenous administration of 20 mg/kg.

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study in rats (CTD 4.2.3.2-5, Study 352007004)

Roxadustat was administered to male and female rats at 5, 15, 30, or 40 mg/kg orally 3 times weekly for 26 weeks, and pharmacokinetics was investigated using the toxicokinetic data. Table 10 shows plasma pharmacokinetic parameters of roxadustat. The C_{max} and $AUC_{0\text{-}48h}$ increased roughly in a dose-proportional manner. No clear accumulation of plasma roxadustat concentrations resulting from repeated-dose administration was observed. There were no differences in the plasma pharmacokinetic parameters between the sexes.

Table 10. Plasma pharmacokinetic parameters during 26-week repeated oral administration in rats[a)]

Roxadustat dose (mg/kg/day)	Time point	Male			Female		
		C_{max} (μg/mL)	t_{max} (h)	AUC_{0-48h} (μg·h/mL)	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-48h} (μg·h/mL)
5	Day 1	11.9	1.0	53.8	12.6	1.0	53.2
	Day 89	20.5	0.5	68.2	15.2	0.5	62.2
	Day 178	19.2	1.0	77.8	22.3	0.5	84.3
15	Day 1	55.8	0.5	218	48.2	0.5	211
	Day 89	62.1	0.5	261	56.2	1.0	253
	Day 178	68.1	1.0	307	78.1	0.5	337
30	Day 1	110	1.0	506	101	0.5	532
	Day 89	113	1.0	637	101	0.5	582
	Day 178	106	1.0	667	152	0.5	862
40	Day 1	142	1.0	703	129	0.5	752
	Day 89	149	1.0	922	87.0	1.0	1040
	Day 178	NA[b)]	NA[b)]	NA[b)]	167	1.0	903

Mean value; NA, not applicable
a) Each parameter was evaluated based on the mean plasma concentration of the data of 2 or 3 rats at each time point.
b) Not calculated because treatment was discontinued on Day 119.

4.1.2.2 Repeated-dose study in monkeys (CTD 4.2.3.2-9, Study 301_06_3520_092)

Roxadustat was administered to male and female monkeys at 3, 10, 20, or 30 mg/kg orally 3 times weekly for 52 weeks, and pharmacokinetics was investigated using the toxicokinetic data. Table 11 shows the plasma pharmacokinetic parameters of roxadustat. Greater-than-dose-proportional increases in C_{max} and AUC_{0-48h} were observed. No clear accumulation of plasma roxadustat concentrations resulting from repeated-dose administration was observed. There were no differences in the plasma pharmacokinetic parameters between the sexes. In the roxadustat 20 and 30 mg/kg groups, C_{max} and AUC_{0-48h} tended to be lower in Weeks 26 and 51 as compared with those on Day 1. The applicant explains that this was due to a greater inter-individual variation in C_{max} and AUC_{0-48h} observed on Day 1 as compared with that in Weeks 26 and 51.

Table 11. Plasma pharmacokinetic parameters during repeated oral administration in monkeys

Roxadustat dose (mg/kg/day)	Time point	Male			Female		
		C_{max} (μg/mL)	t_{max} (h)	AUC_{0-48h} (μg·h/mL)	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-48h} (μg·h/mL)
3	Day 1	0.7 ± 0.5	1.2 ± 0.4	4.0 ± 1.6	0.7 ± 0.1	1.0 ± 0.0	3.1 ± 0.9
	Week 26	0.7 ± 0.4	1.0 ± 0.0	4.0 ± 1.4	0.5 ± 0.2	1.0 ± 0.0	3.5 ± 0.7
	Week 51	0.6 ± 0.3[a)]	1.0 ± 0.0[a)]	4.7 ± 1.9[a)]	0.5 ± 0.2	2.8 ± 4.0	4.5 ± 1.4
10	Day 1	9.7 ± 5.3	1.0 ± 0.0	26.2 ± 8.8	10.9 ± 8.9	1.2 ± 0.4	27.7 ± 21.2
	Week 26	6.6 ± 5.3	1.0 ± 0.0	23.1 ± 8.8	6.6 ± 6.4	1.0 ± 0.0	25.4 ± 19.7
	Week 51	7.4 ± 3.4[a)]	1.0 ± 0.0[a)]	27.2 ± 9.4[a)]	8.5 ± 8.5	1.2 ± 0.4	29.0 ± 21.7
20	Day 1	50.5 ± 25.2	1.4 ± 0.5	120 ± 31.6	73.7 ± 40.0	1.0 ± 0.0	209 ± 138
	Week 26	18.0 ± 11.3	1.0 ± 0.0	61.8 ± 29.4	27.7 ± 12.7	1.0 ± 0.0	100 ± 62.3
	Week 51	10.7 ± 4.5	1.0 ± 0.0	48.8 ± 20.7	11.4 ± 6.8	1.4 ± 0.5	93.2 ± 56.6
30	Day 1	71.9 ± 35.0	1.2 ± 0.4	197 ± 81.0	96.2 ± 16.9	1.2 ± 0.4	260 ± 68.6
	Week 26	43.5 ± 17.4	1.0 ± 0.0	132 ± 35.1	59.9 ± 44.4	1.8 ± 1.3	162 ± 72.8
	Week 51	41.1 ± 16.5	1.0 ± 0.0	144 ± 59.7	35.7 ± 19.6	1.2 ± 0.4	152 ± 63.0

Mean value ± standard deviation; n = 5
a) n = 4

4.2 Distribution

4.2.1 Tissue distribution in pigmented rats (CTD 4.2.2.2-1, Study 301_06_3510_093)

A single oral dose of ^{14}C-roxadustat 20 mg/kg was administered to male and female pigmented rats, and radioactivity levels in each tissue[5)] up to 96 hours post-dose were investigated. Radioactivity levels reached their maximum within 1 hour post-dose in the majority of tissues. Up to 1 hour post-dose, higher levels of radioactivity were observed in the liver, kidney, and lung, with the tissue-to-plasma radioactivity ratios in female and male rats, respectively, being 0.61 and 0.65 (liver), 0.61 and 0.66 (kidney), and 0.35 and 0.38 (lung). Tissue radioactivity levels decreased over time, and radioactivity was not detected in the majority of tissues at 96 hours post-dose.

4.2.2 Protein binding (CTD 5.3.2.1-1, Study 1517-ME-0033)

Protein binding of ^{14}C-roxadustat (2 to 400 μg/mL) was studied using plasma from mice, rats, guinea pigs, rabbits, and monkeys. Protein binding was 90.1% to 94.5% in mouse plasma, 95.2% to 98.6% in rat plasma, 92.4% to 97.6% in guinea pig plasma, 97.1% to 98.6% in rabbit plasma, and 98.1% to 98.7% in monkey plasma. The results of protein binding indicated no evident concentration dependence within the concentration range studied.

4.2.3 Uptake into blood cells (CTD 5.3.2.1-2, Study 1517-ME-0032)

Uptake of ^{14}C-roxadustat (0.4 to 400 μg/mL) into blood cells was studied using blood from mice, rats, rabbits, and monkeys. The percentage uptake of ^{14}C-roxadustat into blood cells was 23.7% to 49.5% in mouse blood, 4.3% to 19.5% in rat blood, 3.8% to 11.5% in rabbit blood, and 3.9% to 8.8% in monkey blood. The blood-to-plasma concentration ratios were 0.8 to 1.1, 0.6 to 0.7, 0.6, and 0.6 to 0.7, respectively, indicating no clear concentration-dependent changes in the concentration range studied.

4.2.4 Placental transfer in rats (CTD 4.2.3.5.3-1, Study 352013012)

Roxadustat 5, 10, or 20 mg/kg was administered orally once daily to pregnant rats from gestation days 7 to 20, and plasma roxadustat concentrations in dams and fetuses were measured on gestation day 20. Roxadustat was detected in fetal plasma at all dose levels studied, and the plasma roxadustat concentration in fetuses was 0.08 to 0.14 times that in dams. Based on the results, the applicant explains that roxadustat, albeit in small amounts, may transfer across the placenta to the fetus.

4.3 Metabolism

4.3.1 *In vitro* metabolite studies (CTD5.3.2.2-1 and 5.3.2.2-2, Studies 301_05_3010_029 and 301_09_3020_132)

The metabolism of roxadustat was investigated using mouse, rat, dog, and monkey liver microsomes. Roxadustat was incubated with liver microsomes in the presence of nicotinamide adenine dinucleotide

5) The adrenal gland, bile, bone, bone marrow, cecum, cecal contents, cerebellum, cerebrum, diaphragm, epididymis, esophageal contents, esophagus, extraorbital lacrimal gland, eyeball, ocular lens, abdominal fat, brown adipose, Harderian gland, intraorbital lacrimal gland, kidney, large intestine contents, large intestine, liver, lung, medulla, muscle, myocardium, nasal concha, olfactory lobe, ovary, pancreas, pituitary gland, preputial gland, prostate, renal cortex, renal medulla, salivary gland, seminal vesicle, skin, small intestine contents, small intestine, spinal cord, spleen, stomach, stomach contents, testis, thymus, thyroid, bladder, urine, uterus, uvea, blood, and plasma.

phosphate (NADPH) for 90 minutes. Roxadustat was hardly metabolized by liver microsomes in any of the animal species investigated.

The metabolism of ^{14}C-roxadustat was also investigated using mouse, rat, monkey, and human hepatocytes. Roxadustat was hardly metabolized by hepatocytes in any of the animal species investigated, and no metabolites specific to humans were found.

4.3.2 Metabolites in plasma and urine (CTD 4.2.2.2-1 and 4.2.2.4-1, Studies 301_06_3010_093 and 1517-ME-0028)

A single oral dose of 20 mg/kg of ^{14}C-roxadustat was administered to male and female rats to investigate unchanged roxadustat and metabolites in plasma. Up to 24 hours post-dose, unchanged compound was the major component in plasma radioactivity. In urine, main metabolites detected up to 24 hours post-dose included MET12 (produced by sulfate conjugation of hydroxylated roxadustat), MET11-1 (hydroxylated roxadustat), and MET1 (4-*O*-β-glucuronidated roxadustat). In female and male rat urine, MET12 accounted for 4.9% (female) and 8.3% (male) of the total radioactivity administered, MET11-1 accounted for 3.9% (female) and 1.3% (male), and MET1 accounted for 1.8% (female) and 2.5% (male). In feces, unchanged roxadustat and MET11-1 were the main components up to 48 hours post-dose. In female and male rat urine, unchanged roxadustat accounted for 25.5% (female) and 21.1% (male) of the total radioactivity administered and MET11-1 accounted for 20.0% (female) and 23.6% (male).

A single oral dose of 10 mg/kg of ^{14}C-roxadustat was administered to male monkeys to investigate unchanged roxadustat and metabolites in plasma. Up to 8 hours post-dose, unchanged roxadustat and MET3 (produced by sulfate conjugation of 4'-hydroxylated roxadustat) were detected in plasma, and accounted for 58.8% to 81.8% and 9.5% to 19.7%, respectively, of the plasma radioactivity. Up to 24 hours post-dose, MET1 and MET3 were detected as the main metabolites in urine, and accounted for 10.5% and 5.0%, respectively, of the administered radioactivity. In bile, mainly MET1 and MET3 were detected up to 24 hours post-dose, and accounted for 22.4% and 17.6%, respectively, of the administered radioactivity.

The above results suggest that oxidative metabolism, glucuronidation, and sulfate conjugation are mainly involved in the metabolism of roxadustat.

4.4 Excretion

4.4.1 Urinary and fecal excretion in rats (CTD 4.2.2.2-1, Study 301_06_3010_093)

A single oral dose of 20 mg/kg of ^{14}C-roxadustat was administered to male and female rats to investigate urinary and fecal excretion in rats. Up to 120 hours post-dose, 16.3% (female) and 16.8% (male) of administered radioactivity was excreted in urine, and 77.4% (female) and 78.5% (male) in feces, indicating that in rats the majority of roxadustat was excreted in feces.

4.4.2 Urinary, fecal, and biliary excretion in monkeys (CTD 4.2.2.2-2, Study 1517-ME-0027)

A single oral dose of 10 mg/kg of ^{14}C-roxadustat was administered to male monkeys to investigate urinary, fecal, and biliary excretion in monkeys. Up to 168 hours post-dose, 24.9% and 73.5% of administered radioactivity was excreted in urine and feces, respectively, indicating that roxadustat was excreted mostly in feces.

A single oral dose of 10 mg/kg of ^{14}C-roxadustat was administered to bile duct-cannulated male monkeys. Up to 72 hours post-dose, 30.9% and 51.7% of administered radioactivity was cumulatively excreted in urine and bile, respectively.

The above results suggest that following the oral administration of roxadustat to monkeys, administered radioactivity is excreted primarily in feces via bile.

4.4.3 Excretion in rat breast milk (CTD 4.2.3.5.3-1, Study 352013012)

Roxadustat 5, 10, or 20 mg/kg was administered orally once daily to female rats from gestation day 7 to lactation day 20 to investigate excretion in breast milk. Roxadustat was detected in breast milk on lactation day 10 and in plasma of suckling rats on postnatal days 4 and 21. The above results indicated that roxadustat is excreted in breast milk.

4.R Outline of the review conducted by PMDA

PMDA asked the applicant to explain the cause of the trend toward greater than dose-proportional increases in exposure observed in single and repeated oral dose studies in monkeys [Sections 4.1.1 and 4.1.2.2].

The applicant's explanation:

The total clearance (CL_{tot}) following single-dose intravenous administration of roxadustat at 3, 10, and 30 mg/kg to male and female monkeys was 181, 126, and 57.4 mL/h/kg, respectively, in male monkeys, and 283, 102, and 54.0 mL/h/kg, respectively, in female monkeys, indicating that CL_{tot} decreased with increase in dose. Since oxidative metabolism and glucuronidation are involved in the elimination of roxadustat in monkeys, greater than dose-proportional increases in exposure in monkeys are attributable to a decrease in clearance due to saturation of the metabolic processes. However, given that following single-dose oral administration of 0.3 to 4 mg/kg of roxadustat or repeated-dose oral administration of 0.3 to 3 mg/kg to Japanese subjects in clinical pharmacology studies, exposure increased approximately in a dose-proportional manner [see Sections 6.2.1.1 and 6.2.1.2], suggesting the unlikeliness of greater than a dose-proportional increase in exposure at a clinical dose of roxadustat.

PMDA accepted the applicant's explanation.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies of roxadustat were conducted: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other studies (juvenile animal toxicity studies, phototoxicity studies, and studies on impurities). In *in vivo* studies, unless otherwise stated, a solution of 0.5% carboxymethylcellulose and 0.1% polysorbate 80 was used as a vehicle for oral administration, and phosphate buffered saline for intravenous administration.

5.1 Single-dose toxicity

Single oral dose toxicity studies in rats and monkeys, and a single intravenous dose toxicity study in rats were conducted (Table 12). The approximate lethal dose for oral administration was 200 mg/kg in rats, and >100 mg/kg in monkeys, which were 16 times and >13 times, respectively, the estimated C_{max} for the maximum clinical dose (300 mg 3 times weekly) of roxadustat.

Table 12. Single-dose toxicity studies

Species	Route of admini-stration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male/female (M/F) rat (SD)	Oral	0, 30, 100, 200, 300	Died or sacrificed moribund, 200 (F, 1/5), 300 (M, 5/5; F, 5/5) Hunchback position, emaciation, labored respiration, irregular respiration, feeling cold, unkempt fur, decrease in locomotor activity ≥30 mg/kg, increase in erythropoiesis, low total blood cholesterol ≥100 mg/kg, body weight decreased, decrease in food intake, low platelet count, high monocyte count, high blood urea nitrogen, high triglycerides, high total bilirubin, low blood potassium ≥200 mg/kg, high lymphocyte count 300 mg/kg, high white blood cell count	200	4.2.3.1-1
M/F cynomolgus monkey	Oral	0, 3, 30, 60, 100	≥3 mg/kg, increase in total blood iron levels, increase in plasma EPO concentrations	>100	Reference 4.2.3.1-2
	Intra-venous	3	3 mg/kg, increase in total blood iron levels, increase in plasma EPO concentrations	>3	Reference 4.2.3.1-2

5.2 Repeated-dose toxicity

Repeated oral-dose toxicity studies were conducted in mice (13 weeks), rats (4 and 26 weeks), and monkeys (4, 22, and 52 weeks) (Table 13). Major toxicity findings were effects on hematological parameters, an increase in bone marrow cell count/hyperplastic changes (mice, rats, and cynomolgus monkeys), systemic congestion, high spleen weight, and extramedullary hemopoiesis (mice and rats), change in iron parameters (rats and cynomolgus monkeys), and cardiac valvulopathy and thromboembolism (rats). These changes were deemed direct or secondary effect of increased erythropoiesis. In the 26-week repeated oral-dose toxicity study in rats (5 to 15 mg/kg/week), the exposure at the no-observed adverse effect level (NOAEL) were 2.61 to 4.96 times (C_{max}) and 0.46 to 0.95 times (AUC) the estimated exposure at the maximum clinical dose (300 mg, 3 times weekly). In the 52-week oral toxicity study in monkeys (30 mg/kg/week), the exposure at NOAEL were 2.61 times (C_{max}) and 0.44 times (AUC) the estimated exposure at the maximum clinical dose.

Table 13. Repeated-dose toxicity studies

Species	Route of admini-stration	Treatment period	Dose (mg/kg)	Major findings	No-observed adverse effect level (NOAEL) (mg/kg)	CTD
Male(M)/ female(F) mouse (ICR)	Oral	13 weeks (3 times weekly)	0, 10, 30, 60, 80/45[a)]	≥30 mg/kg, high MCV and MCH levels ≥60 mg/kg, high spleen weight and extramedullary hemopoiesis in the spleen	60	4.2.3.2-1
M/F mouse (ICR)	Oral	13 weeks (3 times weekly)	0, 60, 100, 150	Died or sacrificed moribund, 150 (male, 2/10) Emaciation, unkempt fur, hunchback position ≥60 mg/kg, increase in erythropoiesis, high spleen weight, extramedullary hemopoiesis in the spleen ≥100 mg/kg, the skin and the tongue turning deep dark red to purple; splenic swelling; congestion in the adrenal gland and bone marrow 150 mg/kg, high monocyte count (M), high blood total bilirubin (M), systemic organ congestion, marrow hyperplasia	60	Reference 4.2.3.2-2
M/F rat (SD)	Oral	4 weeks (once daily) + 4-week washout period	0, 2, 20, 60[b)]	Died or sacrificed moribund, 60 (male, 9/24; female, 10/24) Decrease in locomotor activity, emaciation, labored respiration, blackened rail end, reduced skin elasticity, reddish contamination around nose and mouth, paled liver color ≥20 mg/kg, low body weight; suppression of body weight increase; increase in erythropoiesis; low platelet count; polychromatic erythrocytes; high blood total bilirubin; high triglycerides; high total iron binding capacity (TIBC); high unsaturated iron binding capacity (UIBC); splenic swelling; the kidney color becoming darker; high spleen weight; hyperplasia of erythroid cells in the sternal marrow; extramedullary hemopoiesis in the spleen; chronic or chronic active valve inflammation, increased production, myxomatous degeneration, and fibrinous thrombus in the heart; glandular mucosal erosion, ulcer, and inflammation in the stomach; renal tubular degeneration; chronic progressive nephropathy; mesenteric lymph node hemorrhage; lung chronic or chronic active inflammation 20 mg/kg, low liver weight and darkened liver (M), red region in the lung (M), blackened lesion in the stomach (M) 60 mg/kg, red blood cells of unequal size; high blood alkaline phosphatase (ALP); swelling of the liver, high liver and kidney weight; hyperostosis, myelofibrosis, and thrombosis of femoral bone marrow; extramedullary hemopoiesis and hepatocellular hypertrophy in the liver; hyaline deposition in renal tubules and tubular pigmentation; thymus cortical atrophy; seminiferous epithelium atrophy of the testis; necrosis of adrenal cortex (F) Reversibility: partially reversible (high total bilirubin, high hemoglobin, and chronic inflammation of the heart valve were observed.)	2	4.2.3.2-3
M/F rat (SD)	Oral	26 weeks (3 times weekly) + 30-day washout period	0, 5, 15, 30,[c)] 40[c)]	Died or sacrificed moribund,[d)] 30 (M, 10/24), 40 (M, 5/24; F, 9/24) Adhesion and reddening of the cecum; watery yellow contents of the ileum; high spleen and heart weight; reddening of organs (e.g., kidney, lung, liver); faded kidney color; aortic thrombosis ≥5 mg/kg, reddening of extremities ≥15 mg/kg, high urine output, positive urine leukocyte test (M), increase in erythropoiesis, low platelet count,	<5[e)] (male) 5 (female)	4.2.3.2-4

Species	Route of admini-stration	Treatment period	Dose (mg/kg)	Major findings	No-observed adverse effect level (NOAEL) (mg/kg)	CTD
				increase in bone marrow cell count, extramedullary hemopoiesis in the spleen 30 mg/kg, high blood urea nitrogen (M), low blood potassium (M), splenic swelling (F), faded kidney color (F), high heart and spleen weight (F), gliosis (F) ≥30 mg/kg, hunchback position, positive urine occult blood test, high neutrophil count, high basophil count, high blood aspartate aminotransferase (AST), high total bilirubin, low blood calcium, low total protein, decrease in splenic hemosiderin, hemosiderin deposition in renal tubular epithelium, cardiac valvulopathy (atrioventricular valve, aortic valve), thromboembolism (renal infarct; basophilic tubule in infarct area; inflammation, hemorrhage and necrosis of digestive tract) 40 mg/kg, low body weight, decrease in food intake, hemoglobin pigmentation on renal tubular epithelium Reversibility: partially reversible (high spleen and heart weight; renal atrophy, scarring, and color fading; cardiac valvulopathy; thromboembolism; and hemorrhage, necrosis, and inflammation of the cecum were observed)		
M/F rat (F344)	Oral	26 weeks (3 times weekly) + 6-week washout period	0, 5, 15, 30, 40 [f)]	Died or sacrificed moribund,[g)] 30 (M, 2/24), 40 (M, 6/24; F, 4/24) High blood urea nitrogen, high creatinine, high inorganic phosphorus ≥5 mg/kg, erythroid hyperplasia in the femoral and sternal marrow ≥15, increase in erythropoiesis, low platelet count, high blood total bilirubin, high AST, high urea nitrogen, low blood glucose, high heart and spleen weight 30 mg/kg, low testis weight, testis atrophy and degeneration, testicular infarction ≥30 mg/kg, decrease in locomotor activity; hunchback position; labored respiration; abnormal breath sound; emaciation; soiled fur; unkempt fur; generalized weakening; positive urine occult blood test; high urine bilirubin; high urobilinogen; high white blood cell count; high kidney weight; splenic swelling; discoloration, thickening, and serosal adhesion of the ileum and cecum; softening, size reduction, and mottling of the testis; discolored region of the kidney; extramedullary hemopoiesis in the spleen; cardiac valvulopathy (e.g., thickening of left atrioventricular valve and aortic valve); renal tubular necrosis, tubular calcification, basophilic tubules, greenish brown granular pigmentation in tubular epithelial cells, and macrophage infiltration in the kidney; thromboembolism (necrosis of the glandular stomach, ileum, and cecum); necrosis of pyramidal cells in the hippocampus 40 mg/kg, clonic convulsion, limited movement of hindlimbs, lateral position, chronic progressive nephropathy Reversibility: partially reversible (erythroid hyperplasia in bone marrow, cardiac valvulopathy, chronic renal infarction, and tubular pigmentation were observed)	15	4.2.3.2-5

Species	Route of admini-stration	Treatment period	Dose (mg/kg)	Major findings	No-observed adverse effect level (NOAEL) (mg/kg)	CTD
M/F cynomolgus monkey	Oral	4 weeks (once daily) + 4-week washout period (control group and 30 mg/kg group)	0, 1, 10, 30	≥10 mg/kg, increase in erythropoiesis, low white blood cell count, low lymphocyte count, low blood total cholesterol 30 mg/kg, increase in erythroid erythropoiesis of bone marrow, high plasma EPO concentrations, low blood glucose, low serum iron (M), high blood UIBC and TIBC Reversibility: partially reversible (high hematocrit and high hemoglobin concentration were observed)	30	4.2.3.2-7
M/F cynomolgus monkey	Oral	22 weeks (3 times weekly) + 6-week washout period (control group, 30 and 40 mg/kg groups)	0, 1, 10, 30, 40[h)]	Died or sacrificed moribund, 40 (M, 1/5) Circulatory collapse, convulsion, lateral position, forming saliva, decrease in body temperature, hunchback position, limited movement of hindlimbs, indifference, reddening of the tongue, faded color and congestion of the cecum, colon, jejunum, and ileum ≥1 mg/kg, erythroid hyperplasia in the sternal marrow ≥10 mg/kg, red blood cells of unequal size, macrocytosis, polychromatic erythrocytes, reddening of the stomach (hemorrhage) ≥30 mg/kg, reddening of oral mucosa and gums; increase in erythropoiesis; high blood total bilirubin; low blood total cholesterol; low total blood iron; reddening of adipose tissue, bone marrow, thymus, and uterus; congestion of adipose tissue 40 mg/kg, high blood AST, low blood glucose, high blood transferrin, pulmonary thrombosis (M) Reversibility: partially reversible (reddening and hemorrhage of the stomach was observed)	30 (M) 40 (F)	4.2.3.2-8
M/F cynomolgus monkey	Oral	52 weeks (3 times weekly) + 8-week washout period	0, 3, 10, 20, 30	Died or sacrificed moribund,[i)] 3 (M, 1/7), 10 (M, 1/7) ≥20 mg/kg, increase in erythropoiesis, low blood total cholesterol	30	4.2.3.2-9

a) Due to the incidence of deaths in the 26-week oral intermittent dose toxicity study in Sprague-Dawley (SD) rats, which was conducted in parallel, the dose was reduced to 45 mg/kg from 80 mg/kg on Day 3.
b) Because the number of rats died or sacrificed moribund increased, all surviving rats in the 60 mg/kg group were sacrificed on Days 21 to 22.
c) Because the number of rats that died increased, treatment was discontinued in males in the 30 mg/kg group on Day 131, in males in the 40 mg/kg group on Day 61, and in females in the 40 mg/kg group on Day 98.
d) The animals were assessed to have erythrocytosis or related changes, which were attributed to markedly accelerated erythropoiesis.
e) Because mild cardiac valvulopathy occurred in 1 of 5 rats in the 5 mg/kg recovery group after the recovery period, the NOAEL was determined to be <5 mg/kg.
f) Due to increased deaths in male rats, treatment of males was discontinued on Day 119, and necropsies were performed.
g) Cardiac valvulopathy and thromboembolic lesion were determined to be the causes of moribund condition or early deaths.
h) Because circulatory collapse and circulatory disturbance, convulsion, spasm, syncope, mucosal reddening, and decrease in locomotor activity were noted in 2 males, doses were interrupted on Days 71 to 73 and Day 75.
i) It was concluded that the animals died of bacteremia because colonies of gram-positive bacteria were found in multiple organs.

5.3 Genotoxicity

Genotoxicity studies consisted of *in vitro* bacterial reverse mutation assays, an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes, and an *in vivo* mouse bone marrow micronucleus assay (Table 14). All assays tested negative, and thus roxadustat is unlikely to be genotoxic.

Table 14. Genotoxicity studies

Type of testing		Species/strain	S9 (treatment)	Concentration (µg/plate or µg/mL) dose (mg/kg/day)	Test result	CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*, TA98, TA100, TA1535, TA1537	−/+	0,[a)] 10, 33.3, 100, 333, 1000, 5000	Negative	4.2.3.3.1-1
		Escherichia coli, WP2*uvrA*				
	Chromosomal aberration assay in cultured mammalian cells	Human peripheral blood lymphocytes	− (3, 22 hours)	0, [a)] 25, 50, 100, 200	Negative	4.2.3.3.1-2
			+ (3 hours)	0, [a)] 100, 200, 250, 300		
In vivo	Micronucleus assay in rodents	Bone marrow of male Institute of Cancer Research (ICR) mice		0, 50, 150, 500 (oral, single dose)	Negative	4.2.3.3.2-1

a) DMSO

5.4 Carcinogenicity

Carcinogenicity studies in mice and rats were conducted (Table 15). It was concluded that roxadustat is not carcinogenic.

Table 15. Carcinogenicity studies

Species/ strain	Route of admini-stration	Treatment period	Major lesions	Sex	Dose (mg/kg)				Non-carcinogenic dose (mg/kg)	CTD
					0	15	30	60		
				n	60	60	60	60		
M/F mouse (ICR)	Oral	M, 104 weeks; F, 104 to 106 weeks (3 times weekly)	Neoplastic lesions						60	4.2.3.4.1-1
			Lung, bronchioloalveolar carcinoma[a)]	M	10	14	17	9		
				F	5	11	7	6		
			Lung, bronchioloalveolar adenocarcinoma[a)]	M	0	11	4	8		
				F	2	5	3	1		
			Systemic malignant lymphoma[b)]	M	5	2	3	5		
				F	9	10	7	16		
			Liver, hepatocellular adenoma[c)]	M	10	8	13	6		
				F	1	0	0	0		
			Mammary adenocarcinoma[d)]	M	NA	NA	NA	NA		
				F	1	0	5	3		
			Non-neoplastic lesions	F M	None					
			Major lesions	Sex	Dose (mg/kg)				Non-carcinogenic dose (mg/kg)	CTD
					0	2.5	5	10		
				n	75	75	75	75		
M/F rat (SD)	Oral	M, 104 weeks; F, 98 weeks (3 times weekly)	Neoplastic lesions						10	4.2.3.4.1-2
			Breast adenoma[e)]	M	2	0	0	0		
				F	8	11	23	9		
			Mammary adenocarcinoma	M	0	0	0	0		
				F	9	9	13	13		
			Fibroadenoma of breast	M	0	0	1	0		
				F	28	39	32	25		
			Spleen, angiosarcoma[f)]	M	0	0	0	2		
				F	0	0	0	0		
			Non-neoplastic lesions							
			Femoral bone marrow, increase in the number of cells	M	17	20	20	31		
				F	26	34	34	39		
			Sternal bone marrow, increase in the number of cells	M	18	22	21	33		
				F	24	33	31	34		
			Heart, atrial/aortic thrombosis	M	0	0	0	7		
				F	0	1	0	0		
			Liver, hepatocyte vacuolation	M	15	20	16	19		
				F	17	24	31	34		

NA, not applicable

a) The incidence of bronchioloalveolar adenocarcinoma in males in the 15 mg/kg group was greater than the range of historical data of ICR mice at the study site. However, the result was considered not associated with roxadustat, given that the incidence of other types of tumors was within the range of ICR mice data at the site, and because of no dose dependency observed.

b) The incidence in females in the 60 mg/kg group was greater than the range of historical data of ICR mice at the study site. However, the result was considered not associated with roxadustat, given that the incidence showed no statistically significant difference from that of the vehicle group and was within the range of ICR mice data at other study sites.

c) The incidence in males in the 30 mg/kg group was greater than the range of historical data of ICR mice at the study site. However, the result was considered not associated with roxadustat, given the small difference and no dose dependence or no statistically significant difference from that of the vehicle group.

d) The incidence in females at ≥30 mg/kg was the upper limit of the historical data, and the incidence showed no dose dependence or no statistically significant difference from the vehicle group. Therefore, it was concluded that the result was not associated with roxadustat.

e) Ale statistically significant high incidence was observed in females in the 5 mg/kg group as compared with the vehicle group. However, the result was considered not associated with roxadustat given that no statistically significant high incidence in females in the 10 mg/kg group as compared with the vehicle group.

f) The incidence in males in the 10 mg/kg group indicated no statistically significant difference as compared with the vehicle group. No similar types of tumors were observed in other groups. Spontaneous development of angiosarcoma of the spleen in 9-week old SD rats has been reported (*J Toxicol Pathol*. 2012;25:273-6). Thus, the finding was not associated with roxadustat.

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rats, embryonic and fetal development studies in rats and rabbits, and a study on prenatal and postnatal development and maternal function in rats were conducted (Table 16). In the study of fertility and early embryonic development to

implantation in rats, decreased embryonic survival, high post-implantation embryonic mortality, and high proportion of dams with embryonic deaths were noted. In the embryonic and fetal development studies, no teratogenicity was observed. In the study on prenatal and postnatal development and maternal function in rats, a high number of liveborn pup deaths, and developmental delays associated with low body weight of liveborn pups were observed. The exposure at the lowest-observed-adverse-effect-level (LOAEL; 5 mg/kg/day) for the development of F1 generation rats were 0.47 times (C_{max}) and 0.44 times (AUC) the estimated exposure at the maximum clinical dose (300 mg, 3 times weekly).

Table 16. Reproductive and developmental toxicity studies

Study type	Species	Route of admini-stration	Treatment period	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
Study of fertility and early embryonic development to implantation	M/F rat (SD)	Oral	Males: 2 weeks prior to mating throughout the mating period (3 times weekly) Females: 2 weeks prior to mating throughout the mating period (3 times weekly), during pregnancy (gestation days 0 to 7) (once daily)	0, 5, 15, 30	Males: Died or sacrificed moribund, 30 (1/25) Body weight decreased, the color of the lung becoming dark red ≥15 mg/kg, splenic swelling 30 mg/kg, dark reddening of the liver; low epididymis and seminal vesicle weight; high spleen weight No effects on sperm parameters or fertility Females: ≥15 mg/kg, accelerated body weight increase (prior to mating period), splenic swelling 30 mg/kg, decrease in food intake, (gestational days 7 to 8), increase in food intake (gestational days 10 to 13), low number of live embryos per dam, low embryonic survival rate, high post-implantation mortality, high proportion of dams with embryonic deaths, dark reddening of the liver, white region in the spleen, high liver and spleen weight	Parental animal (general toxicity), 5 Parental animal (fertility, early embryonic development), 30 (M); 15 (F)	4.2.3.5.1 -1
Embryo-fetal development study	F rat (SD)	Oral	Gestation days 7 to 17 (once daily) Cesarean section on gestation day 21	0, 5, 15, 30	Dams: ≥5 mg/kg, low platelet count ≥15 mg/kg, increase in erythropoiesis 30 mg/kg, transient suppression of body weight increase, decrease in food intake Fetuses: 30 mg/kg, low body weight, high placenta weight (M), high incidence of cervical rib[c)]	Dam (general toxicity), 15 Embryo-fetal development, 15	4.2.3.5.2 -2
	F rabbit (NZW)	Oral	Gestation days 7 to 19 (once daily) Cesarean section on gestation day 29	0, 15, 35, 100	Dams: ≥35 mg/kg, abortion, emaciation 100 mg/kg, suppression of body weight increase, decrease in food intake, abnormal stool consistency, increase in erythropoiesis Fetuses: No effects	Dam (general toxicity), 15 Embryo-fetal development, 100	4.2.3.5.2 -4

Study type	Species	Route of admini-stration	Treatment period	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
Study on prenatal and postnatal development and maternal function	F rat (SD)	Oral	Dams: gestation day 7 to lactation day 20 (once daily)	0, 5, 10, 20	Dams: ≥10 mg/kg, high hematocrit levels 20 mg/kg, accelerated body weight increase (gestation days 7 to 18), suppression of body weight increase, decrease in food intake (gestation days 18 to 20, lactation period), high proportion of dams with all fetuses dead, high spleen weight F1 pups: Preweaning ≥5 mg/kg, low body weight, delayed air-righting reflex, delayed acoustic startle response, early incisor eruption ≥10 mg/kg, low live pups, low nursing rate, dehydration, decrease in locomotor activity, early eyelid opening 20 mg/kg, marked decrease in surviving pups; pallor of the auricle, limbs, and whole body; hypothermia; soiled fur; emaciation; gastric residual of breast milk; low hematocrit levels Postweaning[a)] Died or sacrificed moribund, 10 (2/25 each for males and females) decrease in locomotor activity, dehydration, emaciation, eyelid ptosis, soiled fur, urine soiled fur on the abdomen, loss of righting reflex, bradypnea, feeling cold, low weight ≥5 mg/kg, low body weight, decrease in food intake, suppression of body weight increase, effects on performance of passive avoidance learning task, delayed sexual maturation, high testis and epididymis weight, low spleen weight F1 dams: 10 mg/kg, low mean corpus luteum, low number of implantations[b)] F2 pups: Abnormal external surface of fetus[c)] (5/608)	Dam (general toxicity, reproductive ability), 10 Development and reproductive ability of F1 pups, <5	4.2.3.5.3-1
Foster nursing study	F rat (SD)	Oral	Foster nursing: treatment during pregnancy or during lactation period No foster nursing: no treatment or treatment gestation day 7 to lactating day 20	0, 15	Dams: No effects Liveborn pups: Liveborn pups undergoing only postnatal exposure: Significant decrease in liveborn pup survival rate, dehydration, high proportion of pups not carried into the nest or not breastfed Liveborn pups undergoing intrauterine and/or postnatal exposure: High mortality, low body weight, low plasma iron Liveborn pups undergoing intrauterine and postnatal exposure: Significantly low body weight	—	4.2.3.5.3-2

a) Because of the high preweaning mortality, surviving pups in the 20 mg/kg group were sacrificed at the time of weaning.
b) Because the data are within the range of the historical data at the study site, the result was considered not associated with roxadustat.
c) Because of the low incidence and absence of abnormalities in F1 animals, the result was considered not associated with roxadustat.

5.6 Juvenile animal study

A toxicity study was conducted in juvenile rats (Table 17). The results were similar to those of repeated oral-dose toxicity studies in adult rats [see Section 5.2].

Table 17. Toxicity study in juvenile animals

Species	Route of administration	Treatment period	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
M/F rat (SD)	Oral	6 weeks (Postnatal days 15 to 56) (3 times weekly)	0, 15, 30, 60	Died or sacrificed moribund, 30 (M, 5/5; F, 5/5), 60 (M, 5/5; F, 5/5) Dehydration, decrease in locomotor activity, abnormal gait ≥15 mg/kg, low body weight, suppression of weight increase, increase in erythropoiesis, low blood total protein, low globulin, low albumin, high blood triglycerides, low serum iron 30 mg/kg, high blood potassium, high chlorine, low blood sodium ≥30 mg/kg, acute hemorrhage and acute thrombi in multiple tissues; blood clots in the pericardium; edema in the lung and thymus; erythrophagocytosis of the lung; hepatocellular necrosis and vacuolation; necrosis of femoral metaphysis, adrenal cortex, and adrenal medulla	—	Reference 4.2.3.5.4-2

5.7 Other toxicity studies

5.7.1 Phototoxicity

An *in vitro* phototoxicity study demonstrated that roxadustat is not phototoxic (Table 18).

Table 18. Phototoxicity study

Type of testing	Species/strain	Testing method	Major findings	CTD
Phototoxicity	Mouse fibroblast Balb/c 3T3	Test 1: 0.0027, 0.0048, 0.015, 0.027, 0.085, 0.15, 0.27, 0.48 mg/L Test 2: 0.0048, 0.0085, 0.015, 0.048, 0.085, 0.15, 0.27, 0.48 mg/L UVA irradiation	Not phototoxic (Photo irritation factor: −0.012 [Test 1], −0.003 [Test 2])	4.2.3.7.7-1

5.7.2 Impurity

A bacterial reverse mutation study was performed on Related Substance 1 of roxadustat. Based on the negative test results, it was concluded that Related Substance 1 would not induce gene mutation (Table 19).

Table 19. Impurity study

	Type of testing	Species/strain	S9 (treatment)	Concentration[a)] (µg/plate)	Test result	CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*, TA98, TA100, TA1535, TA1537	−/+	0,[b)] 50, 150, 500, 1500, 5000	Negative	4.2.3.7.7-2
		Escherichia coli, WP2*uvrA*				

a) Related Substance 1
b) DMSO

5.R Outline of the review conducted by PMDA

5.R.1 Toxicity profiles of roxadustat

The applicant's explanation about the toxicity profiles of roxadustat:

The general toxicity studies in rats and monkeys revealed high values in the red blood cell parameters, which were considered attributable to the pharmacological action (promoting erythropoiesis) of roxadustat. Cardiac valvulopathy was observed in the study in rats. Because cardiac valvulopathy is known to occur due to excessive erythropoiesis following high-dose ESA treatment (*Toxicol Pathol.* 2014;42:510-23, *Toxicol Pathol.* 2014;42:524-39), the cardiac valvulopathy in rats was attributed to increased blood viscosity resulting from increased red blood cells following the administration of roxadustat. Lesions with inflammation, hemorrhage, and necrosis in the kidney, lung, digestive organs, etc. were observed frequently in rats, and were considered associated with thromboembolism. Because the safety margin for these findings is 0.46-fold to 0.95-fold, and thromboembolism is caused by excessive pharmacological action of roxadustat (promoting erythropoiesis), the possibility cannot be ruled out that these events occur in the clinical use of roxadustat. However, given that the dose of roxadustat is adjusted according to Hb levels, and Hb levels are measured on a regular basis during roxadustat therapy, cardiac valvulopathy and thromboembolism resulting from excessive erythropoiesis are unlikely to pose a problem in the clinical use of roxadustat.

PMDA accepted the applicant's explanation.

5.R.2 Roxadustat therapy in pregnant women, nursing mothers, and women of childbearing potential

The applicant's explanation about roxadustat therapy in women who are or may be pregnant and women of childbearing potential:

In the study of fertility and early embryonic development to implantation in rats, decreased embryonic survival, high post-implantation mortality, and high embryonic mortality were observed in the 30 mg/kg group. The AUC for the 30 mg/kg group was 2.9 times the AUC at the maximum clinical dose (300 mg).

In the study on prenatal and postnatal development and maternal function in rats, low body weight of liveborn pups at ≥5 mg/kg and preweaning deaths of liveborn pups at ≥10 mg/kg were observed. The maternal AUC in the 5 and 10 mg/kg groups was approximately 0.4 times and 0.8 times, respectively, the estimated AUC following the maximum clinical dose.

Based on the above, the possibility cannot be ruled out that roxadustat affects the embryo, fetus, or liveborn pup in its clinical use, and roxadustat should not be given to women who are or may be pregnant. Women of childbearing potential treated with roxadustat require contraception during therapy and for a certain post-therapy period.

The applicant's explanation about roxadustat therapy in breastfeeding mothers:

The findings from the study on prenatal and postnatal development and maternal function in rats showed deaths of liveborn pups in the preweaning period at ≥10 mg/kg, developmental delays associated with

low body weight of liveborn pups at ≥5 mg/kg, and the transfer of roxadustat to breast milk after administration to dams (AUC at 5 and 10 mg/kg was 0.4 and 0.8 times, respectively, the estimated exposure at the maximum clinical dose). In a foster nursing study in rats, the survival rate of liveborn pups was lower in those exposed postnatally to roxadustat via breast milk. Body weight was lower in liveborn pups exposed to roxadustat both pre- and postnatally. Given that roxadustat was shown to be transferred into breast milk [see Section 4.4.3], the possibility cannot be ruled out that roxadustat may have directly affected liveborn pups via breast milk, reducing their survival rate and body weight. Therefore, when breastfeeding mothers need to receive roxadustat for a compelling reason, they should be advised not to breastfeed their child for a specified time period after the last dose.

PMDA accepted the applicant's explanation.

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

Table 20 shows formulations used in the major Japanese clinical studies (evaluation data) for the present application. For the change from Formulation A to the proposed commercial formulation, [redacted] and dissolution test were performed and demonstrated the bioequivalence between the 2 formulations.

Table 20. Formulations used in major Japanese clinical studies (evaluation data)

Clinical study	Formulation
Phase [redacted] studies ([redacted] study [Study CL-[redacted]], [redacted] study [Study CL-[redacted]]), phase [redacted] study (Study CL-[redacted])	**Formulation A: [redacted] (a [redacted] containing 20, 50, or 100 mg of roxadustat)**
Phase [redacted] studies ([redacted] [Study CL-[redacted]], drug-drug interaction studies [Studies CL-[redacted] CL-[redacted]]), phase III studies (Studies CL-0307, CL-0308), long-term treatment study (Study CL-0312), general clinical study (Study CL-0302)	**Proposed commercial formulation: Film-coated tablet (a tablet containing 20, 50, or 100mg of roxadustat)**

The concentrations of unchanged roxadustat in plasma, urine, and peritoneal dialysis fluid were measured by LC/MS/MS. The lower limit of quantitation was 1.0 ng/mL.

6.1.1 Japanese Phase I study (food effect) (CTD 5.3.1.1-1, Study 1517-CL-0202 [July 2016 to August 2016])

A randomized, open-label, 2-treatment, 2-period, crossover study was conducted in healthy Japanese adult men (target sample size, 16 subjects) at 1 study center in Japan to investigate the effect of food on the pharmacokinetics, etc. of a single oral dose of roxadustat 100 mg.

Subjects received a single oral dose of roxadustat 100 mg under fasting conditions or within 10 minutes of a high-fat meal.

All 16 randomized subjects were included in the pharmacokinetic analysis set. Pharmacokinetic data are summarized in Table 21. Subjects withdrew from the study for the following reasons: "consent withdrawal" and "adverse events"[6] in 1 subject each (1 subject each under fasting and fed conditions in Treatment Period 1).

Table 21. Pharmacokinetic parameters of unchanged roxadustat in plasma following the administration of roxadustat 100 mg under fasting or fed conditions

Treatment period	n	C_{max} (μg/mL)	t_{max} (h)[a]	AUC_{last} (μg·h/mL)	$t_{1/2}$ (h)
Fasting	15	10.4 (23.1)	2.00 (1.00, 4.00)	85.7 (21.8)	12.4 (31.1)
Fed	15	8.3 (21.5)	3.00 (1.00, 4.00)	81.2 (18.8)	11.9 (27.5)

Geometric mean value (geometric coefficient of variation, %)
a) Median (minimum value, maximum value)

The geometric mean ratios [90% confidence interval (CI)] of fed conditions to fasting conditions for C_{max} and $AUC_{0\text{-}inf}$ were 0.80 [0.72, 0.89] and 0.94 [0.90, 0.99], respectively. The applicant explained that the results were similar between subjects under fasting and fed conditions.

No adverse events occurred under fasting conditions, while adverse events occurred in 6.3% (1 of 16) of subjects under fed conditions (AST increased, blood creatine phosphokinase [CPK] increased, blood lactate dehydrogenase increased, and blood urine present). A causal relationship to roxadustat was ruled out for all of the events.

6.1.2 Studies using human biomaterials

6.1.2.1 Plasma protein binding (CTD 5.3.2.1-1, Study 1517-ME-0033)

The average plasma protein binding of roxadustat was 99.0% when ^{14}C-roxadustat (2 to 40 μg/mL) was added to human plasma, and no concentration dependence was observed within the concentration range studied. When ^{14}C-roxadustat (2 μg/mL) was added to 40 mg/mL of human serum albumin solution, 1 mg/mL of α_1- acid glycoprotein solution, and 10 mg/mL of γ-globulin solution, the average plasma protein binding of roxadustat was 99.1%, 3.5%, and 9.6%, respectively, suggesting that roxadustat binds primarily to albumin in human plasma.

6.1.2.2 Uptake into blood cells (CTD 5.3.2.1-2, Study 1517-ME-0032)

When ^{14}C-roxadustat (0.4 to 40 μg/mL) was added to human blood, the percentage uptake was 2.2% to 6.3%, and the blood-to-plasma concentration ratio of ^{14}C-roxadustat was 0.6 at all concentrations studied. The results indicated no evident concentration dependence, suggesting that uptake of roxadustat into blood cells is unlikely.

[6] Adverse events observed were AST increased, blood CPK increased, blood lactate dehydrogenase increased, and blood urine present, and a causal relationship to the study drug was ruled out for all of the events.

6.1.2.3 *In vitro* metabolite studies (CTD 5.3.2.2-1, 5.3.2.2-2, 5.3.2.2-3, 5.3.2.2-7, and 5.3.2.2-8, Studies 301_05_3010_029, 301_09_3520_132, 1517-ME-0201, 3520-13-007, and 3520-13-011)

The metabolic processes of main metabolites in human hepatocytes, namely, MET1 (4-*O*-β-glucuronidated roxadustat) and MET4 (4'-hydroxylated roxadustat), were studied.

Using human liver microsomes and the expression system of recombinant human cytochrome P450 (CYP) isoforms (CYP1A1, CYP1A2, CYP2A6, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5), CYP isoforms involved in the formation of MET4 were studied, and the results showed that MET4 was formed by CYP1A1 and CYP2C8. Lower expression levels of CYP1A1 in human liver microsomes suggested that the metabolic process from roxadustat to MET4 in the human liver is mediated by CYP2C8. Using human liver microsomes, human kidney microsomes, and the expression system of recombinant human uridine diphosphate-glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15, and UGT2B17), to which uridine diphosphate glucuronic acid was added, UGT isoforms involved in the formation of MET1 were studied. MET1 was formed from roxadustat by UGT1A7, UGT1A8, and UGT1A9. In human liver microsomes, UGT1A7 and UGT1A8 were not expressed, suggesting that the metabolic process from roxadustat to MET1 in the human liver is mediated by UGT1A9, and by UGT1A7 and UGT1A8 other than in the liver.

6.1.2.4 Induction of human hepatic drug-metabolizing enzymes by roxadustat (CTD 5.3.2.2-11, Study 3520-09-025)

Roxadustat (5 to 500 μmol/L) was incubated with human hepatocytes, and induction of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5) by roxadustat was studied. Roxadustat did not induce any of the CYP isoforms through enzymatic activity or mRNA within the concentration range studied.

6.1.2.5 Inhibition of human hepatic drug-metabolizing enzymes by roxadustat (CTD 5.3.2.2-9, 5.3.2.2-10, and 5.3.2.2-12, Studies 301_08_3510_123, 1517-ME-0048, and 352013008)

Roxadustat (0 to 1000 μmol/L) was incubated with human liver microsomes, and inhibition of the enzymatic activity of CYP isoforms[7)] (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) by roxadustat was studied. Roxadustat inhibited CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 with an IC_{50} of 370, 340, 230, 27, 320, and 370 μmol/L, respectively. Inhibition of other CYP isoforms was not observed within the concentration range studied.

[7)] The following compounds were evaluated as substrates: phenacetin (CYP1A2), coumarin (CYP2A6), bupropion (CYP2B6), paclitaxel (CYP2C8), diclofenac (CYP2C9), S-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), chlorzoxazone (CYP2E1), and midazolam and testosterone (CYP3A4/5).

Roxadustat (0 to 300 μmol/L) was incubated with human liver microsomes, and inhibition of the enzymatic activity of UGT isoforms[8)] (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was studied. Roxadustat inhibited UGT1A1, UGT1A3, UGT1A4, UGT1A9, and UGT2B7 with an IC_{50} of 58, 230, 31, 200, and 140 μmol/L, respectively. Roxadustat did not inhibit UGT1A6 within the concentration range studied.

The applicant's explanation:
Based on the above results, and in light of the exposure levels,[9)] plasma protein binding, and the maximum theoretical intestinal concentration[10)] of roxadustat in healthy adults treated with the recommended clinical dosage, roxadustat may inhibit CYP2C8 and UGT1A4 in the liver in its clinical use.

6.1.2.6 Study of substrate characteristics for transporters and inhibitory effect (CTD 5.3.2.3-2, 5.3.2.3-3, and 5.3.2.3-4, Studies 352013003, 352016009, and 3520-13-010)

The addition of 1, 10, or 100 μmol/L of ^{14}C-roxadustat to Lilly Laboratories Cell-Porcine Kidney 1 (LLC-PK1) cells expressing human Multidrug Resistance 1 (MDR1) demonstrated that roxadustat is not a substrate for P-glycoprotein (P-gp). The inhibitory effect of roxadustat (1 to 360 μmol/L) on P-gp was investigated.[11)] The IC_{50} of roxadustat was >360 μmol/L, the maximum concentration studied, suggesting that roxadustat is unlikely to inhibit P-gp.

^{14}C-roxadustat (0 to 300 μmol/L) was added to human embryonic kidney cell line 293 (HEK293) expressing human organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, organic anion transporter (OAT) 1, OAT3, or multidrug and toxic extrusion transporter (MATE) 1, membrane vesicles expressing human bile salt export pump (BSEP) or multidrug resistance protein 2 (MRP2), Martin-Darby canine kidney (MDCK) II cells expressing breast cancer resistance protein (BCRP). The results indicated that roxadustat is a substrate for OATP1B1, OAT1, OAT3, and BCRP, while it is not a substrate for OATP1B3, OCT1, OCT2, MATE1, BSEP, or MRP2.

Using HEK293 cells expressing OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2-K, membrane vesicles expressing BSEP, or MDCKII cells expressing BCRP, inhibitory effects[12)] of roxadustat on transporters were investigated. Roxadustat inhibited the transport activity of OATP1B1, OATP1B3, OAT1, OAT3, BSEP, and BCRP, with an IC_{50} of 2.59, 61.1, 20.4, 15.0, 86.7, and 3.05 μmol/L, respectively. Given that IC_{50} was 100 μmol/L for OCT1, >200 μmol/L for MATE2-K, and >300 μmol/L for OCT2 and MATE1, roxadustat is unlikely to inhibit the transporters in its clinical use.

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8) The following compounds were evaluated as substrates: 17β-estradiol (UGT1A1), chenodeoxycholic acid (UGT1A3), trifluoperazine (UGT1A4), 1-naphthol (UGT1A6), propofol (UGT1A9), and morphine (UGT2B7).
9) Based on the C_{max} of 12,512 ng/mL (35.51 μmol/L) following single-dose administration of roxadustat 200 mg to healthy adults in Study CL-0525, and the fraction of roxadustat unbound in blood of 0.01 obtained in Study 1517-ME-0033.
10) The maximum gastrointestinal concentration was obtained by dividing roxadustat 200 mg (clinical dose) by 250 mL.
11) Digoxin was evaluated as the substrate for P-gp.
12) The following compounds were evaluated as substrates: estradiol glucuronide (OATP1B1 and OATP1B3), tetraethylammonium bromide (OCT1), metformin (OCT2), *p*-aminohippuric acid (OAT1), estrone 3-sulfate (OAT3), metformin (MATE1 and MATE2-K), taurocholic acid (BSEP), and prazosin (BCRP).

The applicant's explanation:

Based on the above results and in light of the exposure levels,[9)] the percent plasma protein binding and the maximum theoretical intestinal concentration[10)] of roxadustat in healthy adults treated at the recommended clinical dose, roxadustat may inhibit BCRP, OATP1B1, OATP1B3, and OAT3 in its clinical use.

6.2 Clinical pharmacology

6.2.1 Japanese phase I single-dose and repeated-dose study (CTD 5.3.3.1-1, Study 1517-CL-0201 [August 2009 to June 2010])

6.2.1.1 Single oral dose study

A randomized, single-blind, placebo-controlled study was conducted in healthy Japanese adult men (target sample size, 40 subjects; 10 in the placebo group and 6 each in the roxadustat groups) to evaluate the pharmacokinetics, etc. of a single oral dose of roxadustat.

Subjects received a single oral dose of placebo or 0.3, 1, 2, 3, or 4 mg/kg of roxadustat.

All 40 subjects (10 in the placebo group and 6 each in the roxadustat groups) who were randomized and received the study drug were included in the pharmacokinetic analysis set.

Table 22 shows plasma pharmacokinetic parameters of unchanged roxadustat following single oral dose administration. The C_{max} and $AUC_{0\text{-}inf}$ increased in a dose-proportional manner.

Table 22. Plasma pharmacokinetic parameters of unchanged roxadustat following a single oral dose of roxadustat

Roxadustat dose	n	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)
0.3 mg/kg	6	1.9 ± 0.3	3.2 ± 0.8	13.8 ± 3.4	8.3 ± 0.9
1 mg/kg	6	5.4 ± 1.0	2.3 ± 0.5	43.6 ± 11.9	8.4 ± 2.3
2 mg/kg	6	12.9 ± 2.3	2.3 ± 1.0	99.7 ± 13.3	9.3 ± 2.1
3 mg/kg	6	18.9 ± 3.5	2.5 ± 0.8	139.3 ± 18.9	9.0 ± 1.9
4 mg/kg	6	20.8 ± 2.3	2.8 ± 1.0	168.8 ± 22.0	8.0 ± 0.5

Mean value ± standard deviation

6.2.1.2 Repeated oral dose study

A randomized, single-blind, placebo-controlled study was conducted in healthy Japanese adult men (target sample size, 60 subjects; 9 in each placebo groups and 7 in each roxadustat groups) to evaluate the pharmacokinetics and other parameters following multiple oral administration of roxadustat.

Subjects received placebo or 0.3, 1, or 3 mg/kg of roxadustat twice or 3 times weekly for 2 weeks.

All 60 subjects who were randomized and received the study drug (9 each in the placebo groups and 7 each in the roxadustat groups) were included in the pharmacokinetic analysis set.

Table 23 shows plasma pharmacokinetic parameters of unchanged roxadustat following oral administration of roxadustat 3 times weekly. The plasma unchanged roxadustat concentrations on Day 1 are similar to those on Day 12 following 3 times weekly administration, indicating that multiple-dose administration did not lead to the accumulation of roxadustat.

The plasma pharmacokinetic parameters of roxadustat following twice-weekly oral doses were similar to those following 3 times-weekly doses.

Table 23. Plasma pharmacokinetic parameters of unchanged roxadustat following multiple oral doses of roxadustat (3 times weekly)

Roxadustat dose	Measuring time point	n	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-24} (μg·h/mL)	$t_{1/2}$ (h)
0.3 mg/kg	Day 1	7	1.6 ± 0.2	2.0 ± 0.8	10.7 ± 1.3	9.9 ± 1.2
	Day 12	7	1.8 ± 0.4	2.1 ± 1.0	12.0 ± 1.6	10.4 ± 1.8
1.0 mg/kg	Day 1	7	5.4 ± 1.4	2.4 ± 1.9	37.4 ± 4.2	9.6 ± 1.1
	Day 12	7	5.2 ± 0.8	3.7 ± 1.3	39.7 ± 3.8	9.0 ± 1.6
3.0 mg/kg	Day 1	7	18.8 ± 4.2	1.7 ± 0.5	138.5 ± 32.9	9.9 ± 2.4
	Day 12	7	18.1 ± 2.5	2.4 ± 1.0	153.1 ± 31.9	9.7 ± 1.1

Mean ± standard deviation

6.2.2 Foreign mass balance study (CTD 5.3.3.1-5, Study FGCL-4592-058 [April 2012 to May 2012])

An open label study was conducted in healthy non-Japanese adult men (target sample size, 6 subjects) to investigate the mass balance, etc. following single oral administration of ^{14}C- roxadustat.

Subjects received a single oral dose of ^{14}C-roxadustat 200 mg under fasting conditions.

All 6 subjects enrolled in the study were included in the pharmacokinetic analysis set.

Table 24 shows the pharmacokinetic parameters of unchanged roxadustat. The AUC_{0-inf} of unchanged roxadustat represented 78.5% of the total radioactivity in plasma, indicating that unchanged roxadustat was the major compound in plasma.

Up to 192 hours post-dose, 45.8% and 50.4% of the administered radioactivity was excreted in urine, and feces, respectively. Besides unchanged roxadustat, other major metabolites detected include MET1 in urine, and MET4 in feces, representing 28.3% and 17.2% of the administered radioactivity, respectively.

Table 24. Plasma pharmacokinetic parameters following a single oral dose of ^{14}C-roxadustat

Roxadustat dose	n	Compound measured	C_{max} (μg/mL)	t_{max}[a)] (h)	AUC_{0-inf} (μg·h/mL)
200 mg	6	Unchanged roxadustat	16.0 ± 5.9	2.0 (1.5, 6.0)	108.7 ± 33.2

Mean value ± standard deviation

a) Median (minimum value, maximum value)

6.2.3 Japanese phase I study in hemodialysis patients with renal anemia (CTD 5.3.3.2-1, Study 1517-CL-0203 [February 2010 to June 2010])

An open-label, dose-escalation study was conducted in hemodialysis (HD) patients with renal anemia (target sample size, 12 subjects; 6/group) to investigate the effects of HD on the pharmacokinetics of roxadustat. All 12 subjects enrolled and received the study drug were included in the pharmacokinetic analysis set.

Patients received a single oral dose of 1 or 2 mg/kg of roxadustat before HD or 2.5 hours after HD.

Table 25 shows the plasma pharmacokinetic parameters of roxadustat. The applicant explained that HD had only a small impact on the pharmacokinetic parameters of roxadustat. Based on data from a Japanese phase II study in Japanese patients with renal anemia on dialysis (CL-0304) and a phase III studies (Studies CL-0302, 0307, and 0308), a population pharmacokinetic analysis[13)] was performed. No clear difference was observed in the pharmacokinetics of HD patients and peritoneal dialysis (PD) patients.

Table 25. Pharmacokinetic parameters of plasma unchanged roxadustat following a single oral dose of roxadustat in HD patients with renal anemia

Roxadustat dose	n	Treatment timing	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)
1 mg/kg	6	After HD	5.6 ± 1.3	2.3 ± 2.0	65.6 ± 24.3	15.5 ± 3.1
		2.5 hours before HD	4.4 ± 0.5	2.9 ± 0.9	56.6 ± 18.7	15.8 ± 5.1
2 mg/kg	6	After HD	13.0 ± 2.0	2.3 ± 1.2	149.9 ± 73.3	20.9 ± 10.5
		2.5 hours before HD	9.4 ± 1.2	2.8 ± 1.3	135.3 ± 80.5	16.2 ± 7.1

Mean value ± standard deviation

6.2.4 Foreign phase I study (effects of renal impairment) (CTD 5.3.3.3-2, Study 1517-CL-0543 [December 2016 to December 2017])

An open-label, parallel-group study in non-Japanese subjects with normal renal function (eGFR, ≥90 mL/min/1.73 m^2) and patients with severe renal impairment (eGFR, <30 mL/min/1.73 m^2) was conducted at 2 study centers outside Japan (target sample size, 24 subjects; 12/group) to investigate the effects of renal impairment on the pharmacokinetics of roxadustat.

Subjects received a single oral dose of roxadustat of 100 mg.

All 21 subjects enrolled in the study (12 in the normal renal function group and 9 in the severely impaired renal function group) were included in the pharmacokinetic analysis set.

The geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ in subjects with severe renal impairment to those in subjects with normal renal function, with its 90% confidence interval (CI), were 1.07 [0.87, 1.33] and 2.23 [1.85, 2.68], respectively, indicating that $AUC_{0\text{-}inf}$ of roxadustat increased due to renal impairment.

13) A PPK analysis (NONMEM ver.7.3) was performed using plasma roxadustat concentration data (367 subjects, 1285 time points) obtained from the Japanese phase II study (CL-0304), and phase III studies (Studies CL-0302, 0307, and 0308). The final model was described using a 2-compartment elimination model with first-order absorption, incorporating inter-individual variability in CL/F, Vc/F, and ka.

6.2.5 Foreign phase I study (effects of hepatic impairment) (CTD 5.3.3.3-3, Study 1517-CL-0513 [September 2013 to December 2013])

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

Subjects received a single oral dose of roxadustat 100 mg.

All 16 subjects (8/group) enrolled in the study and received the study drug were included in the pharmacokinetic analysis set.

The geometric mean ratio (subjects with moderate hepatic function/those with normal hepatic function) of unbound plasma roxadustat with its 90% CI was 1.16 [0.93, 1.45] for C_{max}, and 1.70 [1.19, 2.43] for $AUC_{0\text{-}inf}$, indicating that $AUC_{0\text{-}inf}$ of roxadustat increased due to hepatic impairment.

6.2.6 Foreign phase I studies (Studies on drug-drug interaction with CYP2C8 and OATP1B1 inhibitor, and with UGT and OAT inhibitor) (CTD 5.3.3.4-3 and CTD 5.3.3.4-8, Study 1517-CL-0508 [April 2015 to May 2015] and Study 1517-CL-0532 [April 2015 to June 2015])

The results from *in vitro* studies [see Section 6.1.2.3] and mass balance study [see Section 6.2.2] have demonstrated that roxadustat is metabolized primarily by CYP2C8 and UGT1A9. Findings from *in vitro* studies have suggested that roxadustat is a substrate for BCRP, OATP1B1, OAT1, and OAT3 [see Section 6.1.2.6]. Accordingly, effects of repeated-dose administration of gemfibrozil (CYP2C8 and OATP1B1 inhibitor) and probenecid (UGT and OAT inhibitor) on the pharmacokinetics of roxadustat were investigated in 2 studies in healthy non-Japanese adults (target sample size, 18 subjects).

Table 26 shows the geometric mean ratios for C_{max} and $AUC_{0\text{-}inf}$ of roxadustat (roxadustat + gemfibrozil or probenecid to roxadustat alone). The C_{max} and $AUC_{0\text{-}inf}$ of roxadustat were higher when gemfibrozil or probenecid was used concomitantly.

Table 26. The geometric mean ratios of plasma pharmacokinetic parameters of unchanged roxadustat administered with concomitant CYP2C8/OATP1B1 or UGT/OAT inhibitor

Roxadustat dose	Concomitant drug (oral administration)	n	C_{max}	$AUC_{0\text{-}inf}$
100 mg	Gemfibrozil 600 mg[a)]	18	1.37 [1.29, 1.46]	2.35 [2.15, 2.56]
	Probenecid 500 mg[b)]	18	1.38 [1.22, 1.56]	2.25 [2.14, 2.37]

Geometric mean ratio [90% CI]

a) Subjects received a single dose of 100 mg of roxadustat on Day 1, 600 mg of gemfibrozil twice daily from Days 5 to 13, and a single dose of 100 mg of roxadustat + gemfibrozil on Day 8. The geometric mean ratio (roxadustat + gemfibrozil to roxadustat alone) of C_{max} or $AUC_{0\text{-}inf}$ is presented.

b) Subjects received a single dose of 100 mg of roxadustat on Day 1, 500 mg of probenecid twice daily on Days 5 to 13, and a single dose of 100 mg of roxadustat + probenecid on Day 8. The geometric mean ratio (roxadustat + probenecid to roxadustat alone) of C_{max} or $AUC_{0\text{-}inf}$ is presented.

6.2.7 Foreign phase I studies (Studies on drug-drug interaction with CYP substrates) (CTD 5.3.3.4-4, 5.3.3.4-7, and 5.3.3.4-12, Studies 1517-CL-0509 [September 2013 to November 2013], 1517-CL-0531 [January 2015 to April 2015], and FGCL-4592-037 [March 2010 to May 2010])

Results from *in vitro* studies using human liver microsomes have suggested inhibition of CYP2B6, CYP2C8, and CYP2C9 by roxadustat [see Section 6.1.2.5]. Accordingly, effects of alternate-day oral doses of roxadustat on the pharmacokinetics of bupropion (CYP2B6 substrate), rosiglitazone (CYP2C8 substrate), and warfarin (CYP2C9 substrate) were investigated in 3 studies in healthy non-Japanese adults.

Table 27 shows the geometric mean ratios for C_{max} and $AUC_{0\text{-}inf}$ of the CYP substrates (each CYP substrate + roxadustat to each CYP substrate alone). No effects of concomitant roxadustat on the C_{max} or $AUC_{0\text{-}inf}$ of the CYP substrates were observed.

Table 27. The geometric mean ratios of plasma pharmacokinetic parameters of each CYP substrate administered with roxadustat

Roxadustat dose	Concomitant drug (oral administration)	n	Compound measured	C_{max}	$AUC_{0\text{-}inf}$
200 mg	**Bupropion 100 mg[a)]**	**24**	**Bupropion**	**1.03 [0.92, 1.15]**	**1.05 [1.00, 1.11]**
150 mg	**Rosiglitazone 4 mg[b)]**	**20**	**Rosiglitazone**	**0.90 [0.84, 0.96]**	**0.91 [0.89, 0.93]**
200 mg	**Warfarin 25 mg[c)]**	**22**	**S-warfarin**	**0.99 [0.93, 1.06]**	**1.12 [1.08, 1.15]**
			R-warfarin	**1.02 [0.97, 1.07]**	**1.11 [1.08, 1.14]**

Geometric mean ratio [90% CI]

a) Subjects received a single oral dose of bupropion 100 mg in Period 1; in Period 2, roxadustat 200 mg every other day on Days 1 to 13, and concomitant bupropion 100 mg on Day 7. The geometric mean ratio (with concomitant bupropion to without concomitant bupropion) for C_{max} or $AUC_{0\text{-}inf}$ is presented.

b) Subjects received a single oral dose of rosiglitazone 4 mg on Day 1, roxadustat 150 mg on Days 3, 5, and 7, every other day, and concomitant rosiglitazone 4 mg 2 hours after roxadustat administration on Day 9. The geometric mean ratio (with concomitant rosiglitazone to without concomitant rosiglitazone) for C_{max} or $AUC_{0\text{-}inf}$ is presented.

c) Subjects received a single oral dose of warfarin 25 mg in Period 1, roxadustat 200 mg every other day from Days 1 to 15 and concomitant warfarin 25 mg on Day 7 in Period 2. The geometric mean ratio (with concomitant warfarin to without concomitant warfarin) for C_{max} or $AUC_{0\text{-}inf}$ is presented.

6.2.8 Foreign phase I studies (Studies on drug-drug interaction with OATP1B1 substrates) (CTD 5.3.3.4-9 to 11, Studies 1517-CL-0537 [July 2014 to September 2014], 1517-CL-0538 [July 2014 to August 2014], and 1517-CL-0541 [March 2015 to May 2015])

Results from *in vitro* studies have suggested the inhibitory effect of roxadustat on transport activity of OATP1B1, OATP1B3, OAT3, and BCRP [see Section 6.1.2.6]. Accordingly, the effects of roxadustat on the pharmacokinetics of simvastatin (the acid form of simvastatin, an active metabolite of simvastatin, is a substrate for OATP1B1), rosuvastatin (a substrate for OATP1B1, OATP1B3, OAT3, and BCRP), and atorvastatin (a substrate for OATP1B1 and OATP1B3) were investigated in 3 studies in healthy non-Japanese adults.

Table 28 shows the geometric mean ratios (with concomitant roxadustat to without concomitant roxadustat) of each OATP1B1 substrate for C_{max} and $AUC_{0\text{-}inf}$. There were increases in the C_{max} and

$AUC_{0\text{-inf}}$ of unchanged simvastatin, the acid form of simvastatin, unchanged rosuvastatin, and unchanged atorvastatin when roxadustat was used concomitantly.

Table 28. The geometric mean ratios of plasma pharmacokinetic parameters of each OATP1B1 substrate with concomitant roxadustat

Roxadustat dose	Concomitant drug (oral administration)	Dose timing of concomitant drug	n	Compound measured	C_{max}	$AUC_{0\text{-inf}}$
200 mg	Simvastatin 40 mg	Together with roxadustat[a)]	28	Simvastatin	1.87 [1.56, 2.23]	1.75 [1.47, 2.09]
		2 hours before roxadustat[b)]	24		2.32 [1.92, 2.79]	1.68 [1.44, 1.96]
		4 hours after roxadustatn[b)]			3.10 [2.57, 3.74]	1.74 [1.50, 2.03]
		10 hours after roxadustat[b)]			2.39 [1.98, 2.87]	1.56 [1.34, 1.82]
		Together with roxadustat[a)]	28	Acid form of simvastatin	2.76 [2.34, 3.24]	1.85 [1.54, 2.23]
		2 hours before roxadustat[b)]	24		2.34 [1.99, 2.76]	1.89 [1.62, 2.21]
		4 hours after roxadustat[b)]			5.98 [5.08, 7.04]	3.42 [2.94, 3.99]
		10 hours after roxadustat[b)]			3.37 [2.86, 3.97]	2.51 [2.16, 2.93]
	Rosuvastatin 10 mg	Together with roxadustat[c)]	28	Rosuvastatin	4.47 [3.86, 5.18]	2.93 [2.63, 3.25]
	Atorvastatin 40 mg	Together with roxadustat[d)]	24	Atorvastatin	1.34 [1.11, 1.63]	1.96 [1.71, 2.26]

Geometric mean ratio [90% CI]

a) Subjects received an oral dose of simvastatin 40 mg on Day 1, roxadustat 200 mg every other day on Days 7 to 23, and simvastatin 40 mg and roxadustat 200 mg simultaneously on Day 13. The geometric mean ratio (with concomitant simvastatin to without concomitant simvastatin) for C_{max} or $AUC_{0\text{-inf}}$ is presented.

b) Subjects received an oral dose of simvastatin 40 mg on Day 1, roxadustat 200 mg every other day on Days 3 to 17, and a single oral dose of simvastatin 40 mg concomitantly 2 hours before, 4 hours after, or 10 hours after administration of roxadustat on Days 9, 13, or 17. The geometric mean ratio (with concomitant simvastatin to without concomitant simvastatin) for C_{max} or $AUC_{0\text{-inf}}$ is presented.

c) Subjects received an oral dose of rosuvastatin 10 mg on Day 3, roxadustat 200 mg every other day on Days 7 to 23, and a single oral dose of 10 mg of rosuvastatin and 200 mg of roxadustat simultaneously on Day 17. The geometric mean ratio (with concomitant rosuvastatin to without concomitant rosuvastatin) for C_{max} or $AUC_{0\text{-inf}}$ is presented.

d) Subjects received an oral dose of atorvastatin 40 mg on Day 1, roxadustat 200 mg every other day on Days 4 to 14, and an oral dose of atorvastatin 40 mg and an oral dose of roxadustat 200 mg simultaneously on Day 10. The geometric mean ratio (with concomitant atorvastatin to without concomitant atorvastatin) for C_{max} or $AUC_{0\text{-inf}}$ is presented.

6.2.9 Japanese and foreign phase I studies (Studies on drug-drug interaction with phosphate binders) (CTD 5.3.3.4-2 and 5.3.3.4-5, Studies 1517-CL-0205 [November 2016 to December 2016] and 1517-CL-0526 [July 2014 to October 2014])

A study was conducted in healthy non-Japanese adults to investigate the effects of sevelamer carbonate or calcium acetate on the pharmacokinetics of roxadustat. Another study in healthy Japanese adults was conducted to investigate the effects of lanthanum carbonate hydrate on the pharmacokinetics of roxadustat.

Table 29 shows the geometric mean ratios (with concomitant phosphate binder to without concomitant phosphate binder) for the C_{max} and $AUC_{0\text{-inf}}$ of roxadustat. There were no effects on the C_{max} and $AUC_{0\text{-inf}}$ of roxadustat when roxadustat and lanthanum carbonate hydrate were administered together. In contrast, C_{max} and $AUC_{0\text{-inf}}$ of roxadustat decreased when roxadustat was administered with sevelamer

carbonate or calcium acetate together. The applicant explained that, with the exception of phosphate-binding polymers or lanthanum carbonate hydrate, when a phosphate binder containing multivalent cations is administered simultaneously with roxadustat, blood roxadustat concentrations may decrease, attenuating the effect of roxadustat. This risk will be communicated to healthcare professionals via the package insert

Table 29. The geometric mean ratios of plasma pharmacokinetic parameters of unchanged roxadustat with concomitant use of phosphate binders

Roxadustat dose	Concomitant drug (oral administration)	Dose timing of roxadustat	n	C_{max}	$AUC_{0\text{-}inf}$
200 mg	Sevelamer carbonate (2400 mg, 3 times daily)[a)]	Together with sevelamer carbonate	24	0.34 [0.31, 0.38]	0.33 [0.31, 0.36]
		1 hour before sevelamer carbonate administration	30	0.74 [0.68, 0.82]	0.59 [0.56, 0.63]
		1 hour after sevelamer carbonate administration		0.88 [0.79, 0.97]	0.76 [0.72, 0.81]
	Calcium acetate (1900 mg, 3 times daily)[a)]	Together with calcium acetate	24	0.48 [0.43, 0.54]	0.54 [0.49, 0.58]
		1 hour before calcium acetate administration	30	0.81 [0.73, 0.89]	0.69 [0.65, 0.73]
		1 hour after calcium acetate administration		0.98 [0.89, 1.07]	0.83 [0.78, 0.88]
100 mg	Lanthanum carbonate hydrate (750 mg, 3 times daily)[b)]	Together with lanthanum carbonate hydrate	18	0.88 [0.84, 0.92]	0.99 [0.93, 1.05]

Geometric mean ratio [90% CI]

a) The study consisted of Parts 1 and 2. In Part 1, on Days 1, 6, and 11, subjects received either one of the following: roxadustat 200 mg alone; roxadustat 200 mg and sevelamer carbonate 2400 mg together; or roxadustat 200 mg and calcium acetate 1900 mg together. In Part 2, on Days 1, 6, 11, 16, and 21, subjects received either one of the following: roxadustat 200 mg alone; roxadustat 200 mg followed by sevelamer carbonate or calcium acetate 1 hour later; sevelamer carbonate or calcium acetate followed by roxadustat 1 hour later; sevelamer carbonate or calcium acetate followed by roxadustat 2 hours later; or sevelamer carbonate or calcium acetate followed by roxadustat 3 hours later. The geometric mean ratio (with concomitant phosphate binder to without concomitant phosphate binder) for C_{max} or $AUC_{0\text{-}inf}$ is presented.

b) The study consisted of Periods I and II. On Day 1 in each period, subjects received roxadustat 100 mg alone immediately after breakfast, or roxadustat 100 mg concomitantly with lanthanum carbonate hydrate 750 mg immediately after breakfast. From immediately after lunch on Day 1 to immediately after supper on Day 2, lanthanum carbonate hydrate 750 mg was administered 3 times daily. The geometric mean ratio (with concomitant lanthanum carbonate hydrate to without concomitant lanthanum carbonate hydrate) for C_{max} or $AUC_{0\text{-}inf}$ is presented.

6.2.10 Japanese phase I study (Study on drug-drug interaction with spherical adsorptive carbon) (CTD 5.3.3.4-1, Study 1517-CL-0204 [February 2016 to April 2016])

A study was conducted in healthy Japanese adults to investigate the effects of spherical adsorptive carbon (fine granules) on the pharmacokinetics of roxadustat.

The geometric mean ratio (with concomitant spherical adsorptive carbon to without concomitant spherical adsorptive carbon) and its 90% CI was 0.89 [0.82, 0.97] for C_{max} and 0.90 [0.86, 0.95] for $AUC_{0\text{-}inf}$, indicating no effects of the concomitant spherical adsorptive carbon on the C_{max} or $AUC_{0\text{-}inf}$ of roxadustat.

6.2.11 Foreign phase I study (Study on drug-drug interaction with omeprazole) (CTD 5.3.3.4-6, Study 1517-CL-0527 [September 2014 to November 2014])

A study was conducted in healthy non-Japanese adults to investigate the effects of omeprazole[14)] on the pharmacokinetics of roxadustat.

Subjects received either a single oral dose of roxadustat 100 mg, or oral omeprazole 40 mg once daily from Days 1 to 9 and an oral roxadustat 100 mg on Day 7.

The geometric mean ratio (roxadustat + omeprazole to roxadustat alone) and its 90% CI was 1.04 [0.91, 1.20] for C_{max} and 1.04 [0.98, 1.12] for $AUC_{0\text{-}inf}$ of unchanged roxadustat, indicating no effects of the concomitant omeprazole on the C_{max} or $AUC_{0\text{-}inf}$ of roxadustat.

6.2.12 Foreign phase I study (QT/QTc evaluation study) (CTD 5.3.4.1-1, Study FGCL-4592-065 [June 2012 to August 2012])

A randomized, double-blind,[15)] placebo and active controlled, 4-treatment, 4-period crossover study was conducted in healthy non-Japanese adults (target sample size, 48 subjects) at 1 study center outside Japan to investigate the effect of a single oral dose of roxadustat on QT/corrected QT (QTc) intervals.

Subjects received a single oral dose of placebo, roxadustat 2.75 or 5 mg/kg, or a positive control of moxifloxacin 400 mg under fasting conditions.

All 45 randomized subjects received the study drug. The QTc analysis set and pharmacokinetic analysis set included 44 subjects for the placebo, moxifloxacin, and roxadustat 2.75 mg/kg treatment periods, except 1 discontinued, and 43 subjects for the roxadustat 5 mg/kg treatment period, except 2 discontinued. The reasons for discontinuation were “lost to follow-up” and “consent withdrawal” in 1 subject each.

The maximum difference from placebo in change from baseline in individual-corrected QT interval (QTcI) (ΔΔQTcI) was −6 milliseconds at roxadustat 2.75 mg/kg and −7 milliseconds at roxadustat 5 mg/kg, both resulting in <10 milliseconds. In contrast, the maximum ΔΔQTcI in the moxifloxacin treatment period was 15 milliseconds, indicating that the lower limit of 90% CI was >5 milliseconds. It was therefore concluded that sufficient analytical sensitivity was achieved.

The geometric mean (geometric coefficient of variation) of C_{max} and $AUC_{0\text{-}inf}$ of unchanged roxadustat was 15,091 ng/mL (19.1%) and 111,662 ng·h/mL (23.3%), respectively, in the roxadustat 2.75 mg/kg treatment period, and 28,715 ng/mL (20.9%) and 242,080 ng·h/mL (21.8%), respectively, in the roxadustat 5 mg/kg treatment period.

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14) The effects of omeprazole on the pharmacokinetics of roxadustat were studied because the solubility of roxadustat increases with increase in pH, and omeprazole is a proton pump inhibitor, which alters exposure to drugs with pH-dependent solubility.

15) The active control drug (moxifloxacin) was given unblinded.

Adverse events occurred in 13.6% (6 of 44) of subjects in the placebo period, 20.5% (9 of 44) of subjects in the roxadustat 2.75 mg/kg treatment period, 53.5% (23 of 43) of subjects in the roxadustat 5 mg/kg treatment period, and 22.7% (10 of 44) of subjects in the moxifloxacin treatment period. Adverse events that occurred in ≥5 subjects in the roxadustat 2.75 or 5 mg/kg treatment period were headache (6 in the roxadustat 2.75 mg/kg period and 11 in the 5 mg/kg period), and nausea (5 in the roxadustat 2.75 mg/kg period and 5 in the 5 mg/kg period). Adverse drug reactions occurred in 9.1% (4 of 44) of subjects in the placebo period, 15.9% (7 of 44) of subjects in the roxadustat 2.75 mg/kg treatment period, 46.5% (20 of 43) of subjects in the roxadustat 5 mg/kg treatment period, and 18.2% (8 of 44) of subjects in the moxifloxacin treatment period.

6.R Outline of the review conducted by PMDA

6.R.1 Effects of other drugs on the pharmacokinetics of roxadustat

The applicant's explanation about the effects of CYP2C8, OATP1B1, UGT, and OAT inhibitors on the pharmacokinetics of roxadustat:

The results of the foreign drug-drug interaction studies (Studies CL-0508 and CL-0532) demonstrated that the CYP2C8 and OATP1B1 inhibitor (gemfibrozil) and the UGT and OAT inhibitor (probenecid) increased roxadustat exposure [see Section 6.2.6]. In Japanese phase III studies (anemia correction study in HD patients, conversion/maintenance study in HD patients, and long-term study), the effect of the concomitant use of CYP2C8, OATP1B1, UGT, or OAT inhibitor, which is one of patient characteristic factors, on safety was investigated. There were no differences in the incidence of adverse events that could cause clinical problems associated with the concomitant use of these inhibitors. Based on the results, while exposure to roxadustat may increase when CYP2C8, OATP1B1, UGT, or OAT inhibitor is used concomitantly, given that the dose of roxadustat is adjusted according to Hb levels, and Hb levels are monitored on a regular basis, there are no particular problems with CYP2C8, OATP1B1, UGT, or OAT inhibitor being used concomitantly with roxadustat at present

PMDA's view:

At present, the concomitant use of CYP2C8, OATP1B1, UGT, or OAT inhibitor with roxadustat is unlikely to cause clinically significant problems. However, increased roxadustat exposure by these inhibitors should be communicated to healthcare professionals via the package insert.

6.R.2 Effects of roxadustat on pharmacokinetics of other drugs

The applicant's explanation about the effects of roxadustat on the pharmacokinetics of drugs that are the substrates for OATP1B1, OATP1B3, OAT3, and BCRP:

The results of foreign studies on drug-drug interaction (Studies CL-0537, CL-0538, and CL-0541) demonstrated that roxadustat increased the exposure to simvastatin (the acid form of simvastatin, an active metabolite of simvastatin, is a substrate for OATP1B1), rosuvastatin (a substrate for OATP1B1, OATP1B3, OAT3, and BCRP), and atorvastatin (a substrate for OATP1B1 and OATP1B3) [see Section 6.2.8]. Increased exposure to simvastatin and its acid form was observed not only when roxadustat and simvastatin were administered together, but also when simvastatin was administered 2 hours before, 4

hours after, and 10 hours after administration of roxadustat. However, no definite reason for the increase was concluded. Based on the above, the possibility should be highlighted in the package insert that the use of roxadustat with concomitant HMG-CoA reductase inhibitors such as simvastatin, rosuvastatin, and atorvastatin causes adverse drug reactions associated with increased exposure to these inhibitors.

PMDA's view:

When roxadustat was used concomitantly with simvastatin, rosuvastatin, or atorvastatin, exposure to these HMG-CoA reductase inhibitors increased. Exposure to simvastatin increased not only when simvastatin and roxadustat were administered at the same time, but also when simvastatin was administered 2 hours before, 4 hours after, and 10 hours after administration of roxadustat, suggesting that exposure to HMG-CoA reductase inhibitors may be elevated even when there is a dosing interval between roxadustat and an HMG-CoA reductase inhibitor. HMG-CoA reductase inhibitors are myotoxic. Of the 132 subjects who received HMG-CoA reductase inhibitors concomitantly in Japanese phase III studies, 1 PD patient who received pravastatin concomitantly with roxadustat experienced rhabdomyolysis, and the event was assessed as a serious adverse drug reaction [See Section 7.2.4]. Accordingly, possible muscle disorders attributed to increased exposure to concomitant simvastatin, rosuvastatin, atorvastatin, or other HMG-CoA reductase inhibitors should be communicated to healthcare professionals via the package insert. Safety information including the occurrence of muscle disorders following treatment with roxadustat plus a concomitant HMG-CoA reductase inhibitor should be continuously collected via the post-marketing surveillance.

6.R.3 Effects of hepatic impairment on the pharmacokinetics of roxadustat

The applicant's explanation about the reason for elevated $AUC_{0\text{-}inf}$ of roxadustat in subjects with moderate hepatic impairment in the foreign phase I study (Study CL-0513):

Roxadustat is metabolized primarily by CYP2C8 and UGT1A9. The activity and expression of CYP are known to decrease in patients with hepatic impairment (*Clin Pharmacokinet.* 2010;49:189-206). While roxadustat is suggested to be a substrate for BCRP, OATP1B1, OAT1, and OAT3 [see Section 6.1.2.6], even the expression of OATP1B1 is shown to decrease in patients with hepatic impairment (*Drug Metab Dispos.* 2016;44:1752-8). Therefore, increased $AUC_{0\text{-}inf}$ of roxadustat in subjects with moderate hepatic impairment is attributable to the decline in the clearance of CYP2C8 and OATP1B1, the major routes of elimination, due to hepatic impairment.

PMDA's view:

Hepatic impairment may increase exposure to roxadustat. Healthcare professionals should be advised via the package insert that patients with moderate or severe hepatic impairment be closely monitored for their condition during roxadustat therapy, which may be started at a reduced dose.

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

The applicant submitted the results of 5 Japanese clinical studies as evaluation data (Table 30).

Table 30. Summary of evaluation data on efficacy and safety

Phase	Study ID (objective)	Target patients	Design (treatment period)	Group, number of subjects	Primary endpoint
Phase II	1517-CL-0304 (dose-finding)	HD patients in washout period of ESA therapy	Randomized, double-blind, uncontrolled (24 weeks)	Starting dose (up to Week 6) Roxadustat 50 mg, 33 Roxadustat 70 mg, 32 Roxadustat 100 mg, 32 Darbepoetin alfa (genetical recombination) (DA) 20 µg (Reference group), 32 Maintenance dose (from Week 6) Roxadustat 0-200 mg (adjust dose) DA 10-60 µg (adjust dose)	Rate of rise in Hb (g/dL/week) up to Week 6 (mean ± standard deviation) Roxadustat 50 mg, −0.219 ± 0.585 Roxadustat 70 mg, −0.046 ± 0.581 Roxadustat 100 mg, 0.112 ± 0.513 DA 20 µg (Reference group), 0.112 ± 0.174
Phase III	1517-CL-0307 (conversion /maintenance study)	HD patients (converting from ESA therapy)	Randomized, double-blind, active-controlled (24 weeks)	Starting dose (up to Week 4) Roxadustat 70 or 100 mg, 150 DA 10-60 µg, 152 Maintenance dose (from Week 4) Roxadustat 20-300 mg (adjust dose) DA 10-180 µg (adjust dose)	Change from baseline in the mean Hb values at the end of treatment (Weeks 18-24) (least squares mean ± standard error) (g/dL) Roxadustat, −0.04 ± 0.06 DA, −0.03 ± 0.06
Phase III	1517-CL-0312 (conversion /maintenance and long-term study)	HD patients (converting from ESA therapy)	Open-label, uncontrolled (52 weeks)	Starting dose (up to Week 4) Roxadustat 70 mg, 100 Roxadustat 100 mg, 63 Maintenance dose (from Week 4) Roxadustat 20-300 mg (adjust dose)	Percentage of subjects whose Hb values stayed within the target range [95% CI] (%) Weeks 18-24 Roxadustat 70 mg, 83.0 [74.2, 89.8] Roxadustat 100 mg, 73.0 [60.3, 83.4] Weeks 46-52 Roxadustat 70 mg, 74.0 [64.3, 82.3] Roxadustat 100 mg, 66.7 [53.7, 78.0]
Phase III	1517-CL-0308 (anemia correction study)	ESA-naïve, HD patients	Randomized, open-label, uncontrolled (24 weeks)	Starting dose (up to Week 4) Roxadustat 50 mg, 37 Roxadustat 70 mg, 38 Maintenance dose (from Week 4) Roxadustat 20-300 mg (adjust dose)	Cumulative response rate at the end of treatment from baseline (from Week 18 to Week 24) [95% CI] (%) Roxadustat 50 mg, 86.5 [71.2, 95.5] Roxadustat 70 mg, 89.2 [74.6, 97.0]
Phase III	1517-CL-0302 (anemia correction, conversion/maintenance study)	ESA-naïve, PD patients converting from ESA therapy)	Randomized, open-label, uncontrolled (24 weeks)	Starting dose (up to Week 4) ESA-naïve patients: Roxadustat 50 mg, 6 Roxadustat 70 mg, 7 Patients converting from ESA therapy: Roxadustat 70 mg, 23 Roxadustat 100 mg, 20 Maintenance dose (from Week 4) Roxadustat 20-300 mg (adjust dose)	Percentage of subjects whose Hb values stayed within the target range from Week 18 to Week 24 [95% CI] (%) ESA-naïve patients Roxadustat 50 mg, 83.3 [35.9, 99.6] Roxadustat 70 mg, 100.0 [59.0, 100.0] Patients converting from ESA therapy Roxadustat 70 mg, 82.6 [61.2, 95.0] Roxadustat 100 mg, 65.0 [40.8, 84.6]

Subjects in the roxadustat group received the drug orally 3 times weekly. Subjects in the DA group received the drug intravenously once weekly.

7.1 Phase II study

7.1.1 Japanese phase II study in patients on HD undergoing a specified period of ESA washout (dose-finding study) (CTD 5.3.5.1-1, Study 1517-CL-0304 [March 2013 to September 2014])

A multi-center, randomized, double-blind, parallel-group study was conducted at 28 study centers in Japan to assess the efficacy, safety, and dose-response of roxadustat in adult patients on HD undergoing a specified period of washout[16)] after ESA therapy (Table 31) (target sample size, 120 subjects; 30/group).

16) The washout period was specified as ≥2 weeks for recombinant human erythropoietin (rHuEPO), ≥3 weeks for DA, and ≥5 weeks for epoetin beta pegol (genetical recombination; CERA).

Table 31. Main inclusion/ exclusion criteria

Main inclusion criteria • **Patients with stable-stage chronic kidney disease (CKD) who have been on 3 times a week HD for ≥12 weeks prior to enrollment** • **Patients who had an Hb value of ≥10.0 g/dL during ESA treatment, and an Hb value of <9.5 g/dL after interruption of ESA therapy** • **Patients with a post-HD body weight of ≥40 kg and <80 kg** **Main exclusion criteria** • **Patients who received ESA during the washout period or had an Hb value below 7.0 g/dL** • **Patients with retinal neovascularization lesions requiring treatment (e.g., proliferative diabetic retinopathy, exudative age-related macular degeneration, retinal vein occlusion, and macular edema)**

From the start of the treatment to Week 6, roxadustat 50, 70, or 100 mg was administered orally 3 times weekly, or DA 20 μg once weekly intravenously.[17)] From Weeks 6 to 24, oral roxadustat 0 to 200 mg was administered 3 times weekly to subjects in each roxadustat group, and intravenous DA 10 to 60 μg was administered once weekly to subjects in the DA group so that pre-dialysis Hb values stayed within the target range (10.0 to 12.0 g/dL). Subjects in the DA group received the drug under unblinded conditions.

Of the 130 randomized subjects, 1 subject withdrew from the study due to "consent withdrawal" before the start of study drug treatment. The remaining 129 subjects (33 in the roxadustat 50 mg group, 32 in the roxadustat 70 mg group, 32 in the roxadustat 100 mg group, and 32 in the DA 20 μg group) received the study drug and were included in the safety analysis set. Of the 129 subjects who received the study drug, except 2 subjects who did not have baseline Hb measurements, 127 subjects (32 in the roxadustat 50 mg group, 32 in the roxadustat 70 mg group, 31 in the roxadustat 100 mg group, and 32 in the DA 20 μg group) were included in the full analysis set (FAS), which was the main efficacy analysis set. Treatment discontinuation occurred in 50 subjects (18 in the roxadustat 50 mg group, 10 in the roxadustat 70 mg group, 14 in the roxadustat 100 mg group, and 8 in the DA 20 μg group). The reasons for discontinuation were "Hb value of <8.0 g/dL" in 31 subjects (12 in the roxadustat 50 mg group, 8 in the 70 mg group, 6 in the 100 mg group, and 5 in the DA 20 μg group), "consent withdrawal" in 7 subjects (3 in the roxadustat 50 mg group and 4 in the 100 mg group), "adverse events" in 6 subjects (1 in the roxadustat 50 mg group, 2 in the 70 mg group, and 3 in the 100 mg group), "need for prohibited concomitant medication/therapy" in 3 subjects (2 in the roxadustat 50 mg group and 1 in the DA 20 μg group), "death" in 1 subject (roxadustat 50 mg group), "protocol deviation" in 1 subject (roxadustat 50 mg group), and "the discontinuation criteria for the study drug dose increase/decrease are met" in 1 subject (DA 20 μg group).

[17)] In principle, the doses of roxadustat and DA were fixed from Week 1 to 6. However, if the Hb at Week 3 decreased by >1.0 g/dL from the baseline and was <9.5 g/dL, the dose of roxadustat was increased from 50 mg to 70 mg, 70 mg to 100 mg, and 100 mg to 120 mg in each group. If the Hb at Week 3 increased by >1.5 g/dL from the baseline, the dose of roxadustat was decreased from 50 mg to 40 mg, 70 mg to 50 mg, and 100 mg to 70 mg in each group. In the DA group, if the Hb at Week 3 increased by >1.5 g/dL from the baseline, DA 20 μg was decreased to 10 or 15 μg.

Table 32 shows the rate of increase in Hb from baseline[18] at Week 6, the primary endpoint. An analysis of dose-response relationship indicated statistical significance in all the contrasting patterns (p <0.001, contrast test, adjustment of multiplicity of testing by resampling method, at a two-sided significance level of 5%).

Table 32. Rate of increase in Hb from baseline at Week 6 (g/dL/week) (FAS)

		Roxadustat			DA	*P*-value[a]
		50 mg (n = 32)	70 mg (n = 32)	100 mg (n = 31)	20 μg (n = 32)	
Rate of increase in Hb from baseline at Week 6 (g/dL/week)		−0.219 ± 0.585	−0.046 ± 0.581	0.112 ± 0.513	0.112 ± 0.174	
Contrasting patterns	Linear	(−1, 0, 1)				<0.001
	Steep increase from 100 mg	(−1, −1, 2)				<0.001
	Plateau at 70 mg	(−2, 1, 1)				<0.001

Mean value ± standard deviation

a) Contrast testing using regression models with treatment as the factor and baseline Hb and ESA dose prior to washout period as covariates, adjustment of multiplicity of testing by the resampling method, at a two-sided significance level of 5%

Adverse events occurred in 72.7% (24 of 33) of subjects in the roxadustat 50 mg group, 81.3% (26 of 32) of subjects in the roxadustat 70 mg group, 84.4% (27 of 32) of subjects in the roxadustat 100 mg group, and 78.1% (25 of 32) of subjects in the DA 20 μg group. Table 33 shows adverse events with an incidence of ≥5.0% in all roxadustat groups combined. Adverse drug reactions occurred in 24.2% (8 of 33) of subjects in the roxadustat 50 mg group, 21.9% (7 of 32) of subjects in the roxadustat 70 mg group, 37.5% (12 of 32) of subjects in the roxadustat 100 mg group, and 6.3% (2 of 32) of subjects in the DA 20 μg group. Table 34 shows adverse drug reactions that occurred in ≥2 subjects in all roxadustat groups combined.

Table 33. Adverse events with an incidence of ≥5.0% in all roxadustat groups combined

	Roxadustat				DA
	50 mg (n = 33)	70 mg (n = 32)	100 mg (n = 32)	Roxadustat total (n = 97)	20 μg (n = 32)
All adverse events	72.7 (24)	81.3 (26)	84.4 (27)	79.4 (77)	78.1 (25)
Nasopharyngitis	30.3 (10)	31.3 (10)	25.0 (8)	28.9 (28)	43.8 (14)
Vomiting	6.1 (2)	6.3 (2)	21.9 (7)	11.3 (11)	6.3 (2)
Retinal haemorrhage	6.1 (2)	6.3 (2)	15.6 (5)	9.3 (9)	0 (0)
Nausea	9.1 (3)	6.3 (2)	12.5 (4)	9.3 (9)	3.1 (1)
Constipation	3.0 (1)	6.3 (2)	6.3 (2)	5.2 (5)	6.3 (2)
Diarrhoea	6.1 (2)	3.1 (1)	6.3 (2)	5.2 (5)	6.3 (2)

MedDRA ver.15.1

Incidence, % (number of subjects)

[18] Using all Hb values measured weekly during the period from the start of treatment up to Week 6, a linear regression curve was fitted to the data of each patient, and the slope of the linear curve was used to calculate the rate of increase in Hb. When treatment was discontinued or dose was adjusted by Week 6, the rate of increase in Hb by the time of discontinuation or dose adjustment was used.

Table 34. Adverse drug reactions that occurred in ≥2 subjects in all roxadustat groups combined

	Roxadustat				DA
	50 mg (n = 33)	70 mg (n = 32)	100 mg (n = 32)	Roxadustat total (n = 97)	20 μg (n = 32)
All adverse drug reactions	24.2 (8)	21.9 (7)	37.5 (12)	27.8 (27)	6.3 (2)
Vomiting	6.1 (2)	3.1 (1)	12.5 (4)	7.2 (7)	0 (0)
Nausea	3.0 (1)	3.1 (1)	9.4 (3)	5.2 (5)	0 (0)
Retinal haemorrhage	3.0 (1)	0 (0)	6.3 (2)	3.1 (3)	0 (0)
Hypertension	3.0 (1)	3.1 (1)	3.1 (1)	3.1 (3)	3.1 (1)
Blood pressure increased	3.0 (1)	0 (0)	3.1 (1)	2.1 (2)	0 (0)

MedDRA ver.15.1; Incidence, % (number of subjects)

There was 1 death in the roxadustat 50 mg group (embolism venous),[19] and a causal relationship to the study drug was ruled out. Serious adverse events other than deaths occurred in 12.1% (4 of 33) of subjects in the roxadustat 50 mg group (vascular graft occlusion [1]; cardiac failure congestive and haemoglobin decreased [1]; pneumonia bacterial [1]; and myocardial ischaemia [1]), 21.9% (7 of 32) of subjects in the roxadustat 70 mg group (gastric polypectomy/intestinal polypectomy [1]; cerebral infarction [1]; vomiting/dizziness [1]; viral upper respiratory tract infection [1]; intestinal polypectomy [1]; pneumonia aspiration [1]; and liver function test abnormal [1]), 12.5% (4 of 32) of subjects in the roxadustat 100 mg group (cardiac failure congestive [2]; gait disturbance/decreased appetite/lacunar infarction [1]; and ileus [1]), and 6.3% (2 of 32) of subjects in the DA 20 μg group (gastric ulcer haemorrhage [1] and haematoma [1]). Cerebral infarction and vomiting in 1 subject each in the roxadustat 70 mg group, and lacunar infarction and vomiting in 1 subject each in the roxadustat 100 mg group were classified as adverse drug reactions. However, the outcome for all these events was reported as either "resolved," or "resolving." Adverse events leading to treatment discontinuation occurred in 6.1% (2 of 33) of subjects in the roxadustat 50 mg group (embolism venous [1] and haemoglobin decreased [1]), 6.3% (2 of 32) of subjects in the roxadustat 70 mg group (cerebral infarction [1] and vomiting [1]), 9.4% (3 of 32) of subjects in the roxadustat 100 mg group (lacunar infarction [1], ileus [1], and vomiting [1]). Cerebral infarction and vomiting in 1 subject each in the roxadustat 70 mg group and lacunar infarction and vomiting in 1 subject each in the roxadustat 100 mg group were classified as adverse drug reactions. However, the outcome for all these events was reported as either "resolved," or "resolving."

7.2 Phase III studies

7.2.1 Japanese phase III comparative study in HD patients on ESA treatment (conversion/ maintenance study in HD patients) (CTD 5.3.5.1-2, Study 1517-CL-0307 [November 2016 to March 2018])

A multi-center, randomized, double-blind, active-controlled, parallel-group study was conducted at 58 study centers in Japan to assess the efficacy and safety of roxadustat in adult HD patients who were on ESA treatment (Table 35) (target sample size, 300 subjects; 150/group).

[19] A men aged 70 years, who developed pneumonia bacterial on Day 65 of treatment with roxadustat, and was hospitalized on the following day. The patient presented with embolism venous on Day 70, with pneumonia bacterial being unresolved, and roxadustat was discontinued on Day 75. The patient died of embolism venous on Day 77. Embolism venous was attributed to extended hospitalization due to pneumonia bacterial and because of inflammation. Therefore, a causal relationship to the study drug was ruled out. (A causal relationship to the study drug was ruled out also for pneumonia bacterial.)

Table 35. Main inclusion/exclusion criteria

Main inclusion criteria • **Patients with stable-stage chronic kidney disease (CKD) who are on 3 times a week HD for ≥12 weeks prior to enrollment** • **Patients on ESA treatment with an Hb value of 10.0 to 12.0 g/dL** • **Patients with a transferrin saturation (TSAT) of ≥20%, or a serum ferritin of ≥100 ng/mL** **Main exclusion criteria** • **Patients with untreated retinal neovascularization lesions (e.g., proliferative diabetic retinopathy, exudative age-related macular degeneration, retinal vein occlusion, and macular oedema)**

Roxadustat or DA was administered for 24 weeks in accordance with Table 36 so that pre-dialysis Hb values would stay within the target range (10.0 to 12.0 g/dL).

Table 36. Method of dose adjustment

<table>
<tr><th></th><th>Roxadustat</th><th>DA</th></tr>
<tr><td>Dosage regimen</td><td>Orally, 3 times weekly
2- to 3-day intervals (e.g., Mon, Wed, and Fri, or Tue, Thu, and Sat. on fixed days of the week as a rule). On the days of hemodialysis, roxadustat is given after hemodialysis.</td><td>Intravenously, once weekly
On the days of dialysis, DA is given after dialysis.</td></tr>
<tr><td>Starting dose</td><td>Determined according to average ESA dose given before enrollment.
<table>
<tr><th rowspan="2">Roxadustat starting dose (mg/administration)</th><th colspan="3">Average ESA dose given before enrollment</th></tr>
<tr><th>rHuEPO (IU/week)</th><th>DA (μg/week)</th><th>CERA (μg/week)</th></tr>
<tr><td>70</td><td><4500</td><td><20</td><td>≤100</td></tr>
<tr><td>100</td><td>≥4500</td><td>≥20</td><td>>100</td></tr>
</table></td><td>Determined according to average ESA dose given before enrollment.
<table>
<tr><th rowspan="2">DA starting dose (μg/week)</th><th colspan="2">Average ESA dose given before enrollment</th></tr>
<tr><th>rHuEPO (IU/week)</th><th>DA (μg/week)</th></tr>
<tr><td>10</td><td>—</td><td><12.5</td></tr>
<tr><td>15</td><td>≤3000</td><td>≥12.5 and <17.5</td></tr>
<tr><td>20</td><td>>3000 to 4500</td><td>≥17.5 and <25</td></tr>
<tr><td>30</td><td>>4500 to 6000</td><td>≥25 and <35</td></tr>
<tr><td>40</td><td>>6000</td><td>≥35 and <45</td></tr>
<tr><td>50</td><td>—</td><td>≥45 and <55</td></tr>
<tr><td>60</td><td>—</td><td>≥55</td></tr>
</table></td></tr>
<tr><td>Dose adjustment range</td><td>Maximum dose, 3.0 mg/kg (post-dialysis body weight at enrollement)
<table>
<tr><th>Step</th><th>Dose (mg/administration)</th></tr>
<tr><td>1</td><td>20</td></tr>
<tr><td>2</td><td>40</td></tr>
<tr><td>3</td><td>50</td></tr>
<tr><td>4</td><td>70</td></tr>
<tr><td>5</td><td>100</td></tr>
<tr><td>6</td><td>120</td></tr>
<tr><td>7</td><td>150</td></tr>
<tr><td>8</td><td>200</td></tr>
<tr><td>9</td><td>250</td></tr>
<tr><td>10</td><td>300</td></tr>
</table></td><td>
<table>
<tr><th>Step</th><th>Dose (μg/week)</th></tr>
<tr><td>1</td><td>10</td></tr>
<tr><td>2</td><td>15</td></tr>
<tr><td>3</td><td>20</td></tr>
<tr><td>4</td><td>30</td></tr>
<tr><td>5</td><td>40</td></tr>
<tr><td>6</td><td>50</td></tr>
<tr><td>7</td><td>60</td></tr>
<tr><td>8</td><td>80</td></tr>
<tr><td>9</td><td>100</td></tr>
<tr><td>10</td><td>120</td></tr>
<tr><td>11</td><td>140</td></tr>
<tr><td>12</td><td>160</td></tr>
<tr><td>13</td><td>180</td></tr>
</table></td></tr>
</table>

<table>
<tr><th></th><th>Roxadustat</th><th>DA</th></tr>
<tr><td>Dose adjust-ment criteria</td><td>
Dose increase/reduction criteria:
Determine the dose every 2 weeks at Week 4 and thereafter.
Increase or decrease the dose according to the table below step by step.
Once modified, maintain the dose for ≥ 4 weeks.
If a dose reduction criterion is met at the minimum dose or a dose increase criterion at the maximum dose, do not modify the dose.
<table>
<tr><th rowspan="2">Change in pre-dialysis Hb from 4 weeks before</th><th colspan="3">Pre-dialysis Hb</th></tr>
<tr><th><10.5 g/dL</th><th>≥10.5 and ≤11.5 g/dL</th><th>>11.5 g/dL and ≤12.5 g/dL</th></tr>
<tr><td><−1.0 g/dL</td><td>Increase dose</td><td>Increase dose</td><td>No change</td></tr>
<tr><td>−1.0 to 1.0 g/dL</td><td>Increase dose</td><td>No change</td><td>Decrease dose</td></tr>
<tr><td>>1.0 g/dL</td><td>No change</td><td>Decrease dose</td><td>Decrease dose</td></tr>
</table>
Dose interruption/resumption criteria:
Interrupt doses if Hb is >12.5 g/dL.
If Hb decreases to< 11.0 g/dL during interruption, resume treatment at a dose 1 step lower than the pre-interruption dose.

Excessive decrease in Hb:
If Hb is <9.0 g/dL by Week 3, increase the dose by 1 step. However, this dose modification is allowed only once.

Excessive increase in Hb:
If change in Hb within 4 weeks is >2.0 g/dL, decrease the dose by 1 step. Once reduced, maintain the dose for ≥ 4 weeks.
</td><td>
Dose increase/reduction criteria:
Determine the dose every 2 weeks oncethe treatment begins.
Increase or decrease thedose step by step.

Increase the dose if Hb is <10.5 g/dL for consecutive 2 weeksn.
Decrease the dose if Hb is >11.5 g/dL for consecutive2 weeks in succession.

Dose interruption/resumption criteria:
Interrupt doses if Hb is>12.5 g/dL.
If Hb decreases to <11.0 g/dL, resume treatment at a dose 1 step lower than the pre-interruption dose. If the pre-interruption dose is 10 μg, resume at 10 μg.
</td></tr>
</table>

All 303 subjects randomized (151 in the roxadustat group and 152 in the DA group) received the study drug. Of these, 1 subject was excluded due to no re-consent obtained, and the remaining 302 subjects (150 in the roxadustat group and 152 in the DA group) were included in the safety analysis set. Of those receiving the study drug, 58 subjects (37 in the roxadustat group and 21 in the DA group)[20)] were excluded, and the remaining 245 subjects (114 in the roxadustat group and 131 in the DA group) were included in the per protocol set (PPS), which was the main efficacy analysis set. Treatment discontinuation occurred in 53 subjects (32 in the roxadustat group and 21 in the DA group). The reasons for discontinuation were "adverse events" in 20 subjects (12 in the roxadustat group and 8 in the DA group), "protocol deviation" in 11 subjects (7 in the roxadustat group and 4 in the DA group), "study discontinuation requested by the patient" in 9 subjects (5 in the roxadustat group and 4 in the DA group), "death" in 2 subjects (2 in the roxadustat group), "insufficient effectiveness" in 2 subjects (1 each in the roxadustat group and DA group), and "other reasons" in 9 subjects (5 in the roxadustat group and 4 in the DA group).

20) Failure in measuring baseline Hb or measurements from Weeks 18 to 24 <4 time points in 49 subjects (30 in the roxadustat group and 19 in the DA group), treatment period of <18 weeks in 45 subjects (29 in the roxadustat group and 16 in the DA group), use of prohibited concomitant drugs (ESAs) in 13 subjects (8 in the roxadustat group and 5 in the DA group), violation of exclusion criteria that may affect efficacy evaluation in 5 subjects (1 in the roxadustat group and 4 in the DA group), prescription error in 2 subjects (the roxadustat group), unable to obtain re-consent in 1 subject (the roxadustat group), use of prohibited concomitant drug (intravenous iron preparation) in 1 subject (the roxadustat group), use of prohibited concomitant therapy (red blood cell transfusion) in 1 subject (the roxadustat group), unable to obtain post-dosing efficacy data in 1 subject (the DA group), and other in 3 subjects (1 in the roxadustat group and 2 in the DA group) (multiple answers possible).

Table 37 shows change from baseline in mean Hb values from Weeks 18 to 24, the primary endpoint. Difference between the roxadustat group and DA group [95% CI] was −0.02 [−0.18, 0.15] g/dL. The lower limit of the 95% CI exceeded the prescribed non-inferiority margin, −0.75 g/dL,[21] demonstrating non-inferiority of the roxadustat group to the DA group.

Table 37. Change from baseline in mean Hb values from Weeks 18 to 24 (g/dL) (PPS)

	Roxadustat (n = 114)	DA (n = 131)
Mean baseline Hb (g/dL) (Mean ± standard deviation)	11.05 ± 0.56	10.98 ± 0.61
Mean Hb from Weeks 18 to 24[a] (g/dL) (Mean ± standard error)	10.99 ± 0.06	10.97 ± 0.05
Change from baseline in mean Hb from Weeks 18 to 24[b] (g/dL) (least squares mean ± standard error)	−0.04 ± 0.06	−0.03 ± 0.06
Between-group difference in change in mean Hb (roxadustat group − DA group)[b] [95% CI]	−0.02 [−0.18, 0.15]	

a) The mean Hb value from Weeks 18 to 24 was calculated by averaging weekly Hb values from Weeks 18 to 24.
b) Calculated using a mixed-effect model for repeated measures with treatment, visit, baseline Hb, ESA dose immediately before enrollment, past history or complication of retinal vascular diseases, presence of diabetes, interaction between treatment and visit as explanatory variables, assuming within-subject unstructured covariance.

Adverse events occurred in 86.0% (129 of 150) of subjects in the roxadustat group and 82.9% (126 of 152) of subjects in the DA group. Adverse events with an incidence of ≥2.0% in any group are shown in Table 38. Adverse drug reactions occurred in 22.0% (33 of 150) of subjects in the roxadustat group and 13.2% (20 of 152) of subjects in the DA group. Adverse drug reactions that occurred in ≥2 subjects in any group are shown in Table 39.

Table 38. Adverse events with an incidence of ≥2.0% in any group

	Roxadustat (n = 150)	DA (n = 152)		Roxadustat (n = 150)	DA (n = 152)
All adverse events	86.0 (129)	82.9 (126)	Influenza	2.0 (3)	2.6 (4)
Nasopharyngitis	34.7 (52)	26.3 (40)	Gastroenteritis	2.0 (3)	0.7 (1)
Shunt stenosis	7.3 (11)	8.6 (13)	Wound	2.0 (3)	3.3 (5)
Diarrhoea	7.3 (11)	7.9 (12)	Hypoalbuminaemia	2.0 (3)	0 (0)
Contusion	6.7 (10)	6.6 (10)	Back pain	2.0 (3)	4.6 (7)
Vomiting	6.7 (10)	2.0 (3)	Muscle spasms	2.0 (3)	1.3 (2)
Shunt occlusion	4.7 (7)	2.0 (3)	Neck pain	2.0 (3)	0 (0)
Skin exfoliation	4.0 (6)	1.3 (2)	Headache	2.0 (3)	0.7 (1)
Retinal haemorrhage	3.3 (5)	3.9 (6)	Upper respiratory tract inflammation	2.0 (3)	2.0 (3)
Dental caries	3.3 (5)	0 (0)	Oropharyngeal pain	2.0 (3)	0.7 (1)
Upper respiratory tract infection	3.3 (5)	1.3 (2)	Pruritus	2.0 (3)	0 (0)
Procedural hypotension	3.3 (5)	0.7 (1)	Internal haemorrhage	1.3 (2)	3.9 (6)
Hyperkalaemia	3.3 (5)	0.7 (1)	Arthralgia	1.3 (2)	2.6 (4)
Hypertension	3.3 (5)	4.6 (7)	Insomnia	1.3 (2)	2.0 (3)
Nausea	2.7 (4)	1.3 (2)	Vertigo	0.7 (1)	2.0 (3)
Eczema	2.7 (4)	2.0 (3)	Osteoarthritis	0 (0)	2.6 (4)
Constipation	2.0 (3)	2.0 (3)	Tinea pedis	0 (0)	2.0 (3)
Malaise	2.0 (3)	1 (0.7)			

MedDRA ver.19.0; incidence, % (number of subjects)

[21] Specified as 0.75 g/dL, which is <1/2 of the target range of Hb, 2 g/dL.

Table 39. Adverse drug reactions that occurred in ≥2 subjects in any group

	Roxadustat (n = 150)	DA (n = 152)
All adverse drug reactions	**22.0 (33)**	**13.2 (20)**
Hypertension	**3.3 (5)**	**2.0 (3)**
Retinal haemorrhage	**2.0 (3)**	**2.6 (4)**
Vomiting	**2.0 (3)**	**0 (0)**
Hypoalbuminaemia	**2.0 (3)**	**0 (0)**
Nausea	**1.3 (2)**	**0.7 (1)**
Diarrhoea	**1.3 (2)**	**0 (0)**
Malaise	**1.3 (2)**	**0 (0)**
Hyperkalaemia	**1.3 (2)**	**0 (0)**
Vertigo	**0.7 (1)**	**1.3 (2)**

MedDRA ver.19.0; incidence, % (number of subjects)

Deaths occurred in 2 subjects in the roxadustat group (acute myocardial infarction[22)] [1] and cardiac failure congestive[23)] [1]), and the cardiac failure congestive in 1 subject was assessed as an adverse drug reaction. Serious adverse events other than deaths occurred in 19.3% (29/150) of subjects in the roxadustat group and 14.5% (22 of 152) of subjects in the DA group as shown in Table 40. Of these events, adverse drug reactions were coronary artery stenosis (1), sudden hearing loss (1), cerebral infarction (1), and deep vein thrombosis (1) in the roxadustat group; and angina pectoris (1), atrioventricular block complete (1), shunt occlusion (1), haemoglobin decreased (1), malignant neoplasm of renal pelvis (1), lip and/or oral cavity cancer (1) in the DA group. The outcome was reported as "unresolved" for cerebral infarction and deep vein thrombosis in the roxadustat group and atrioventricular block complete, haemoglobin decreased, malignant neoplasm of renal pelvis, and lip and/or oral cavity cancer in the DA group.

Table 40. List of serious adverse events

Treatment	n	Adverse event
Roxadustat	**6**	**Shunt stenosis**
	3	**Shunt occlusion**
	2	**Cellulitis, deep vein thrombosis**
	1	**Angina pectoris, bradycardia, coronary artery stenosis, sudden hearing loss, gastrointestinal haemorrhage, vascular stent occlusion, urinary tract infection, joint dislocation, spinal column injury, arteriogram coronary, investigation, lumbar spinal stenosis, gastric cancer, cerebral infarction, asthma, coronary angioplasty, orthostatic hypotension, venous occlusion, subclavian vein stenosis**
DA	**7**	**Shunt stenosis**
	2	**Angina pectoris, shunt occlusion**
	1	**Aortic valve stenosis, atrioventricular block complete, cardiac failure, myocardial ischaemia, subcutaneous haematoma, haemoglobin decreased, basal cell carcinoma, malignant neoplasm of renal pelvis, transitional cell carcinoma, lip and/or oral cavity cancer, suicidal ideation, pulmonary oedema, angioplasty, large intestinal polypectomy, peripheral arterial occlusive disease**

MedDRA ver.19.0

22) A man aged 64 years. Roxadustat therapy was discontinued on Day 97. The patient presented with acute myocardial infarction on Day 111 and died on the same day. It was concluded that the event was due to cardiac failure chronic and long-term HD, and a causal relationship to the study drug was ruled out.

23) A man aged 75 years, who had hypertension, angina pectoris, and dyslipidaemia. Roxadustat therapy was discontinued on Day 94. The patient developed cardiac failure congestive on Day 97 and died on the same day. The investigator considered that congestion was due to poor body fluid control, but concluded that a causal relationship to the study drug could not be ruled out.

Adverse events leading to treatment discontinuation occurred in 8.7% (13 of 150) of subjects in the roxadustat group (haemorrhagic anaemia [1], acute myocardial infarction [1], cardiac failure congestive, sudden hearing loss, macular oedema, vascular stent occlusion, cellulitis [1], cerebral infarction [1], anxiety [1], coronary angioplasty [1], hypertension [1], jugular vein thrombosis [1], and deep vein thrombosis [1]), and 5.3% (8 of 152) of subjects in the DA group (angina pectoris [1], atrioventricular block complete [1], haemoglobin decreased [1], basal cell carcinoma [1], malignant neoplasm of renal pelvis [1], transitional cell carcinoma [1], lip and/or oral cavity cancer [1], and peripheral arterial occlusive disease [1]). Among these events, adverse drug reactions were cardiac failure congestive, sudden hearing loss, macular oedema, cerebral infarction, anxiety, hypertension, jugular vein thrombosis, and deep vein thrombosis in 1 subject each in the roxadustat group; and angina pectoris, atrioventricular block complete, haemoglobin decreased, malignant neoplasm of renal pelvis, lip and/or oral cavity cancer in 1 subject each in the DA group. The adverse drug reactions leading to treatment discontinuation that "resolved" were coronary angioplasty, anxiety, and hypertension in 1 subject each in the roxadustat group and angina pectoris and haemoglobin decreased in 1 subject each in the DA group. The remaining events (cardiac failure congestive, sudden hearing loss, macular oedema, cerebral infarction, jugular vein thrombosis, and deep vein thrombosis in the roxadustat group; and atrioventricular block complete, malignant neoplasm of renal pelvis, and lip and/or oral cavity cancer in the DA group) were "unresolved."

7.2.2 Japanese phase III study in HD patients on ESA therapy (long-term study) (CTD 5.3.5.2-3, Study 1517-CL-0312 [May 2016 to November 2017])

A multi-center, open-label, uncontrolled study was conducted at 25 study centers in Japan to assess the long-term safety and efficacy of roxadustat in adult HD patients who were on ESA therapy (Table 35) (target sample size, 160 subjects).

Roxadustat was administered to subjects orally 3 times weekly for 52 weeks in accordance with the dosing method, dose adjustment range, and dose adjustment criteria specified in Table 36 so that pre-dialysis Hb values stayed within the target range (10.0 to 12.0 g/dL). The starting dose were determined according to the average ESA dose levels prior to enrollment as shown in Table 41.

Table 41. Starting dose of roxadustat

Starting dose of roxadustat (mg/administration)	Average ESA dosage prior to registration		
	rHuEPO (IU/week)	DA (μg/ week)	CERA (μg/4 weeks)
70	<4500	<20	≤100
100	≥4500	≥20	>100

Of the 164 subjects enrolled in the study, 163 subjects received roxadustat, excluding 1 subject whose treatment had been discontinued at the patient's request. All 163 subjects receiving roxadustat were included in the safety analysis set and the FAS, which was the main efficacy analysis set. Treatment discontinuation occurred in 38 subjects. The reasons for discontinuation were "adverse events" (15),

"discontinuation at the patient's request" (9), "death" (2), "protocol deviation" (1), "nonadherence to the study drug" (1), and "other reasons" (10).

Table 42 shows the time course of mean Hb values and the percentage of subjects whose Hb values stayed within the target range (mean Hb was 10.0 to 12.0 g/dL) by evaluation period.

Table 42. Time course of mean Hb values, and the percentage of subjects whose Hb values stayed within the target range by evaluation period (FAS)

Evaluation period	Baseline (n = 163)	Weeks 4-10 (n = 156)	Weeks 12-16 (n = 149)	Weeks 18-24 (n = 148)	Weeks 26-30 (n = 144)	Weeks 32-38 (n = 137)	Weeks 40-44 (n = 132)	Weeks 46-52 (n = 128)
Mean Hb (g/dL)	10.96 ± 0.57	11.23 ± 0.79	11.05 ± 0.68	10.93 ± 0.69	10.90 ± 0.71	10.93 ± 0.68	10.95 ± 0.72	11.11 ± 0.67
Number of subjects with Hb values maintained in the target range	158	130	130	129	126	122	115	116
Percentage of subjects with Hb values maintainedin the target range (%)	96.9 [93.0, 99.0]	83.3 [76.5, 88.8]	87.2 [80.8, 92.1]	87.2 [80.7, 92.1]	87.5 [81.0, 92.4]	89.1 [82.6, 93.7]	87.1 [80.2, 92.3]	90.6 [84.2, 95.1]

Mean Hb value is expressed as mean ± standard deviation; the percentage of subjects whose Hb values were stayed within the target range is expressed as percentage of subjects, % [95% CI]

Adverse events occurred in 95.7% (156 of 163) of subjects. Table 43 shows adverse events with an incidence of ≥2.0%. Adverse drug reactions occurred in 27.6% (45/163) of subjects. Table 44 shows adverse drug reactions that occurred in ≥2 subjects.

Table 43. Adverse events with an incidence of ≥2.0%

	Roxadustat (n = 163)		Roxadustat (n = 163)
All adverse events	95.7 (156)	Neck pain	3.7 (6)
Nasopharyngitis	52.8 (86)	Pain in extremity	3.7 (6)
Diarrhoea	11.0 (18)	Insomnia	3.7 (6)
Vomiting	10.4 (17)	Oropharyngeal pain	3.7 (6)
Contusion	9.8 (16)	Dermatitis contact	3.7 (6)
Back pain	7.4 (12)	Pruritus	3.7 (6)
Shunt stenosis	7.4 (12)	Faeces soft	3.1 (5)
Constipation	6.1 (10)	Periodontitis	3.1 (5)
Shunt occlusion	6.1 (10)	Lipase increased	3.1 (5)
Dental caries	5.5 (9)	Muscle spasms	3.1 (5)
Headache	5.5 (9)	Dizziness	3.1 (5)
Musculoskeletal pain	4.9 (8)	Hyperkeratosis	3.1 (5)
Haemorrhage subcutaneous	4.9 (8)	Abdominal pain	2.5 (4)
Abdominal discomfort	4.3 (7)	Pyrexia	2.5 (4)
Pharyngitis	4.3 (7)	Pneumonia	2.5 (4)
Oral herpes	4.3 (7)	Wound	2.5 (4)
Excoriation	4.3 (7)	Procedural hypotension	2.5 (4)
Nausea	3.7 (6)	Eczema	2.5 (4)
Gastroenteritis	3.7 (6)	Rash	2.5 (4)
Influenza	3.7 (6)	Skin ulcer	2.5 (4)
Arthralgia	3.7 (6)	Hypertension	2.5 (4)
Myalgia	3.7 (6)		

MedDRA ver.19.0; incidence, % (number of subjects)

Table 44. Adverse drug reactions that occurred in ≥2 subjects

	Roxadustat (n = 163)		Roxadustat (n = 163)
All adverse drug reactions	**27.6 (45)**	**Hypothyroidism**	**1.2 (2)**
Vomiting	**3.1 (5)**	**Abdominal pain**	**1.2 (2)**
Shunt occlusion	**2.5 (4)**	**Gastric disorder**	**1.2 (2)**
Abdominal discomfort	**2.5 (4)**	**Shunt stenosis**	**1.2 (2)**
Diarrhoea	**1.8 (3)**	**Dizziness**	**1.2 (2)**
Lipase increased	**1.8 (3)**	**Nausea**	**1.2 (2)**
Constipation	**1.2 (2)**	**Iron deficiency**	**1.2 (2)**
Hypertension	**1.2 (2)**		

MedDRA ver.19.0; incidence, % (number of subjects)

There were 2 deaths (pancreatic carcinoma[24)] and shock haemorrhagic[25)] in 1 subject each), and a causal relationship to roxadustat was ruled out for both events. Serious adverse events other than deaths occurred in 28.2% (46 of 163) of subjects as shown in Table 45. Shunt occlusion (4), cerebral infarction (1), lacunar infarction (1), subarachnoid haemorrhage (1), acute myocardial infarction (1), angina unstable (1), cardiac failure congestive (1), myocardial ischaemia (1), blood pressure increased (1), nausea (1), vomiting (1), and decreased appetite (1) were assessed as adverse drug reactions. Events that remained unresolved were shunt occlusion, lacunar infarction, cardiac failure congestive, myocardial ischaemia, nausea, and decreased appetite in 1 subject each.

Table 45. List of serious adverse events (Study 1517-CL-0312)

n	Adverse event
9	**Shunt occlusion**
3	**Angina pectoris, pneumonia**
2	**Myocardial ischaemia, shunt stenosis, arteriogram coronary, skin ulcer, peripheral arterial occlusive disease**
1	**Acute myocardial infarction, angina unstable, atrioventricular block, cardiac failure congestive, diabetic retinopathy, vitreous haemorrhage, abdominal pain upper, duodenitis, gastritis erosive, nausea, vomiting, gastric stenosis, volvulus of small bowel, cholelithiasis, hepatic congestion, anaphylactic shock, cellulitis, gastroenteritis, nasopharyngitis, periodontitis, sepsis, urinary tract infection, patella fracture, contusion, blood pressure decreased, blood pressure increased, lactic acidosis, decreased appetite, type 2 diabetes mellitus, spinal column stenosis, carpal tunnel syndrome, cerebral infarction, subarachnoid haemorrhage, lacunar infarction, acute pulmonary oedema, skin mass, angioplasty, carpal tunnel decompression, pancreatic carcinoma, thrombectomy, wisdom teeth removal, cataract operation, gastrointestinal endoscopic therapy, large intestinal polypectomy, aortic dissection, thrombophlebitis superficial, shock haemorrhagic**

MedDRA ver.19.0

Adverse events leading to treatment discontinuation occurred in 10.4% (17 of 163) of subjects (shunt occlusion [2], myocardial ischaemia [1], diarrhoea [1], gastrointestinal disorder [1], faeces soft [1], hepatic congestion [1], hepatic function abnormal [1], shunt stenosis [1], decreased appetite/nausea/vomiting [1], pancreatic carcinoma [1], myoclonus [1], subarachnoid haemorrhage [1], lacunar infarction [1], interstitial lung disease [1], hypertension [1], shock haemorrhagic [1]). Among these, adverse drug reactions were shunt occlusion in 2 subjects; myocardial ischaemia; diarrhea;

24) A man aged 79 years experienced pancreatic carcinoma on Day 52 and died on Day 255. Roxadustat was discontinued on Day 218. Taking into account the time course from the start of roxadustat to the detection of multiple metastasis to the liver, pancreatic carcinoma was unlikely to have developed after the start of roxadustat. Thus, a causal relationship to roxadustat was ruled out.

25) A man aged 67 years experienced multiple gastric ulcers and shock haemorrhagic caused by duodenal ulcer on Day 250 and died on the same day. Roxadustat was discontinued on Day 248. A causal relationship to roxadustat was ruled out.

gastrointestinal disorder; faeces soft; hepatic function abnormal; decreased appetite/nausea/vomiting; myoclonus; subarachnoid haemorrhage; lacunar infarction; interstitial lung disease; and hypertension in 1 subject each. Resolved adverse drug reactions leading to treatment discontinuation included shunt occlusion, vomiting, and subarachnoid haemorrhage in 1 subject each, while the other adverse drug reactions (shunt occlusion; myocardial ischaemia; diarrhoea; gastrointestinal disorder; faeces soft; hepatic function abnormal; decreased appetite/nausea; myoclonus; lacunar infarction; interstitial lung disease; and hypertension in 1 subject each) remained unresolved.

7.2.3 Japanese phase III study in ESA-naïve HD patients (anemia correction study in HD patients) (CTD 5.3.5.2-2, Study 1517-CL-0308 [June 2016 to December 2017])

A multi-center, randomized, open-label, uncontrolled study was conducted at 47 study centers in Japan to assess the efficacy and safety of roxadustat in ESA-naïve, adult patients on HD (Table 46) (target sample size, 70 subjects; 35/group).

Table 46. Main inclusion/exclusion criteria (Study 1517-CL-0308)

Main inclusion criteria
• **Patients with CKD who have been on HD ≥ once weekly at the pre-screening assessment**
• **Patients who have not received ESA after starting dialysis**
• **Patients with an Hb value of ≤10.0 g/dL**
• **Patients with a TSAT of ≥5% or a serum ferritin of ≥30 ng/mL**
Main exclusion criteria
• **Patients with retinal neovascularization lesions requiring treatment (e.g., proliferative diabetic retinopathy, exudative age-related macular degeneration, retinal vein occlusion, and macular oedema)**

Roxadustat was administered to subjects orally 3 times weekly for 24 weeks. The starting dose was 50 or 70 mg, and at Week 4 and thereafter, the dose was adjusted in accordance with the dosing method, dose adjustment range, and dose adjustment criteria specified in Table 36 so that the pre-dialysis Hb values were maintained within the target range (10.0 to 12.0 g/dL).

All 75 subjects randomized (37 in the roxadustat 50 mg group and 38 in the 70 mg group) received roxadustat and were included in the safety analysis set. Of the 75, 1 subject was excluded because efficacy endpoint parameters were not measured, and the remaining 74 subjects (37 each in the roxadustat 50 and 70 mg groups) were included in the FAS, which was the main efficacy analysis set. Treatment discontinuation occurred in 10 subjects (4 in the roxadustat 50 mg group and 6 in the 70 mg group), and the reasons for discontinuation were “adverse events” in 3 subjects (1 in the 50 mg group and 2 in the 70 mg group), “insufficient effectiveness” in 1 subject (50 mg group), and “other reasons” in 6 subjects (2 in the 50 mg group and 4 in the 70 mg group).

Table 47 shows mean Hb values from Weeks 18 to 24, and cumulative response rate at the end of treatment (at Week 24 or at treatment discontinuation) (Hb response was defined as achieving an Hb of ≥10.0 g/dL and an increase in Hb by ≥1.0 g/dL from baseline).

Table 47. Mean Hb values from Weeks 18 to 24, and cumulative response rate at the end of treatment (at Week 24 or at treatment discontinuation) (FAS)

	Roxadustat 50 mg (n = 37)	Roxadustat 70 mg (n = 37)	Total (n = 74)
Mean baseline Hb (g/dL)	8.63 ± 0.77	8.67 ± 0.79	8.65 ± 0.78
Mean Hb from Weeks 18 to 24 (g/dL)	10.96 ± 0.78	10.90 ± 0.81	10.93 ± 0.79
Change from baseline in mean Hb from Weeks 18 to 24 (g/dL)	2.29 ± 1.05	2.24 ± 1.01	2.26 ± 1.02
Number of subjects responded	32	33	65
Cumulative response rate [95% CI] (%)	86.5 [71.2, 95.5]	89.2 [74.6, 97.0]	87.8 [78.2, 94.3]

Mean value ± standard deviation

Adverse events occurred in 86.5% (32 of 37) of subjects in the roxadustat 50 mg group and 94.7% (36 of 38) of subjects in the 70 mg group (90.7% [68 of 75] of total subjects). Table 48 shows adverse events that occurred in ≥2.0% of total subjects. Adverse drug reactions occurred in 13.5% (5 of 37) of subjects in the roxadustat 50 mg group and 28.9% (11 of 38) of subjects in the 70 mg group (21.3% [16 of 75] of total subjects). Adverse drug reactions that occurred in ≥2 of total subjects were shunt occlusion in 2 subjects (2 subjects in roxadustat 70 mg group) and lipase increased in 2 subjects (1 subject each in the roxadustat 50 and 70 mg groups).

Table 48. Adverse events that occurred in ≥2.0% of total subjects

	Roxadustat 50 mg (n = 37)	Roxadustat 70 mg (n = 38)	Total (n = 75)		Roxadustat 50 mg (n = 37)	Roxadustat 70 mg (n = 38)	Total (n = 75)
All adverse events	86.5 (32)	94.7 (36)	90.7 (68)	Cataract	0 (0)	5.3 (2)	2.7 (2)
Nasopharyngitis	8.1 (3)	31.6 (12)	20.0 (15)	Gastroenteritis	0 (0)	5.3 (2)	2.7 (2)
Dermatitis contact	10.8 (4)	15.8 (6)	13.3 (10)	Excoriation	0 (0)	5.3 (2)	2.7 (2)
Shunt occlusion	8.1 (3)	10.5 (4)	9.3 (7)	Thermal burn	0 (0)	5.3 (2)	2.7 (2)
Constipation	2.7 (1)	10.5 (4)	6.7 (5)	Hyperkalaemia	0 (0)	5.3 (2)	2.7 (2)
Shunt stenosis	5.4 (2)	7.9 (3)	6.7 (5)	Bursitis	0 (0)	5.3 (2)	2.7 (2)
Hyperphosphataemia	5.4 (2)	7.9 (3)	6.7 (5)	Skin exfoliation	0 (0)	5.3 (2)	2.7 (2)
Diarrhoea	2.7 (1)	7.9 (3)	5.3 (4)	Nausea	2.7 (1)	2.6 (1)	2.7 (2)
Contusion	5.4 (2)	5.3 (2)	5.3 (4)	Subcutaneous haematoma	2.7 (1)	2.6 (1)	2.7 (2)
Insomnia	5.4 (2)	5.3 (2)	5.3 (4)	Wound	2.7 (1)	2.6 (1)	2.7 (2)
Eczema	5.4 (2)	5.3 (2)	5.3 (4)	Tooth fracture	2.7 (1)	2.6 (1)	2.7 (2)
Vomiting	8.1 (3)	2.6 (1)	5.3 (4)	Lipase increased	2.7 (1)	2.6 (1)	2.7 (2)
Back pain	8.1 (3)	2.6 (1)	5.3 (4)	Eczema asteatotic	2.7 (1)	2.6 (1)	2.7 (2)
Dermatitis	2.7 (1)	5.3 (2)	4.0 (3)	Pruritus	2.7 (1)	2.6 (1)	2.7 (2)
Cardiac failure congestive	5.4 (2)	2.6 (1)	4.0 (3)	Hypotension	2.7 (1)	2.6 (1)	2.7 (2)
Conjunctivitis	8.1 (3)	0 (0)	4.0 (3)	Arthralgia	5.4 (2)	0 (0)	2.7 (2)
Procedural hypotension	8.1 (3)	0 (0)	4.0 (3)	Restless legs syndrome	5.4 (2)	0 (0)	2.7 (2)
Muscle spasms	0 (0)	7.9 (3)	4.0 (3)	Cough	5.4 (2)	0 (0)	2.7 (2)

MedDRA ver.19.0; incidence, % (number of subjects)

There were no deaths. Serious adverse events occurred in 24.3% (9 of 37) of subjects in the roxadustat 50 mg group and 34.2% (13 of 38) of subjects in the 70 mg group (29.3% [22 of 75] of total subjects) as shown in Table 49. Adverse drug reactions included interstitial lung disease in 1 subject in the roxadustat 50 mg group, and cerebral infarction and shunt occlusion in 1 subject each in the roxadustat 70 mg group. The cerebral infarction resolved while the interstitial lung disease and shunt occlusion remained unresolved.

Table 49. List of serious adverse events

Treatment	n	Adverse event
50 mg	2	Cardiac failure congestive, shunt occlusion
	1	Dental caries, femur fracture, shunt stenosis, shunt malfunction, tooth fracture, interstitial lung disease, cataract operation
70 mg	3	Shunt occlusion
	1	Myocardial ischaemia, acute coronary syndrome, deafness neurosensory, cataract, lower gastrointestinal haemorrhage, cellulitis, type 2 diabetes mellitus, cerebral infarction, bronchitis chronic, pleural effusion, angioplasty, hernia repair, weight control

MedDRA ver.19.0

Adverse events leading to treatment discontinuation occurred in 2.7% (1 of 37) of subjects in the roxadustat 50 mg group (interstitial lung disease) and 5.3% (2 of 38) of subjects in the 70 mg group (acute coronary syndrome and lower gastrointestinal haemorrhage in 1 subject each) (4.0% [3 of 75] of total subjects). The interstitial lung disease in 1 subject was assessed as an adverse drug interaction and remained unresolved.

7.2.4 Japanese phase III study in PD patients (anemia correction study, Hb maintenance in patients converting from ESA) (CTD 5.3.5.2-1, Study 1517-CL-0302 [June 2016 to August 2017])

A multi-center, randomized, open-label, uncontrolled study was conducted at 15 study centers in Japan to assess the efficacy and safety of treatment with roxadustat in adult PD patients who had been untreated with ESA for ≥6 weeks and had an Hb value of <10.5 g/dL or those who had been treated with ESA for ≥8 weeks and had an Hb value within the range of 10.0 to 12.0 g/dL (Table 50) (target sample size, 50 subjects).

Table 50. Main inclusion/ exclusion criteria

Main inclusion criteria
ESA-naïve patients:
- **Patients who have been on PD for ≥4 weeks before screening**
- **Patients who have not received ESA after starting PD, or patients who have not received ESA within 6 weeks before enrollment**
- **Patients with an Hb value of <10.5 g/dL**
- **Patients with a TSAT of ≥5%, or a serum ferritin of ≥30 ng/mL**

Patients on ESA therapy:
- **Patients who have been receiving ESA for ≥8 weeks**
- **Patients with an Hb value within 10.0 to 12.0 g/dL**
- **Patients with a TSAT of ≥ 20%, or a serum ferritin of ≥100 ng/mL**

Main exclusion criteria:
- **Patients with retinal neovascularization lesions requiring treatment (e.g., proliferative diabetic retinopathy, exudative age-related macular degeneration, retinal vein occlusion, and macular oedema).**

Roxadustat was administered orally 3 times weekly for 24 weeks. The starting dose was 50 or 70 mg for ESA-naïve patients, and at 70 or 100 mg for patients on ESA therapy depending on their dose level of ESA. At Week 4 and thereafter, the doses were adjusted in accordance with the dosage regimen, dose adjustment range, and dose adjustment criteria specified in Table 36 so that pre-dialysis Hb values stayed

within the target range (10.0 to 12.0 g/dL). As shown in Table 41, the starting dose for patients on ESA therapy was determined based on the average ESA dose levels taken before enrollment.

All 56 randomized subjects (ESA-naïve patients, 6 in the roxadustat 50 mg group and 7 in the 70 mg group; patients on ESA therapy, 23 in the roxadustat 70 mg group and 20 in the 100 mg group) received roxadustat and were included in the safety analysis set and the FAS, which was the main efficacy analysis set. There were no treatment discontinuations in ESA-naïve patients. Among subjects converting from ESA to roxadustat, treatment discontinuation occurred in 7 subjects (3 in the roxadustat 70 mg group and 4 in the 100 mg group). The reasons for discontinuation were "adverse events" in 4 subjects (2 each in the 70 and 100 mg groups), "requested by the patient" in 2 subjects (1 each in the 70 and 100 mg groups), and "other reasons" in 1 subject (100 mg group).

Table 51 shows the mean Hb values from Weeks 18 to 24, and the percentage of subjects whose Hb values stayed within the target range (10.0 to 12.0 g/dL).

Table 51. Time course of mean Hb values from Weeks 18 to 24, and the percentage of subjects whose Hb values stayed within the target range (FAS)

	ESA-naïve patients			Patients converting from ESA		
	Roxadustat 50 mg (n = 6)	Roxadustat 70 mg (n = 7)	Roxadustat Total (n = 13)	Roxadustat 70 mg (n = 23)	Roxadustat 100 mg (n = 20)	Roxadustat Total (n = 43)
Mean baseline Hb (g/dL)	9.57 ± 0.71	9.17 ± 0.78	9.35 ± 0.75	10.82 ± 0.51	10.89 ± 0.59	10.85 ± 0.54
Mean Hb from Weeks 18 to 24 (g/dL)	11.07 ± 0.81	11.03 ± 0.46	11.05 ± 0.62	10.90 ± 0.42	10.96 ± 0.79	10.93 ± 0.61
Change from baseline in mean Hb from Weeks 18 to 24 (g/dL)	1.50 ± 1.02	1.86 ± 1.13	1.69 ± 1.05	0.11 ± 0.66	0.17 ± 0.89	0.14 ± 0.76
Number of subjects whose Hb values stayed within the target range	5	7	12	19	13	32
Percentage of subjects whose Hb values stayed within the target range [95% CI] (%)	83.3 [35.9, 99.6]	100 [59.0, 100]	92.3 [64.0, 99.8]	82.6 [61.2, 95.0]	65.0 [40.8, 84.6]	74.4 [58.8, 86.5]

Mean value ± standard deviation

Adverse events occurred in 76.9% (10 of 13) of ESA-naïve subjects and 90.7% (39 of 43) of subjects converting from ESA (87.5% [49 of 56] of total PD patients). Table 52 shows adverse events that occurred in ≥2.0% of total PD patients. Adverse drug reactions occurred in 30.8% (4 of 13) of ESA-naïve subjects, and 39.5% (17 of 43) of subjects converting from ESA (37.5% [21 of 56] of total PD patients). Table 53 shows adverse drug reactions that occurred in ≥2 of total PD patients.

Table 52. Adverse events that occurred in ≥2.0% of total PD patients

	ESA-naïve patients			Patients converting from ESA			Total (n = 56)
	Roxadustat 50 mg (n = 6)	Roxadustat 70 mg (n = 7)	Roxadustat Total (n = 13)	Roxadustat 70 mg (n = 23)	Roxadustat 100 mg (n = 20)	Roxadustat Total (n = 43)	
All adverse events	83.3 (5)	71.4 (5)	76.9 (10)	91.3 (21)	90.0 (18)	90.7 (39)	87.5 (49)
Nasopharyngitis	0 (0)	0 (0)	0 (0)	26.1 (6)	40.0 (8)	32.6 (14)	25.0 (14)
Back pain	0 (0)	42.9 (3)	23.1 (3)	0 (0)	10.0 (2)	4.7 (2)	8.9 (5)
Diarrhoea	0 (0)	0 (0)	0 (0)	8.7 (2)	10.0 (2)	9.3 (4)	7.1 (4)
Vomiting	0 (0)	0 (0)	0 (0)	8.7 (2)	10.0 (2)	9.3 (4)	7.1 (4)
Catheter site infection	0 (0)	0 (0)	0 (0)	8.7 (2)	10.0 (2)	9.3 (4)	7.1 (4)
Constipation	0 (0)	0 (0)	0 (0)	0 (0)	15.0 (3)	7.0 (3)	5.4 (3)
Pruritus	0 (0)	0 (0)	0 (0)	4.3 (1)	10.0 (2)	7.0 (3)	5.4 (3)
Abdominal pain	0 (0)	0 (0)	0 (0)	8.7 (2)	5.0 (1)	7.0 (3)	5.4 (3)
Nausea	0 (0)	0 (0)	0 (0)	8.7 (2)	5.0 (1)	7.0 (3)	5.4 (3)
Conjunctivitis	16.7 (1)	14.3 (1)	15.4 (2)	0 (0)	5.0 (1)	2.3 (1)	5.4 (3)
Dyspepsia	0 (0)	0 (0)	0 (0)	0 (0)	10.0 (2)	4.7 (2)	3.6 (2)
Oedema peripheral	0 (0)	0 (0)	0 (0)	4.3 (1)	5.0 (1)	4.7 (2)	3.6 (2)
Peritonitis	0 (0)	0 (0)	0 (0)	4.3 (1)	5.0 (1)	4.7 (2)	3.6 (2)
Hyperkalaemia	0 (0)	0 (0)	0 (0)	4.3 (1)	5.0 (1)	4.7 (2)	3.6 (2)
Cough	0 (0)	0 (0)	0 (0)	4.3 (1)	5.0 (1)	4.7 (2)	3.6 (2)
Abdominal pain upper	0 (0)	0 (0)	0 (0)	8.7 (2)	0 (0)	4.7 (2)	3.6 (2)
Alanine aminotransferase (ALT) increased	0 (0)	0 (0)	0 (0)	8.7 (2)	0 (0)	4.7 (2)	3.6 (2)
Hyperphosphataemia	0 (0)	0 (0)	0 (0)	8.7 (2)	0 (0)	4.7 (2)	3.6 (2)
Arthralgia	0 (0)	0 (0)	0 (0)	8.7 (2)	0 (0)	4.7 (2)	3.6 (2)
Asthma	0 (0)	0 (0)	0 (0)	8.7 (2)	0 (0)	4.7 (2)	3.6 (2)
Chronic gastritis	16.7 (1)	0 (0)	7.7 (1)	0 (0)	5.0 (1)	2.3 (1)	3.6 (2)
Dental caries	16.7 (1)	0 (0)	7.7 (1)	0 (0)	5.0 (1)	2.3 (1)	3.6 (2)
Bronchitis	16.7 (1)	0 (0)	7.7 (1)	4.3 (1)	0 (0)	2.3 (1)	3.6 (2)
Medical device site infection	16.7 (1)	0 (0)	7.7 (1)	4.3 (1)	0 (0)	2.3 (1)	3.6 (2)
Oedema	16.7 (1)	14.3 (1)	15.4 (2)	0 (0)	0 (0)	0 (0)	3.6 (2)
Hypercalcaemia	16.7 (1)	14.3 (1)	15.4 (2)	0 (0)	0 (0)	0 (0)	3.6 (2)

MedDRA ver.19.0; incidence, % (number of subjects)

Table 53. Adverse drug reactions that occurred in ≥2 of total PD patients

	ESA-naïve patients			Patients converting from ESA			Total (n = 56)
	Roxadustat 50 mg (n = 6)	Roxadustat 70 mg (n = 7)	Roxadustat Total (n = 13)	Roxadustat 70 mg (n = 23)	Roxadustat 100 mg (n = 20)	Roxadustat Total (n = 43)	
All adverse drug reactions	50.0 (3)	14.3 (1)	30.8 (4)	30.4 (7)	50.0 (10)	39.5 (17)	37.5 (21)
Constipation	0 (0)	0 (0)	0 (0)	0 (0)	15.0 (3)	7.0 (3)	5.4 (3)
Pruritus	0 (0)	0 (0)	0 (0)	4.3 (1)	10.0 (2)	7.0 (3)	5.4 (3)
Diarrhoea	0 (0)	0 (0)	0 (0)	0 (0)	10.0 (2)	4.7 (2)	3.6 (2)
Cough	0 (0)	0 (0)	0 (0)	4.3 (1)	5.0 (1)	4.7 (2)	3.6 (2)
ALT increased	0 (0)	0 (0)	0 (0)	8.7 (2)	0 (0)	4.7 (2)	3.6 (2)
Oedema	16.7 (1)	14.3 (1)	15.4 (2)	0 (0)	0 (0)	0 (0)	3.6 (2)
Conjunctivitis	16.7 (1)	14.3 (1)	15.4 (2)	0 (0)	0 (0)	0 (0)	3.6 (2)

MedDRA ver.19.0; incidence, % (number of subjects)

There were no deaths. Serious adverse events occurred in 23.1% (3 of 13) of ESA-naïve subjects (atrioventricular block second degree [1] and hyperglycaemia [1] in the 50 mg group; head injury [1] in the 70 mg group) and 11.6% (5 of 43) of subjects on ESA therapy (peritonitis [1], rhabdomyolysis [1],

and benign tumour excision [1] in the 70 mg group; general physical health deterioration [1] and peritonitis [1] in the 100 mg group). The rhabdomyolysis in a subject on ESA therapy in the 70 mg group was an adverse drug reaction, which remained unresolved.

No adverse events led to treatment discontinuation among ESA-naïve subjects. In subjects on ESA therapy, adverse events leading to treatment discontinuation occurred in 9.3% (4 of 43) of subjects (rhabdomyolysis/ALT increased/AST increased [1], palpitations/muscular weakness [1], pruritus [1], and dyspepsia [1]), all of which were adverse drug reactions leading to treatment discontinuation. Among these, pruritus and dyspepsia resolved, while the other events (rhabdomyolysis/ALT increased/AST increased in 1 subject and palpitations/muscular weakness in 1 subject) remained unresolved.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the results of discussions in Sections 7.R.1.1 and 7.R.1.2, PMDA considered that the efficacy of roxadustat in the treatment of HD patients has been demonstrated, and roxadustat is also effective in the treatment of patients on PD.

7.R.1.1 HD patients

Based on the discussions in Sections 7.R.1.1.1 and 7.R.1.1.2, PMDA considered that the efficacy of roxadustat in the treatment of HD patients with renal anemia has been demonstrated.

7.R.1.1.1 Efficacy in patients converting from ESA to roxadustat

The applicant explained the efficacy in the conversion/ maintenance in HD patients, a study on the maintenance of Hb levels in HD patients who had been receiving ESA as summarized in Sections 7.R.1.1.1.1 and 7.R.1.1.1.2 below.

7.R.1.1.1.1 The design, endpoints, and other results of the conversion/maintenance study in HD patients

The applicant's explanation about the rationale for the design of the conversion/maintenance study in HD patients, i.e., primary endpoint, control group, and non-inferiority margin, as well as the results for the primary endpoint:

Considering that a study on the maintenance of Hb levels in patients with renal anemia converting from ESA should be aimed to assess whether patients with stable Hb values during an approved ESA therapy be able to maintain the values within the target range after switching to roxadustat, in accordance with the "Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia" (Notification No. 0930-(1) of the Evaluation and Licensing Division, PFSB dated September 30, 2011). The guidelines also recommend a treatment period of ≥24 weeks so that increased and maintained Hb values can be verified. Accordingly, the primary endpoint was defined as the change from baseline in mean Hb values from Weeks 18 to 24.

DA, the most widely used ESA drug in Japan at the time of study planning, was the active control.

With regard to the non-inferiority margin, the target range of Hb for HD patients was 10.0 to 12.0 g/dL, and roxadustat and DA were to be administered while making dose adjustments so that Hb values would stay within the range. It was considered appropriate to use 0.75 g/dL, less than 1/2 of the difference of the upper and lower limits of the target Hb range (12.0 g/dL and 10.0 g/dL), 2 g/dL, as the allowable difference in Hb values for roxadustat and DA.

Table 37 shows the primary endpoint results in the conversion/maintenance study in HD patients. The between-group difference [95% CI] was −0.02 ± 0.08 [−0.18, 0.15] g/dL between the roxadustat and DA groups, indicating that the lower limit of 95% CI was greater than the prescribed value, −0.75 g/dL. Non-inferiority of the roxadustat to the DA group was thus demonstrated.

The percentage of subjects whose Hb values stayed within the target range from Weeks 18 to 24, a secondary endpoint and its 95% CI were 79.3% [72.0, 85.5] (119 of 150 subjects) in the roxadustat group, and 83.4% [76.5, 89.0] (126 of 151 subjects) in the DA group, indicating that a similar percentage in both groups maintained the target Hb.

PMDA's view:
There are no particular problems with the study design for the conversion/maintenance study in HD patients (i.e., primary endpoint, control group, and non-inferiority margin). In the study, the difference [95% CI] in change from baseline in the mean Hb values from Weeks 18 to 24 was −0.02 ± 0.08 [−0.18, 0.15] g/dL between the roxadustat and DA groups. The lower limit of 95% CI was greater than the prescribed value of −0.75 g/dL, demonstrating non-inferiority of roxadustat to DA in HD patients on ESA therapy. The results for the percentage of subjects whose Hb values stayed within the target range from Weeks 18 to 24, a secondary endpoint, also demonstrated that no trends suggesting inferiority of the roxadustat group to the DA group were found.

7.R.1.1.1.2 Efficacy by patient characteristic factors

Table 54 shows mean Hb values from Weeks 18 to 24 in the conversion/maintenance study in HD patients (PPS) by major patient characteristics, showing no significant difference between the roxadustat and DA groups in any subgroup.

Table 54. Mean Hb values from Weeks 18 to 24 in HD patients by patient characteristics (conversion/maintenance study in HD patients, PPS)

Factor	Category	Roxadustat (n = 114)	DA (n = 131)
Sex	Male	10.94 ± 0.60 (79)	10.95 ± 0.60 (93)
	Female	11.09 ± 0.57 (35)	11.02 ± 0.56 (38)
Age	<65 years	10.98 ± 0.63 (54)	11.04 ± 0.53 (57)
	≥65 years	11.00 ± 0.56 (60)	10.92 ± 0.63 (74)
Body weight	<60 kg	11.02 ± 0.64 (67)	10.99 ± 0.56 (72)
	≥60 kg	10.95 ± 0.52 (47)	10.95 ± 0.62 (59)
Underlying illness	Diabetic nephropathy	10.95 ± 0.60 (40)	10.99 ± 0.59 (42)
	Glomerulonephritis chronic	11.07 ± 0.52 (39)	10.84 ± 0.58 (44)
	Nephrosclerosis	10.97 ± 0.76 (15)	11.04 ± 0.74 (18)
	Polycystic kidney	11.08 ± 0.67 (6)	11.06 ± 0.50 (9)
	Pyelonephritis chronic	— (0)	11.40 (1)
	Other	10.87 ± 0.57 (14)	11.13 ± 0.43 (17)
History of dialysis	<5 years	11.03 ± 0.57 (60)	11.02 ± 0.55 (66)
	≥5 years	10.95 ± 0.62 (54)	10.92 ± 0.63 (65)
ESA dose level at enrollment	< rHuEPO 9000 units or DA 40 µg	11.03 ± 0.55 (102)	10.98 ± 0.57 (118)
	≥ rHuEPO 9000 units or DA 40 µg	10.67 ±0.84 (12)	10.93 ± 0.71 (13)
Baseline Hb	<11.0 g/dL	10.91 ± 0.62 (48)	10.99 ± 0.59 (61)
	≥11.0 g/dL	11.05 ± 0.56 (66)	10.95 ± 0.59 (70)
Baseline TSAT	<20%	10.81 ± 0.69 (30)	10.85 ± 0.62 (20)
	≥20%	11.05 ± 0.54 (84)	10.99 ± 0.58 (111)
Concomitant use of phosphate binders during the study period	Yes	10.96 ± 0.59 (104)	10.94 ± 0.58 (115)
	No	11.30 ± 0.51 (10)	11.16 ± 0.61 (16)

Mean value ± standard deviation (number of subjects)

PMDA confirmed that there was no significant difference between the roxadustat and DA groups in any subgroups.

7.R.1.1.2 Efficacy in ESA-naïve, HD patients

The applicant explained the efficacy in the anemia correction study in ESA-naïve HD patients in the following Sections 7.R.1.1.2.1 and 7.R.1.1.2.2.

7.R.1.1.2.1 The primary efficacy endpoint for the anemia correction study in HD patients

The applicant's explanation about the rationale for the design of the anemia correction study in HD patients, as well as the primary efficacy endpoint results:

The study was conducted under unblinded and uncontrolled conditions for the following reasons:

ESA therapy is often initiated at the pre-dialysis stage of renal anemia. The majority of ESA-naïve HD patients have presumably just started dialysis and have not received ESAs. When the study was planned, it was reported that ESA-naïve patients accounted for 11.9% of the total dialysis patients (approximately 30,000 patients) ("An Overview of Regular Dialysis Treatment in Japan (as of 31 December 2012)" edited by The Japanese Society for Dialysis Therapy [JSDT]). In view of these observations, there would be not many ESA-naïve HD patients. A target range of 10.0 to 12.0 g/dL was selected because it was the target range for treatment as recommended in the "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012." By referring to "Guidelines for Clinical Evaluation of

Therapeutic Drugs for Renal Anemia," a treatment period of 24 weeks was determined so as to verify that Hb values would reach the target range after starting roxadustat therapy and stay within the range.

Table 47 shows the results for the primary efficacy endpoint, the mean Hb values from Weeks 18 to 24, and cumulative response rate at the end of treatment (at Week 24 or at the time of treatment discontinuation). The cumulative response rates were ≥80% and were similar in both the roxadustat 50 and 70 mg groups. Table 55 shows the percentage of subjects whose target Hb values stayed within the target range from Weeks 18 to 24, and the rate of rise in Hb up to Week 4,[26)] indicating no significant difference between the groups.

Table 55. The percentage of subjects whose target Hb values stayed within the target range from Weeks 18 to 24, and the rate of rise in Hb up to Week 4 (anemia correction study in HD patients; FAS)

	Roxadustat 50 mg (n = 37)	Roxadustat 70 mg (n = 37)	Total (n = 74)
Mean Hb from Weeks 18 to 24[a)] (g/dL) (mean ± standard deviation)	10.96 ± 0.78	10.90 ± 0.81	10.93 ± 0.79
Number of subjects whose Hb values stayed within the target range from Weeks 18 to 24	28/37	26/37	54/74
Percentage of subjects whose Hb values stayed within the target range from Weeks 18 to 24 [95% CI] (%)	75.7 [58.8, 88.2]	70.3 [53.0, 84.1]	73.0 [61.4, 82.6]
Rate of rise in Hb up to Week 4[b)] (mean ± standard deviation) (g/dL/week)	0.297 ± 0.337	0.238 ± 0.368	0.268 ± 0.352

a) The mean Hb value from Weeks 18 to 24 was calculated by averaging weekly Hb values from Weeks 18 to 24.
b) Rate of rise in Hb up to Week 4, or mean rate of rise in Hb up to treatment discontinuation or dose adjustment by Week 4

PMDA's view:

From the standpoint of feasibility, conducting the anemia correction study in HD patients under unblinded and uncontrolled conditions was unavoidable. The study confirmed that Hb values increased in both the 50 and 70 mg groups, and that target values are achieved and tend to be maintained by the adjustment of roxadustat dose according to Hb values.

7.R.1.1.2.2 Efficacy by patient characteristics

Table 56 shows "cumulative response rate in Hb from baseline through the end of treatment" (FAS) by patient characteristics in the anemia correction study in HD patients. It should be noted that the small number of subjects precluded adequate evaluation in some subgroups. Nevertheless, cumulative response rates were roughly ≥70%, suggesting that there were no patient characteristic factors that would clearly affect the anemia correction by roxadustat.

26) When treatment was discontinued or the dose was adjusted by Week 4, the rate of rise in Hb up to the discontinuation or dose adjustment was used.

Table 56. Cumulative response rate at the end of treatment by patient characteristic factor (anemia correction study in HD patients; FAS)

Factor	Category	Roxadustat 50 mg (n = 37)	Roxadustat 70 mg (n = 37)	Total (n = 74)
Sex	Male	89.3(25/28)	96.3 (26/27)	92.7 (51/55)
	Female	77.8 (7/9)	70.0 (7/10)	73.7 (14/19)
Age	<65 years	100 (15/15)	100 (14/14)	100 (29/29)
	≥65 years	77.3 (17/22)	82.6 (19/23)	80.0 (36/45)
Body weight	<60 kg	89.5 (17/19)	95.0 (19/20)	92.3 (36/39)
	≥60 kg	83.3 (15/18)	82.4 (14/17)	82.9 (29/35)
Underlying illness	Diabetic nephropathy	92.9 (13/14)	82.4 (14/17)	87.1 (27/31)
	Glomerulonephritis chronic	85.7 (6/7)	100 (8/8)	93.3 (14/15)
	Nephrosclerosis	87.5 (7/8)	83.3 (5/6)	85.7 (12/14)
	Polycystic kidney	80.0 (4/5)	100 (2/2)	85.7 (6/7)
	Other	66.7 (2/3)	100 (4/4)	85.7 (6/7)
History of dialysis	<28 days	86.7 (26/30)	85.2 (23/27)	86.0 (49/57)
	≥28 days	85.7 (6/7)	100 (10/10)	94.1 (16/17)
Baseline Hb	<9.0 g/dL	87.5 (21/24)	86.4 (19/22)	87.0 (40/46)
	≥9.0 g/dL	84.6 (11/13)	93.3 (14/15)	89.3 (25/28)
Baseline TSAT	<20%	100 (5/5)	88.9 (8/9)	92.9 (13/14)
	≥20%	84.4 (27/32)	89.3 (25/28)	86.7 (52/60)
Concomitant use of phosphate binders during the study period	Yes	95.2 (20/21)	100 (25/25)	97.8 (45/46)
	No	75.0 (12/16)	66.7 (8/12)	71.4 (20/28)

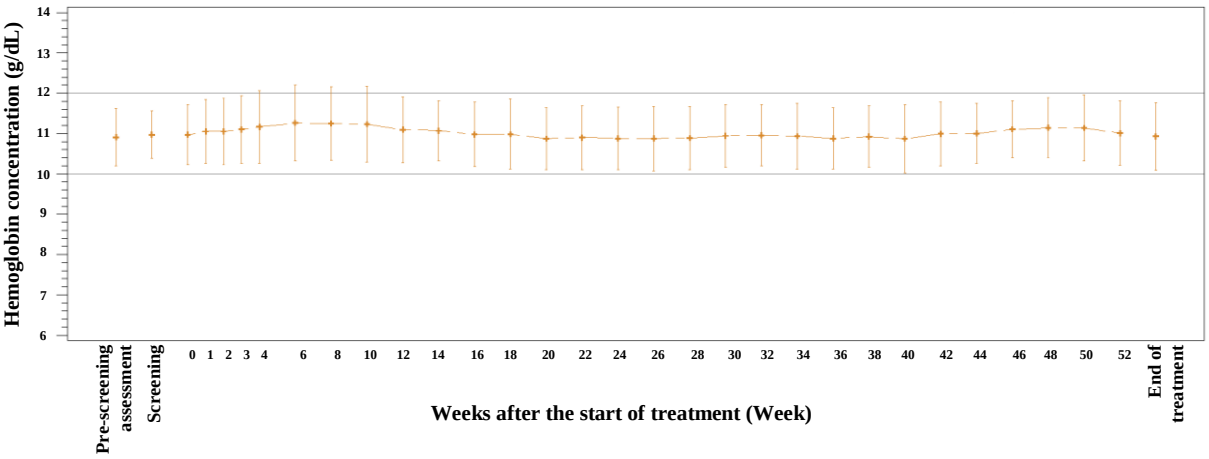
Cumulative response rate, % (cumulative number of subjects with response)

PMDA confirmed that there was no decreasing trend in the efficacy of roxadustat in any specific population of the anemia correction study in HD patients.

7.R.1.1.3 Long-term efficacy in HD patients

The applicant's explanation about the long-term efficacy of roxadustat in HD patients:

The time course of the percentage of subjects whose Hb values stayed within the target range in the Japanese long-term study in HD patients on ESA therapy is shown by evaluation period in Table 42. The results demonstrated that a certain level of effect was maintained at Week 24 and thereafter. Figure 1 shows mean Hb values over the evaluation periods. After converting from ESA to roxadustat, the mean Hb values mostly stayed within the target range (10.0 to 12.0 g/dL).



Evaluation time point (Week)	Pre-screening assessment	Screening	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	End of treatment
n	163	163	163	160	158	156	154	153	152	149	147	147	146	146	147	144	143	140	142	141	137	135	133	130	131	130	128	125	127	126	124	163

Figure 1. Time course of mean Hb values (Mean value ± standard deviation) (Japanese long-term study, FAS)

PMDA confirmed that Hb values tend to stay within the target range (10.0 to 12.0 g/dL) in long-term treatment through appropriate dose adjustment according to Hb values of the HD patients.

7.R.1.2 PD patients

The applicant's explanation about the rationale for the design of the PD study, as well as the primary efficacy endpoint results:

When the study was planned, the reported number of patients who were on PD alone was as small as 7332 ("An Overview of Regular Dialysis Treatment in Japan (as of 31 December 2012)" edited by JSDT). Because of the extremely limited number of PD patients, ESA-naïve patients, patients in a washout period for ESA, and those receiving ESA were also enrolled in the study, and the study was conducted under unblinded and uncontrolled conditions. The target Hb range of 10.0 to 12.0 g/dL was selected based on the "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012." By referring to "Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia," the treatment period was determined as 24 weeks so as to verify that Hb values reach the target range after starting roxadustat therapy and then stay within the target range.

Table 57 shows the results for the primary efficacy endpoints, change from baseline in the mean Hb values, and the percentage of subjects whose target Hb values stayed within the target range from Weeks 18 to 24. Approximately 90% of ESA-naïve patients achieved the target Hb during Weeks 18 to 24. Change from baseline in the mean Hb from Weeks 18 to 24 was 0.14 ± 0.76 g/dL in patients converting from ESA therapy, indicating that Hb values stayed within the target range without significant changes after converting from ESA.

Table 57. Change from baseline in the mean Hb values and percentage of subjects whose Hb values stayed within the target range from Weeks 18 to 24 (conversion/maintenance study in HD patients, anemia correction study in HD patients, PD study; FAS)

	ESA-naïve subjects		Subjects converting from ESA		Total	
	HD[a)] (n = 74)	PD (n = 13)	HD[a)] (n = 150)	PD (n = 43)	HD total[a)] (n = 224)	PD total (n = 56)
Mean baseline Hb (g/dL)	8.65 ± 0.78	9.35 ± 0.75	11.02 ± 0.56	10.85 ± 0.54	10.24 ± 1.28	10.50 ± 0.87
Mean Hb from Weeks 18 to 24 (g/dL)	10.93 ± 0.79	11.05 ± 0.62	11.00 ± 0.60	10.93 ± 0.61	10.97±0.67	10.96 ± 0.61
Change from baseline in mean Hb from Week 18 to Week 24 (g/dL)	2.26 ± 1.02	1.69 ± 1.05	-0.04 ± 0.79	0.14 ± 0.76	0.75 ± 1.40	0.54 ± 1.08
Number of subjects whose Hb values stayed within the target range from Weeks 18 to 24	54	12	119	32	173	44
Percentage of subjects whose Hb values stayed within the target range from Weeks 18 to 24 (%)	73.0 [61.4, 82.6]	92.3 [64.0, 99.8]	79.3 [72.0, 85.5]	74.4 [58.8, 86.5]	77.2 [71.2, 82.6]	78.6 [65.6, 88.4]

Mean Hb value, mean ± standard deviation; percentage of subjects whose Hb values stayed within the target range, the percentage of subjects, % [95% CI]

a) Data for ESA-naïve HD subjects are based on the anemia correction study in HD patients, data for subjects converting from ESA are based on the conversion/maintenance study in HD patients, and the total data are based on the pooled data for the studies.

PMDA's view:

From the standpoint of feasibility, conducting the general Japanese clinical study in PD patients under unblinded and uncontrolled conditions was unavoidable. The study confirmed that Hb values increase in ESA-naïve subjects, and that both ESA-naïve patients and patients converting from ESA therapy keep Hb values within the target range through the adjustment of roxadustat dose according to Hb values as with in HD patients.

7.R.2 Safety

PMDA's view:

Based on the discussions below, in Sections 7.R.2.1 through 7.R.2.5, the safety of roxadustat in patients with renal anemia on HD or PD is acceptable with a view to dose adjustment based on careful monitoring of Hb values, etc. However, further data collection is required on the occurrence of thromboembolism, hypertension, hepatic dysfunction, malignant tumors, and retinal haemorrhage through post-marketing surveillance.

7.R.2.1 HD patients

Table 58 shows the incidences of adverse events in the roxadustat and DA groups in the conversion/maintenance study in HD patients. There were no significant differences between the roxadustat and DA groups in the incidences of adverse events, and the majority of adverse events in the roxadustat group were mild or moderate in severity. Bradycardia, acute myocardial infarction, cardiac failure congestive, cellulitis, and hypotension in 1 subject each in the roxadustat group were severe. A causal relationship to roxadustat was ruled out for all these severe adverse events except for cardiac

failure congestive, which was assessed as an adverse drug reaction. Adverse drug reactions occurred at a slightly higher incidence in the roxadustat group than in the DA group. However, adverse drug reactions that occurred in ≥2 subjects in any group, as shown in Table 39, showed no trend toward increased incidences of particular events in the roxadustat group as compared with the DA group.

There were 2 deaths in the roxadustat group (acute myocardial infarction and cardiac failure congestive in 1 subject each). While a causal relationship to roxadustat was ruled out for acute myocardial infarction, the investigator concluded that a causal relationship could not be ruled out for cardiac failure congestive. The applicant, however, explained that the patient who died of cardiac failure congestive had complications of hypertension, angina pectoris, and dyslipidemia, with poorly controlled body fluid, and the possibility is low that roxadustat adversely affected the patient's condition. While the incidence of serious adverse events tended to be slightly higher in the roxadustat group than in the DA group, there were no trends toward increased incidences of particular events in the roxadustat group as compared with the DA group based on the data on serious adverse events that occurred in ≥2 subjects, namely, shunt stenosis (6), shunt occlusion (3), cellulitis (2), and deep vein thrombosis (2) in the roxadustat group; shunt stenosis (7), angina pectoris (2), and shunt occlusion (2) in the DA group. Furthermore, there were no significant differences in the incidence of serious adverse drug reactions or adverse drug reactions leading to treatment discontinuation between the roxadustat and DA groups. No serious adverse drug reactions or adverse drug reactions leading to treatment discontinuation occurred in ≥2 subjects in any groups.

Table 58. Incidence of adverse events and adverse drug reactions in Japanese phase III comparative study (conversion/maintenance study in HD patients)

	Roxadustat (n = 150)	DA (n = 152)
Adverse event	**86.0 (129)**	**82.9 (126)**
Adverse drug reaction	**22.0 (33)**	**13.2 (20)**
Death	**1.3 (2)**	**0 (0)**
Serious adverse event	**20.7 (31)**	**14.5 (22)**
Serious adverse drug reaction	**3.3 (5)**	**3.9 (6)**
Adverse events leading to treatment discontinuation	**8.7 (13)**	**5.3 (8)**
Adverse drug reaction leading to treatment discontinuation	**5.3 (8)**	**3.3 (5)**
Adverse events with an incidence of ≥5.0% in at least 1 group		
Nasopharyngitis	**34.7 (52)**	**26.3 (40)**
Shunt stenosis	**7.3 (11)**	**8.6 (13)**
Diarrhoea	**7.3 (11)**	**7.9 (12)**
Contusion	**6.7 (10)**	**6.6 (10)**
Vomiting	**6.7 (10)**	**2.0 (3)**

MedDRA ver.19.0; incidence, % (number of subjects)

Table 59 shows the incidences of adverse events in the anemia correction study in HD patients. The majority of the adverse events were mild or moderate in severity. Acute coronary syndrome and femur fracture in 1 subject each were severe; however, a causal relationship to roxadustat was ruled out for these events. As compared with the results from the conversion/maintenance study in HD patients (Table 59), the incidence of dermatitis contact was high in ESA-naïve subjects than in those converting from

ESA. However, a causal relationship to roxadustat was ruled out for all cases. The incidence of serious adverse events tends to be slightly higher in ESA-naïve subjects than in those converting from ESA. However, serious adverse events that occurred in ≥2 subjects were shunt occlusion (5) and cardiac failure congestive (2), and there were no trends of increased incidence of specific events in ESA-naïve subjects as compared with those converting from ESA. The incidence of serious adverse drug reactions or drug reactions leading to treatment discontinuation did not tend to increase in ESA-naïve subjects as compared with subjects converting from ESA. No serious adverse drug reactions or no adverse drug reactions leading to treatment discontinuation occurred in ≥2 subjects.

Table 59. Incidences of adverse events in ESA-naïve, or ESA-converting HD patients following roxadustat administration (anemia correction study in HD patients, and conversion/maintenance study in HD patients)

	ESA-naïve subjects[a)] (n = 75)	Subjects converting from ESA[b)] (n = 150)
Adverse event	**90.7 (68)**	**86.0 (129)**
Adverse drug reaction	**21.3 (16)**	**22.0 (33)**
Death	**0 (0)**	**1.3 (2)**
Serious adverse event	**29.3 (22)**	**20.7 (31)**
Serious adverse drug reaction	**4.0 (3)**	**3.3 (5)**
Adverse events leading to treatment discontinuation	**4.0 (3)**	**8.7 (13)**
Adverse drug reaction leading to treatment discontinuation	**1.3 (1)**	**5.3 (8)**
Adverse events with an incidence of ≥5.0% in at least 1 population		
Nasopharyngitis	**20.0 (15)**	**34.7 (52)**
Dermatitis contact	**13.3 (10)**	**1.3 (2)**
Shunt occlusion	**9.3 (7)**	**4.7 (7)**
Constipation	**6.7 (5)**	**2.0 (3)**
Shunt stenosis	**6.7 (5)**	**7.3 (11)**
Hyperphosphataemia	**6.7 (5)**	**0.7 (1)**
Diarrhoea	**6.7 (5)**	**7.3 (11)**
Contusion	**6.7 (5)**	**6.7 (10)**
Insomnia	**5.3 (4)**	**1.3 (2)**
Eczema	**5.3 (4)**	**2.7 (4)**
Vomiting	**5.3 (4)**	**6.7 (10)**
Back pain	**5.3 (4)**	**2.0 (3)**

MedDRA ver.19.0; incidence, % (number of subjects)
a) Data of ESA-naïve HD subjects are based on the anemia correction study in HD patients.
b) Data of subjects converting from ESA are based on the conversion/maintenance study in HD patients.

PMDA's view:

In the conversion/maintenance study in HD patients, the data of subjects converting from ESA indicated no trend in the occurrence of adverse events that could potentially cause clinical problems in the roxadustat group as compared with the DA group. In the anemia correction study in HD patients, the data of ESA-naïve subjects revealed no particular issues that could potentially cause clinical problems. Adverse events of interest include thromboembolism, hypertension, hepatic dysfunction, malignant tumors, and retinal haemorrhage, which are discussed in Section 7.R.2.5.

7.R.2.2 PD patients

Table 60 shows the incidences of adverse events in the PD study. The adverse events were either mild or moderate in severity. The incidences of adverse drug reactions were somewhat higher in the PD study as compared with the pooled data from the conversion/maintenance study in HD patients and anemia correction study in HD patients. However, with the exception of catheter site infection, which is unique to PD patients, there were no specific adverse events or adverse drug reactions that occurred at a higher incidence solely in PD patients.

Table 60. Incidences of adverse events in HD patients and PD patients following roxadustat administration (conversion/maintenance study in HD patients, anemia correction study in HD patients, and PD study)

	ESA-naïve subjects		Subjects converting from ESA		Total	
	HD[a)] (n = 75)	PD (n = 13)	HD[a)] (n = 150)	PD (n = 43)	HD total[a)] (n = 225)	PD total (n = 56)
Adverse event	**90.7 (68)**	**76.9 (10)**	**86.0 (129)**	**90.7 (39)**	**87.6 (197)**	**87.5 (49)**
Adverse drug reaction	**21.3 (16)**	**30.8 (4)**	**22.0 (33)**	**39.5 (17)**	**21.8 (49)**	**37.5 (21)**
Death	**0 (0)**	**0 (0)**	**1.3 (2)**	**0 (0)**	**0.9 (2)**	**0 (0)**
Serious adverse event	**29.3 (22)**	**23.1 (3)**	**20.7 (31)**	**11.6 (5)**	**23.6 (53)**	**14.3 (8)**
Serious adverse drug reaction	**4.0 (3)**	**0 (0)**	**3.3 (5)**	**2.3 (1)**	**3.6 (8)**	**1.8 (1)**
Adverse events leading to treatment discontinuation	**4.0 (3)**	**0 (0)**	**8.7 (13)**	**9.3 (4)**	**7.1 (16)**	**7.1 (4)**
Adverse drug reaction leading to treatment discontinuation	**1.3 (1)**	**0 (0)**	**5.3 (8)**	**9.3 (4)**	**4.0 (9)**	**7.1 (4)**
Adverse events with an incidence of ≥5.0% in total HD patients or in total PD patients						
Nasopharyngitis	**20.0 (15)**	**0 (0)**	**34.7 (52)**	**32.6 (14)**	**29.8 (67)**	**25.0 (14)**
Back pain	**5.3 (4)**	**23.1 (3)**	**2.0 (3)**	**4.7 (2)**	**3.1 (7)**	**8.9 (5)**
Diarrhoea	**5.3 (4)**	**0 (0)**	**7.3 (11)**	**9.3 (4)**	**6.7 (15)**	**7.1 (4)**
Vomiting	**5.3 (4)**	**0 (0)**	**6.7 (10)**	**9.3 (4)**	**6.2 (14)**	**7.1 (4)**
Catheter site infection	**0 (0)**	**0 (0)**	**0 (0)**	**9.3 (4)**	**0 (0)**	**7.1 (4)**
Constipation	**6.7 (5)**	**0 (0)**	**2.0 (3)**	**7.0 (3)**	**3.6 (8)**	**5.4 (3)**
Pruritus	**2.7 (2)**	**0 (0)**	**2.0 (3)**	**7.0 (3)**	**2.2 (5)**	**5.4 (3)**
Abdominal pain	**0 (0)**	**0 (0)**	**0.7 (1)**	**7.0 (3)**	**0.4 (1)**	**5.4 (3)**
Nausea	**2.7 (2)**	**0 (0)**	**2.7 (4)**	**7.0 (3)**	**2.7 (6)**	**5.4 (3)**
Conjunctivitis	**4.0 (3)**	**15.4 (2)**	**0.7 (1)**	**2.3 (1)**	**1.8 (4)**	**5.4 (3)**
Contusion	**5.3 (4)**	**0 (0)**	**6.7 (10)**	**2.3 (1)**	**6.2 (14)**	**1.8 (1)**
Shunt stenosis	**6.7 (5)**	**0 (0)**	**7.3 (11)**	**0 (0)**	**7.1 (16)**	**0 (0)**
Shunt occlusion	**9.3 (7)**	**0 (0)**	**4.7 (7)**	**0 (0)**	**6.2 (14)**	**0 (0)**
Dermatitis contact	**13.3 (10)**	**0 (0)**	**1.3 (2)**	**0 (0)**	**5.3 (12)**	**0 (0)**

MedDRA ver.19.0; incidence, % (number of subjects)

a) Data of ESA-naïve HD subjects are based on the anemia correction study in HD patients while data of subjects converting from ESA are based on the conversion/maintenance study in HD patients, and the total data are based on the pooled data from the studies.

PMDA's view:

As compared with HD patients, there were no trends in the occurrence of adverse events that could potentially cause clinical problems in PD patients in particular.

7.R.2.3 Long-term safety

Table 61 shows adverse events that occurred in ≥5.0% of subjects throughout the period of the Japanese long-term study. There were no particular differences that could potentially cause clinical problems in

comparison with the results from the conversion/maintenance study in HD patients (Table 38). Table 61 also shows the incidence of adverse events by treatment period. The incidence of adverse events did not tend to increase with increased treatment duration.

Table 61. Incidence of adverse events by period in Japanese long-term study

	Weeks 0-12 (n = 163)	Weeks 12-24 (n = 149)	Weeks 24-36 (n = 144)	Weeks 36-52 (n = 134)	Entire period (n = 163)
Adverse event	**67.5 (110)**	**65.8 (98)**	**70.1 (101)**	**73.9 (99)**	**95.7 (156)**
Adverse drug reaction	**12.3 (20)**	**6.7 (10)**	**9.0 (13)**	**9.0 (12)**	**27.6 (45)**
Death	**0.6 (1)**	**0 (0)**	**0.7 (1)**	**0 (0)**	**1.2 (2)**
Serious adverse event	**9.8 (16)**	**6.7 (10)**	**15.3 (22)**	**9.7 (13)**	**28.2 (46)**
Serious adverse drug reaction	**2.5 (4)**	**1.3 (2)**	**2.1 (3)**	**3.0 (4)**	**6.7 (11)**
Adverse events leading to treatment discontinuation	**4.9 (8)**	**0 (0)**	**2.8 (4)**	**3.7 (5)**	**10.4 (17)**
Adverse drug reaction leading to treatment discontinuation	**3.1 (5)**	**0 (0)**	**2.1 (3)**	**3.7 (5)**	**8.0 (13)**
Adverse events with an incidence of ≥5.0% in overall period					
Nasopharyngitis	**22.7 (37)**	**29.5 (44)**	**20.1 (29)**	**16.4 (22)**	**52.8 (86)**
Diarrhoea	**6.1 (10)**	**1.3 (2)**	**3.5 (5)**	**3.7 (5)**	**11.0 (18)**
Vomiting	**4.3 (7)**	**2.7 (4)**	**2.8 (4)**	**3.7 (5)**	**10.4 (17)**
Contusion	**4.3 (7)**	**3.4 (5)**	**2.1 (3)**	**3.0 (4)**	**9.8 (16)**
Shunt stenosis	**3.1 (5)**	**0.7 (1)**	**3.5 (5)**	**3.7 (5)**	**7.4 (12)**
Back pain	**1.2 (2)**	**2.0 (3)**	**2.1 (3)**	**4.5 (6)**	**7.4 (12)**
Shunt occlusion	**2.5 (4)**	**0.7 (1)**	**0.7 (1)**	**3.7 (5)**	**6.1 (10)**
Constipation	**2.5 (4)**	**4.0 (6)**	**1.4 (2)**	**3.0 (4)**	**6.1 (10)**
Dental caries	**0.6 (1)**	**0.7 (1)**	**2.1 (3)**	**3.0 (4)**	**5.5 (9)**
Headache	**0.6 (1)**	**1.3 (2)**	**3.5 (5)**	**1.5 (2)**	**5.5 (9)**

MedDRA/ver19.0; incidence, % (number of subjects)

7.R.2.4 Safety by patient characteristic factor

Table 62 shows the incidence of adverse events by patient characteristics in Japanese phase III studies (conversion/maintenance study in HD patients, anemia correction study in HD patients, long-term study, and PD study). There were no trends in any subgroups that could potentially cause clinical problems.

Table 62. Incidences of adverse events by main patient characteristics (conversion/maintenance study in HD patients, anemia correction study in HD patients, long-term study, and PD study)

Factor	Category	conversion/maintenance study in HD patients		Roxadustat HD, pooled[a)] (n = 388)	Roxadustat PD[a)] (n = 56)
		Roxadustat (n = 150)	DA (n = 152)		
Sex	Men	84.2 (85/101)	82.4 (89/108)	90.2 (230/255)	88.9 (32/36)
	Women	89.8 (44/49)	84.1 (37/44)	92.5 (123/133)	85.0 (17/20)
Age	<65 years	79.1 (53/67)	71.0 (44/62)	87.9 (160/182)	79.2 (19/24)
	≥65 years	91.6 (76/83)	91.1 (82/90)	93.7 (193/206)	93.8 (30/32)
Body weight	<60 kg	83.9 (78/93)	82.9 (68/82)	90.0 (207/230)	91.3 (21/23)
	≥60 kg	89.5 (51/57)	82.9 (58/70)	92.4 (146/158)	84.8 (28/33)
Underlying illness	Diabetic nephropathy	87.2 (41/47)	83.7 (41/49)	95.5 (126/132)	100 (13/13)
	Glomerulonephritis chronic	84.9 (45/53)	79.6 (43/54)	89.4 (118/132)	89.5 (17/19)
	Nephrosclerosis	83.3 (15/18)	89.5 (17/19)	86.3 (44/51)	81.3 (13/16)
	Polycystic kidney	91.7 (11/12)	80.0 (8/10)	92.0 (23/25)	0 (0/0)
	Other	85.0 (17/20)	85.0 (17/20)	87.5 (42/48)	75.0 (6/8)
History of dialysis	<5 years	84.0 (63/75)	82.1 (64/78)	91.6 (206/225)	87.0 (40/46)
	≥5 years	88.0 (66/75)	83.8 (62/74)	90.2 (147/163)	90.0 (9/10)
ESA dose level at enrollment	< rHuEPO 9000 units, DA 40 µg, or CERA 200 µg	84.3 (113/134)	82.4 (112/136)	90.1 (254/282)	89.2 (33/37)
	≥ rHuEPO 9000 units, DA 40 µg, or CERA 200 µg	100 (16/16)	87.5 (14/16)	100.0 (31/31)	100 (6/6)
Baseline Hb	<11.0 g/dL	91.0 (61/67)	85.3 (58/68)	91.9 (203/221)	86.8 (33/38)
	≥11.0 g/dL	81.9 (68/83)	81.0 (68/84)	89.8 (150/167)	88.9 (16/18)
Baseline TSAT	<20%	89.5 (34/38)	78.3 (18/23)	87.8 (65/74)	60.0 (3/5)
	≥20%	84.8 (95/112)	83.7 (108/129)	91.7 (288/314)	90.2 (46/51)
Concomitant use of phosphate binders during the study period	With	86.2 (119/138)	83.6 (112/134)	90.8 (305/336)	87.0 (40/46)
	Without	83.3 (10/12)	77.8 (14/18)	92.3 (48/52)	90.0 (9/10)

Incidence, % (number of subjects with adverse events/number of subjects analyzed)

a) The pooled data of HD patients are based on the pooled data of roxadustat groups from the conversion/maintenance study in HD patient, anemia correction study in HD patients, and long-term study; data of PD patients are based on the PD study.

7.R.2.5 Adverse events of interest associated with roxadustat therapy

In the following Sections 7.R.2.5.1 through 7.R.2.5.5, PMDA discusses the occurrence of thromboembolism, hypertension, hepatic dysfunction, malignant tumors, and retinal haemorrhage, as adverse events of interest based on the action mechanism of roxadustat, nonclinical and clinical study results, etc.

7.R.2.5.1 Thromboembolism

The toxicity studies of roxadustat yielded thromboembolism-related findings [see Section 5.R.1]. One of the known adverse reactions of ESAs is increased risk of thromboembolism due to increased blood viscosity following anemia correction (2015 Guideline for Renal Anemia in Chronic Kidney Disease), and the current package inserts of ESAs warn of the risk of thromboembolism. PMDA asked the applicant to explain the occurrence of thromboembolism-related events reported in Japanese phase III studies in HD and PD patients.

The applicant's explanation:
The occurrence of thromboembolism-related events in the pooled data from the Japanese phase III studies in HD patients (conversion/maintenance study in HD patients, anemia correction study in HD patients, and long-term study) and the PD study was assessed based on adverse events falling under a MedDRA SMQ of "Embolic and thrombotic events (narrow)."

In pooled data from the Japanese phase III studies in HD patients, the incidence of thromboembolism-related events was 11.3% (44 of 388 subjects) in the roxadustat group and 3.9% (6 of 152 subjects) in the DA group (Table 63). Although their incidences were higher in the roxadustat group than in the DA group, they were mild or moderate in severity except for acute myocardial infarction in 2 subjects. Acute myocardial infarction in 2 subjects was severe and that in 1 of them was an adverse drug reaction; however, the outcome was reported as "resolved" without roxadustat being discontinued. The incidence of thromboembolism-related adverse drug reactions was 3.9% (15 of 388 subjects) in the roxadustat group and 1.3% (2 of 152 subjects) in the DA group, indicating no significant difference. The incidence of serious thromboembolism-related adverse events was 8.2% in the roxadustat group (32 of 388 subjects; shunt occlusion [17], cerebral infarction [3], acute myocardial infarction [2], angioplasty [2], deep vein thrombosis [2], peripheral arterial occlusive disease [2], vascular stent occlusion [1], lacunar infarction [1], thrombectomy [1], coronary angioplasty [1], thrombophlebitis superficial [1], and venous occlusion [1]) and 2.6% in the DA group (4 of 152 subjects; shunt occlusion [2], angioplasty [1], and peripheral arterial occlusive disease [1]). The incidence of thromboembolism-related events as serious adverse drug reactions was 2.3% in the roxadustat group (9 of 388 subjects; shunt occlusion [5], cerebral infarction [3], deep vein thrombosis [1], and lacunar infarction [1]) and 0.7% in the DA group (1 of 152 subjects; shunt occlusion). The outcome of shunt occlusion in 2 subjects and cerebral infarction, deep vein thrombosis, and lacunar infarction in 1 subject each in the roxadustat group was reported as "unresolved."

In the PD study, no thromboembolism-related events occurred (Table 63).

Table 63. Incidences of thromboembolism-related events (conversion/maintenance study in HD patients, anemia correction study in HD patients, long-term study, and PD study)

	Conversion/ maintenance study in HD patients		Roxadustat HD, pooled[a)] (n = 388)	Roxadustat PD[a)] (n = 56)
	Roxadustat (n = 150)	DA (n = 152)		
Thromboembolism-related events total	**9.3 (14)**	**3.9 (6)**	**11.3 (44)**	**0 (0)**
Shunt occlusion	**4.7 (7)**	**2.0 (3)**	**6.2 (24)**	**0 (0)**
Cerebral infarction	**0.7 (1)**	**0 (0)**	**0.8 (3)**	**0 (0)**
Acute myocardial infarction	**0.7 (1)**	**0 (0)**	**0.5 (2)**	**0 (0)**
Angioplasty	**0 (0)**	**0.7 (1)**	**0.5 (2)**	**0 (0)**
Deep vein thrombosis	**1.3 (2)**	**0 (0)**	**0.5 (2)**	**0 (0)**
Peripheral arterial occlusive disease	**0 (0)**	**1.3 (2)**	**0.5 (2)**	**0 (0)**
Thrombosis in device	**0 (0)**	**0 (0)**	**0.5 (2)**	**0 (0)**
Retinal vein occlusion	**0 (0)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Vascular stent occlusion	**0.7 (1)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Shunt thrombosis	**0.7 (1)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Coronary angioplasty	**0.7 (1)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Jugular vein thrombosis	**0.7 (1)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Venous occlusion	**0.7 (1)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Cerebral thrombosis	**0 (0)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Lacunar infarction	**0 (0)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Thrombectomy	**0 (0)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Thrombophlebitis superficial	**0 (0)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Venous thrombosis	**0 (0)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Venous thrombosis limb	**0 (0)**	**0 (0)**	**0.3 (1)**	**0 (0)**
Vascular graft occlusion	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**

MedDRA ver.19.0; incidence, % (number of subjects)

a) The pooled data for HD patients are based on the pooled data for roxadustat groups from the conversion/maintenance study in HD patients, anemia correction study in HD patients, and long-term study; data for PD patients are based on the PD study.

PMDA's view:

Although the majority of thromboembolism-related events in HD patients receiving roxadustat were mild or moderate in severity, the incidence of thromboembolism-related events in the roxadustat group was higher than that in the DA group. Given that the incidence of serious thromboembolism-related events was also higher in the roxadustat group than in the DA group, and that serious adverse drug reactions of shunt occlusion and cerebral infarction occurred in ≥2 subjects, the possibility cannot be ruled out that serious thromboembolism-related events could occur as a result of increased blood viscosity when roxadustat is used for anemia correction. The risk of thromboembolism is warned in the package insert of DA, and it is necessary to give cautionary advice on the risk of thromboembolism associated with roxadustat as well. It is also necessary to continue to investigate the occurrence of thromboembolism in the post-marketing setting.

7.R.2.5.2 Hypertension

It has been suggested that as an adverse drug reaction of ESA, blood pressure increases as a result of anemia correction, leading to the development of hypertension[27)] (2015 Guideline for Renal Anemia in

[27)] The guidelines explain the pathogenic mechanism of hypertension associated with anemia correction as follows: improved anemic condition promotes the improvement in hypoxia in the tissue, causing contraction of expanded peripheral vessels, and increasing blood viscosity, thereby increasing the peripheral blood vessel resistance.

Chronic Kidney Disease), and the current package inserts of ESAs warn about the elevation of blood pressure. PMDA asked the applicant to explain the occurrence of hypertension-related events in the Japanese phase III studies in HD and PD patients.

The applicant's explanation:
The hypertension-related events in the pooled data from the Japanese phase III studies in HD patients (conversion/maintenance study in HD patients, anemia correction study in HD patients, and long-term study) and in the PD study data were investigated based on the occurrence of adverse events falling into a MedDRA SMQ of "hypertension (narrow)."

The pooled data from the Japanese phase III studies in HD patients revealed that the incidence of hypertension-related events was 3.1% (12 of 388 subjects; hypertension [10] and blood pressure increased [2]) in the roxadustat group and 4.6% (7 of 152 subjects; hypertension [7]) in the DA group. Hypertension in 7 subjects and blood pressure increased in 1 subject in the roxadustat group and hypertension in 3 subjects in the DA group were assessed as adverse drug reactions. The incidences of adverse events and adverse drug reactions in the roxadustat group were similar to those in the DA group, and these events were mild or moderate in severity. In the PD study (Study 0302), hypertension-related events occurred in 1.8% (1 of 56) of subjects (hypertension). The event was assessed as an adverse drug reaction while it was mild in severity.

Based on the above, in comparison with DA, the possibility is low that the incidence of hypertension-related events associated with roxadustat could become a clinical problem.

PMDA's view:
The incidence of hypertension-related events in roxadustat-treated patients was similar to that in DA-treated patients. Hypertension-related events reported in the Japanese phase III studies were mild or moderate in severity. These outcomes indicate the low possibility of hypertension-related events associated with roxadustat that could pose a clinical problem as compared with DA. Nevertheless, given that possible rise in blood pressure highlighted in the package insert of DA, along with advice to use DA with close monitoring for changes in blood pressure, safety measures taken for roxadustat therapy should be similar to those for DA. Furthermore, because of the reported hypertensive encephalopathy associated with blood pressure increase in DA-treated patients, investigation on hypertension-related events should be continued in the post-marketing setting.

7.R.2.5.3 Hepatic dysfunction

In nonclinical studies in rats and monkeys, increased AST or ALT, etc., which are suggestive of hepatic dysfunction, were noted. PMDA asked the applicant to explain the occurrence of hepatic dysfunction-related events in the clinical studies in HD and PD patients.

The applicant's explanation:
Hepatic dysfunction-related events were investigated using the pooled data from the Japanese phase III studies in HD patients (conversion/maintenance study in HD patients, anemia correction study in HD patients, and long-term study [up to Week 24]), as well as data from the PD study, based on the occurrence of adverse events falling into MedDRA SMQs of "Drug related hepatic disorders - severe events only (broad)," and "Liver related investigations, signs, and symptoms (broad)."

According to the pooled data from the Japanese phase III studies in HD patients, hepatic dysfunction-related events occurred in 2.1% (8 of 388) of subjects in the roxadustat group (hypoalbuminaemia [4], AST increased [1], hepatic congestion [1], hepatic function abnormal [1], and liver function test abnormal [1]), while no adverse events occurred in the DA group. Although the incidence of hepatic dysfunction-related events was higher in the roxadustat group as compared with the DA group, the events were mild or moderate in severity except for hepatic congestion in 1 subject. Although hepatic congestion was severe, a causal relationship to roxadustat was ruled out for the event.

In the PD study, hepatic dysfunction-related events occurred in 3.6% (2 of 56) of subjects (ALT increased [2], AST increased [1], and blood ALP increased [1] [including duplicates in the same patients]), and the events were mild or moderate in severity.

Therefore, in comparison with DA, the incidence of hepatic dysfunction-related events associated with roxadustat therapy is unlikely to cause a clinical problem.

PMDA's view:
The incidence of hepatic dysfunction-related events with roxadustat was higher than that with DA, but the events were mild or moderate in severity. The incidence of hepatic dysfunction-related events associated with roxadustat is unlikely to cause a clinical problem as compared with DA. However, investigation on the incidence of hepatic dysfunction-related events should be continued in the post-marketing setting.

7.R.2.5.4 Malignant tumors

Roxadustat is known to activate the HIF pathway, increasing the expression of vascular endothelial growth factor (VEGF) (*Cell Death Differ*. 2008;15:621-7), which induces tumor cell proliferation via angiogenesis promotion. PMDA asked the applicant to explain the occurrence of malignant tumors in the Japanese phase III studies in HD and PD patients.

The applicant's explanation:
The malignant tumors in the pooled data from the Japanese phase III studies in HD patients (conversion/maintenance study in HD patients, anemia correction study in HD patients, and long-term study) and in data from the PD study were investigated based on the occurrence of adverse events falling into a MedDRA SMQ of "Malignant or unspecified tumours (narrow)."

According to the pooled data from the Japanese phase III studies in HD patients, the incidence of malignant tumors was 0.5% in the roxadustat group (2 of 388 subjects; gastric cancer [1] and pancreatic carcinoma [1]) and 2.6% in the DA group (4 of 152 subjects; basal cell carcinoma [1], malignant neoplasm of renal pelvis [1], transitional cell carcinoma [1], and lip and/or oral cavity cancer [1]). A causal relationship to roxadustat was ruled out for gastric cancer and pancreatic carcinoma in the roxadustat group, while malignant neoplasm of renal pelvis, and lip and/or oral cavity cancer in 1 subject each in the DA group were adverse drug reactions.

There were no malignant tumors in the PD study.

Based on the above, as compared with DA, malignant tumors associated with roxadustat therapy are unlikely to cause a problem.

PMDA's view:
Until now, there are no particular problems in the occurrence of malignant tumors. However, patients with malignant tumors were excluded from the clinical studies, and the possibility remains that roxadustat could promote tumor cell proliferation by enhancing angiogenesis via HIF pathway activation. Therefore, data collection on the occurrence of malignant tumors should be continued in the post-marketing setting for further investigation.

7.R.2.5.5 Retinal haemorrhage

Retinal haemorrhage occurred in 9.3% (9 of 97) of subjects in the roxadustat group total in the Japanese phase II study, while no retinal haemorrhage occurred in the DA group. PMDA asked the applicant to explain the occurrence of retinal haemorrhage in studies conducted in Japan.

The applicant's explanation:
Ophthalmological examinations (fundoscopy, optical coherence tomography, and visual acuity tests) were performed only in the Japanese phase II study and the conversion/maintenance study in HD patients.

Ophthalmological examinations were performed in the Japanese phase II study. The incidence of retinal haemorrhage was 9.3% (9 of 97 subjects) in the entire roxadustat group, while no retinal haemorrhage occurred in the DA group. There were no changes in retinal thickness in any group during the treatment period. The high incidence of retinal haemorrhage in the roxadustat group in the study may be attributed to the absence of the allocation factor defined as diseases with retinal haemorrhage risk, resulting in the disproportionate allocation of patients in this category to the roxadustat group. Therefore, in the conversion/maintenance study, retinal vascular diseases, either past or concurrent, and diabetes mellitus were added to allocation factors.

In the conversion/maintenance study in HD patients, the incidence of retinal haemorrhage was 3.3% (5 of 150 subjects) in the roxadustat group and 3.9% (6 of 152 subjects) in the DA group, indicating similarity between the groups. The events of retinal haemorrhage in the roxadustat and DA groups were all mild in severity, and none of them were serious or led to treatment discontinuation. Furthermore, there were no changes in retinal thickness during the treatment period in any group. Accordingly, as compared with DA, retinal haemorrhage is unlikely to cause a problem in roxadustat therapy.

PMDA's view:
There are no trends suggesting increased risk for retinal haemorrhage associated with roxadustat at present as compared with DA. However, the clinical studies excluded patients with increased risk of retinal haemorrhage (patients with untreated proliferative diabetic retinopathy, macular edema, exudative age-related macular degeneration, retinal vein occlusion, etc.) and roxadustat may increase angiogenesis via HIF pathway activation. Given these, healthcare professionals should be advised via the package insert to administer roxadustat with caution particularly to patients with increased risk of retinal haemorrhage. Data collection on the occurrence of retinal haemorrhage should be continued in the post-marketing setting for further investigation.

7.R.3 Indication and clinical positioning

The applicant's explanation about the intended patient population and clinical positioning of roxadustat:
The results of Japanese clinical studies demonstrated the effectiveness of roxadustat in the correction of anemia in HD patients and that in maintaining Hb values in patients converting from ESA, as well as the efficacy of roxadustat in the treatment of PD patients [Section 7.R.1]. The safety of roxadustat in the clinical studies was acceptable [Section 7.R.2]. Therefore, the indication of roxadustat was proposed as "renal anemia in patients on dialysis."

Currently, ESAs (intravenous or subcutaneous) are used in the treatment of renal anemia in HD patients and PD patients. Because roxadustat's action mechanism and route of administration differ from those of ESAs, roxadustat is a promising new treatment option for patients with renal anemia on dialysis. Roxadustat is not meant to be used in combination with ESAs, and the efficacy, safety, etc. of roxadustat in combination with ESAs were not evaluated in the clinical studies.

PMDA's view:
The results of clinical studies in HD and PD patients with renal anemia demonstrated the efficacy of roxadustat [see Section 7.R.1] with its acceptable safety [see Section 7.R.2], thus there is no problem seen in the proposed indication of "renal anemia in patients on dialysis." Because roxadustat is an oral drug with its action mechanism different from ESAs, roxadustat can become a new treatment option for dialysis patients with renal anemia. Whether to use roxadustat or an ESA should be determined by the physician based on the patient's condition, medication adherence, etc. At present, the use of roxadustat in combination with ESAs is not recommended due to lack of study data on its efficacy and safety.

7.R.4 Dosage and administration

7.R.4.1 Regimen

The applicant's explanation:

As shown by the results of clinical pharmacology studies in Japan and other countries, exposure to roxadustat increased roughly in a dose proportional manner, but there was non-linearity in the dose-response relationship of roxadustat. Each dose level needed to be increased to a certain degree to achieve efficacy. However, in a once-daily consecutive day regimen, the dose level could be too low to exert the expected efficacy. The dose level in a once weekly regimen was estimated to be higher than 3.0 mg/kg, which was the maximum safe dose in a multiple dose regimen confirmed in the Japanese phase I study. Results of a foreign clinical study[28)] demonstrated the efficacy, etc. of roxadustat therapy with a 3-times weekly regimen in patients with renal anemia. Accordingly, 3 times weekly oral treatment was selected.

In the Japanese phase III studies, the roxadustat dose on a dialysis day was to be administered after dialysis. However, the clinical pharmacology study showed that only a negligible amount of roxadustat is removed by dialysis. It is thus not necessary to require roxadustat be administered after the completion of dialysis.

PMDA's view:

There are no particular problems with the 3 times weekly oral regimen of roxadustat or with not requiring roxadustat be administered after the completion of dialysis.

7.R.4.2 Starting dose for ESA-naïve patients

7.R.4.2.1 Starting dose for ESA-naïve HD patients

The applicant's explanation about the rationale for the starting dose level in the Japanese phase II study in HD patients in a washout period for ESA:

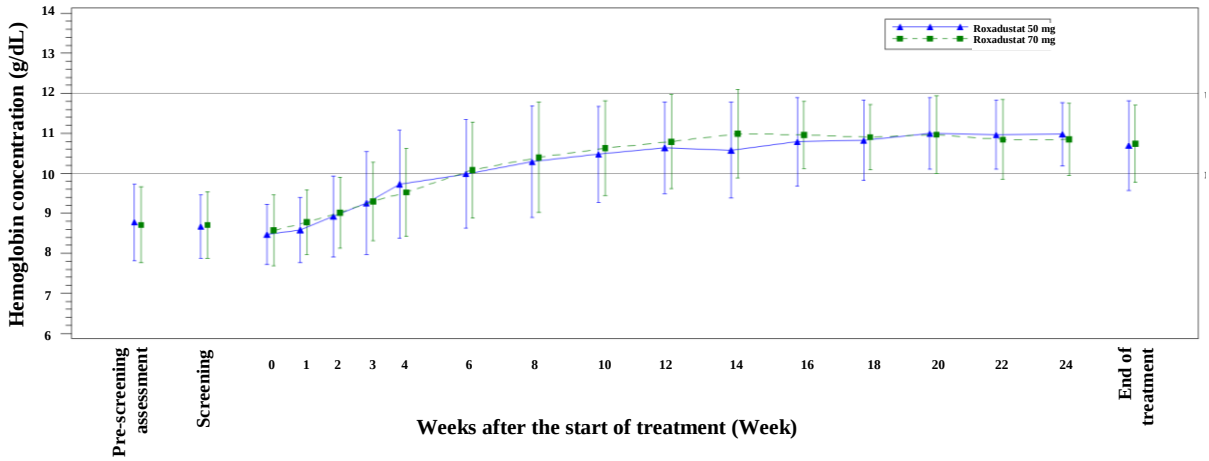
In a foreign clinical study,[28)] following the administration of roxadustat 0.7, 1.5, or 2.0 mg/kg to patients with pre-dialysis stage CKD 3 times weekly for 4 weeks, the mean rate of rise in Hb up to Week 4 was 0.21, 0.5, and 0.49 g/dL/week, respectively. When the rate of rise in Hb values for 4 weeks from baseline exceeded at 0.5 g/dL/week, a cardiovascular risk increased in DA-treated patients (2008 Guideline for Renal Anemia in Chronic Kidney Disease), and therefore the rate of rise in Hb should be carefully monitored. Meanwhile, the 3 times weekly regimen of roxadustat at 0.7 to 1.5 mg/kg will not raise Hb exceeding approximately 0.5 g/dL/week. The use of a fixed starting dose would help start roxadustat therapy easily. Therefore, 50, 70, and 100 mg were selected as the starting doses to be evaluated in the Japanese phase II study based on the mean body weight of Japanese people (60 kg).

In the Japanese phase II study in HD patients in a washout period for ESA, roxadustat 50, 70, or 100 mg was administered orally 3 times weekly, or DA 20 μg intravenously once weekly. The mean rate of rise in Hb up to Week 6 in PPS was 0.099 g/dL/week (roxadustat 50 mg), 0.211 g/dL/week (roxadustat 70

28) A foreign phase II study (dose-finding study) in patients with pre-dialysis stage CKD, in which patients received oral doses of 0.7, 1.5, or 2.0 mg/kg of roxadustat 3 times weekly for 4 weeks.

mg), 0.280 g/dL/week (roxadustat 100 mg), and 0.132 g/dL/week (DA 20 µg). The percentage of subjects whose rate of rise in Hb exceeded 0.5 g/dL/week by Week 6 was 0% (0 of 19 subjects) in the roxadustat 50 mg, 4.2% (1 of 24 subjects) in the roxadustat 70 mg, 14.3% (3 of 21 subjects) in the roxadustat 100 mg, and 0% (0 of 22 subjects) in the DA 20 µg. The incidence of adverse events was 72.7% (24 of 33 subjects) in the roxadustat 50 mg, 81.3% (26 of 32 subjects) in the roxadustat 70 mg, 84.4% (27 of 32 subjects) in the roxadustat 100 mg, and 78.1% (25 of 32 subjects) in the DA 20 µg. Based on the rate of rise in Hb for approved ESAs, 0.25 g/dL/week was considered appropriate as the rate of rise in Hb during the anemia correction period of patients with renal anemia, and a large percentage of subjects whose rate of rise in Hb exceeded 0.5 g/dL/week at 100 mg. Therefore, the starting dosage regimen of roxadustat 50 or 70 mg 3 times weekly was considered appropriate for the Japanese phase III study in ESA-naïve HD patients.

In the Japanese phase III study in ESA-naïve HD patients, the mean rate of rise in Hb up to Week 4 was 0.297 g/dL/week in the roxadustat 50 mg group and 0.238 g/dL/week in the 70 mg group. The percentage of subjects whose rate of rise in Hb exceeded 0.5 g/dL/week was 16.2% (6 of 37 subjects) in the roxadustat 50 mg group and 18.9% (7 of 37 subjects) in the 70 mg group. As for the primary efficacy endpoint, the cumulative response rate (percentage of subjects with Hb achieving ≥10.0 g/dL and increasing by ≥1.0 g/dL from baseline) was 86.5% (32 of 37 subjects) in the roxadustat 50 mg group and 89.2% (33 of 37 subjects) in the 70 mg group. Figure 2 shows the time course of mean Hb values, showing similar trends in both groups.



Evaluation time point (Week)		Pre-screening assessment	Screening	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	End of treatment
n	Roxadustat 50 mg	37	37	37	37	37	36	34	34	34	33	33	33	33	33	32	33	32	37
	Roxadustat 70 mg	37	37	37	37	35	35	35	34	33	33	33	32	32	32	32	32	32	37

Figure 2. Time course of mean Hb (g/dL) (anemia correction study in HD patients, FAS)

The incidence of adverse events was 86.5% (32 of 37 subjects) in the roxadustat 50 mg group and 94.7% (36 of 37 subjects) in the 70 mg group. There were no differences between the groups that could potentially cause a clinical problem.

The above results suggest no significant difference in efficacy or safety in ESA-naïve patients between roxadustat 50 and 70 mg. Accordingly, the starting dose of 70 mg was proposed for the current application, expecting that a higher starting dose would achieve a target Hb level earlier.

PMDA's view:
Given that no significant difference was observed in efficacy or safety in the roxadustat 50 and 70 mg groups in the anemia correction study in HD patients, and that the median [95% CI] time to achieve the lower limit (10.0 g/dL) of the target Hb range was 43.0 [22.0, 71.0] days in the roxadustat 50 mg group and 43.0 [28.0, 57.0] days in the 70 mg group, demonstrating no marked difference. Considering that roxadustat is to be administered with dose adjustment according to Hb values, it is more appropriate to start at 50 mg rather than at 70 mg.

7.R.4.2.2 Starting dose in ESA-naïve PD patients

The applicant's explanation about the starting dose in PD patients:
In the PD study, the starting dosage regimen in ESA-naïve PD patients was 50 or 70 mg orally 3 times weekly, as with in the anemia correction study in HD patients.
In ESA-naïve PD patients, the mean rate of rise in Hb up to Week 4 was 0.193 g/dL/week in the roxadustat 50 mg group and 0.556 g/dL/week in the 70 mg group. The percentage of subjects whose rate of rise in Hb exceeded 0.5 g/dL/week was 0% (0 of 6 subjects) in the roxadustat 50 mg group and 42.9% (3 of 7 subjects) in the 70 mg group. As for the primary efficacy endpoint, the percentage of subjects whose Hb values stayed within the target range was 83.3% (5 of 6 subjects) in the roxadustat 50 mg group and 100% (7 of 7 subjects) in the 70 mg group, indicating that there were no significant differences between the groups.

The incidence of adverse events was 83.3% (5 of 6 subjects) in the roxadustat 50 mg group and 71.4% (5 of 7 subjects) in the 70 mg group, indicating no significant differences that could potentially cause a clinical problem.

Based on the above, while there were no significant differences in efficacy and safety in ESA-naïve PD patients between the 50 and 70 mg groups, the percentage of subjects whose rate of rise in Hb exceeded 0.5 g/dL/week was larger in the 70 mg group as compared with that in the 50 mg group; therefore, 50 mg is the appropriate starting dose.

Based on the results of the PD study, PMDA considered that there are no particular problems in selecting 50 mg to be administered orally 3 times weekly as the starting dose in ESA-naïve PD patients.

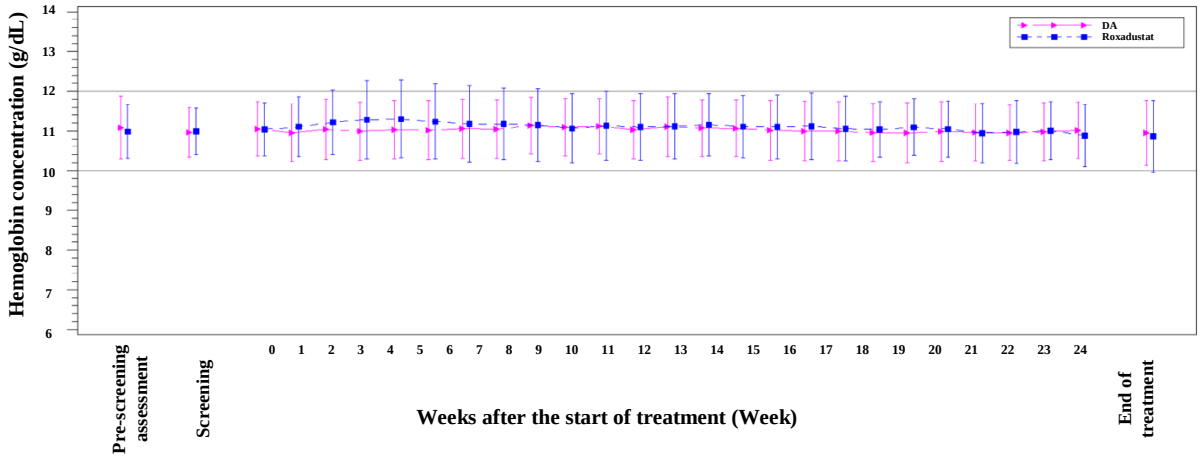
7.R.4.3 Dose for patients converting from ESA

7.R.4.3.1 Switching dose for HD patients converting from ESA

The applicant's explanation about the dose for HD patients converting from ESA:

The switching dose for HD patients who had been receiving ESA was determined based on the dose used in the Japanese phase II study conducted in HD patients who were in a washout period for ESA. The previous ESA dose was compared with the roxadustat dose. The results of comparison showed that when starting at the dose level shown in Table 41, Hb would be maintained stably after conversion to roxadustat. Accordingly, in the conversion/maintenance study in HD patients (Study CL-0307), the switching dose of roxadustat was specified as 70 or 100 mg according to the dose of ESA before conversion (Table 36).

In the conversion/maintenance study in HD patients (Study CL-0307), roxadustat 70 or 100 mg was administered orally 3 times weekly, according to the previous ESA dose, or DA intravenously once weekly. Figure 3 shows the time course of mean Hb in the roxadustat and DA groups. While Hb values slightly increased in the roxadustat group after conversion from ESA, similar time course changes were observed between the groups at Week 8 and thereafter. The Hb values in the roxadustat group were successfully maintained within the target range up to Week 24 by making dose adjustments according to the Hb values. Figure 4 shows the change in the dose levels of roxadustat over time. The dose levels were widely distributed from 20 to 250 mg.



Evaluation time point (Week)		Pre-screening assessment	Screening	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	End of treatment
n	Roxadustat	150	150	150	145	146	143	143	141	140	137	137	136	132	135	135	133	131	130	127	125	124	122	121	120	120	120	118	150
	DA	150	150	151	148	148	147	146	145	143	143	142	142	141	142	142	141	140	139	137	138	135	135	134	131	130	131	131	151

Figure 3. Time course of mean Hb (g/dL) (conversion/maintenance study in HD patients, FAS)

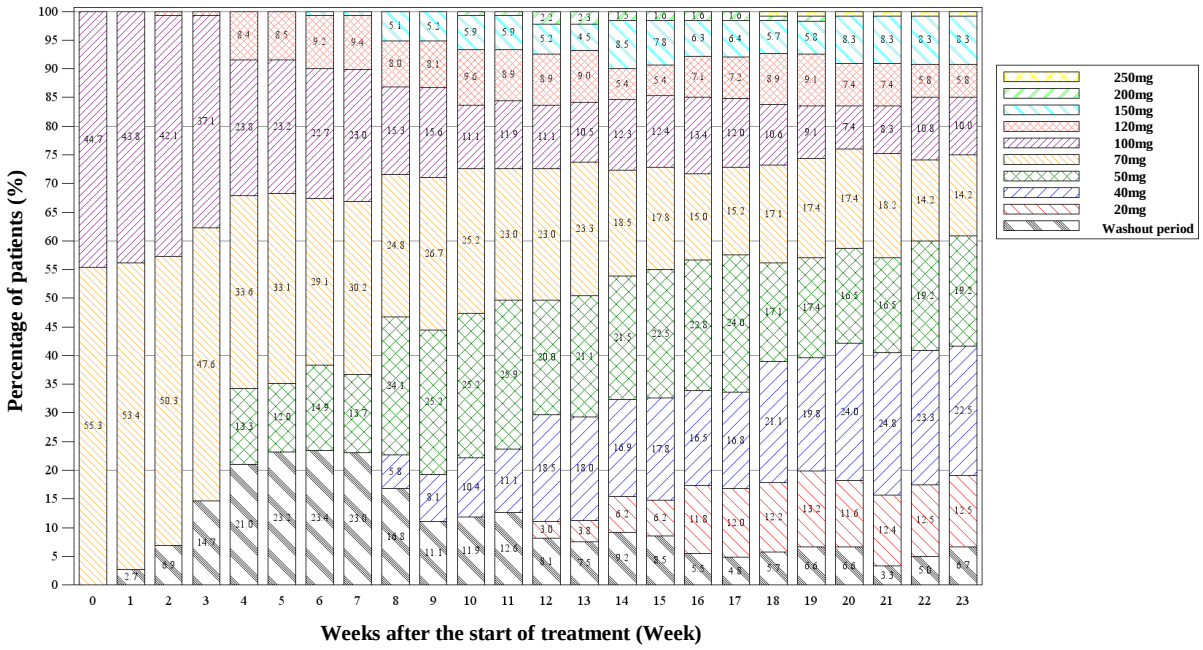


Figure 4. Time course of roxadustat dose levels (conversion/maintenance study in HD patients, FAS)

There were no significant differences in the incidence of adverse events between the roxadustat and DA groups [see Sections 7.R.2.1.1].

There were no significant differences in efficacy and safety between the roxadustat and DA groups in the conversion/maintenance study in HD patients. Accordingly, an appropriate dose level in HD patients after conversion from ESA should be 70 or 100 mg as shown in Table R.4.1.

PMDA's view:

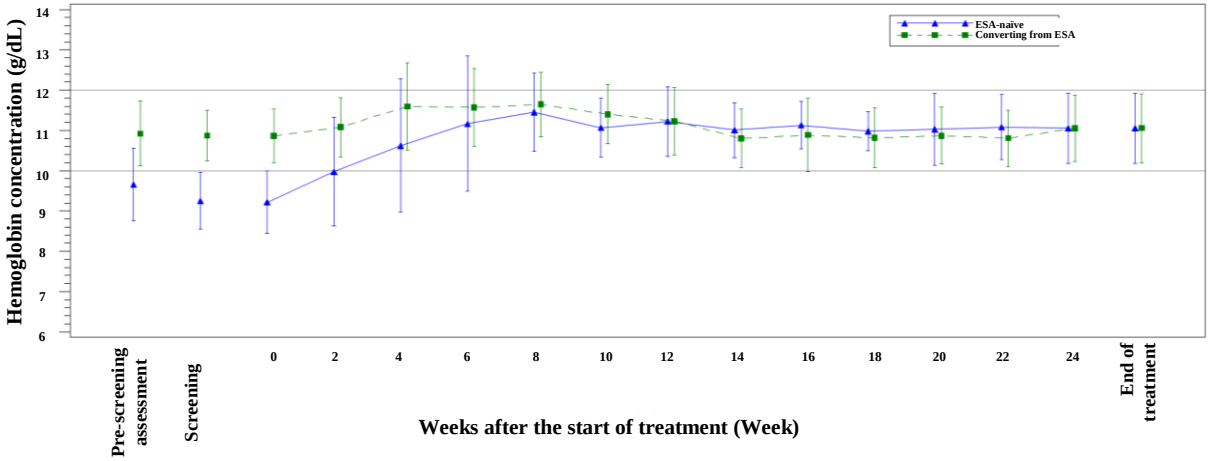
Based on the results from the conversion/maintenance study in HD patients, there are no particular problems in selecting oral 3-times weekly dose of 70 or 100 mg for HD patients converting from ESA. However, as Hb tended to increase slightly after conversion from ESA in the roxadustat group, attention should be paid to any change in Hb values after conversion.

7.R.4.3.2 Switching dose for PD patients converting from ESA

The applicant's explanation about the switching dose for PD patients converting from ESA:

The switching dose for PD patients converting from ESA was determined according to the previous ESA dose in the PD study (Table 36) as with the study in HD patients. The switching dose was specified as 70 or 100 mg, which was to be administered orally 3 times weekly.

Figure 5 shows the time course of mean Hb. While the Hb values slightly increased after converting from ESA, the values were successfully maintained within the target range up to Week 24 by appropriate dose adjustment according to the Hb values. Figure 6 shows the change in the dose levels of roxadustat over time. The dose levels widely ranged from 20 to 200 mg.



Evaluation time point (Week)		Pre-screening assessment	Screening	0	2	4	6	8	10	12	14	16	18	20	22	24	End of treatment
n	ESA-naïve	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	Converting from ESA	43	43	43	41	40	40	39	39	39	39	38	37	36	36	36	43

Figure 5. Time course of mean Hb (g/dL) (PD study, FAS)

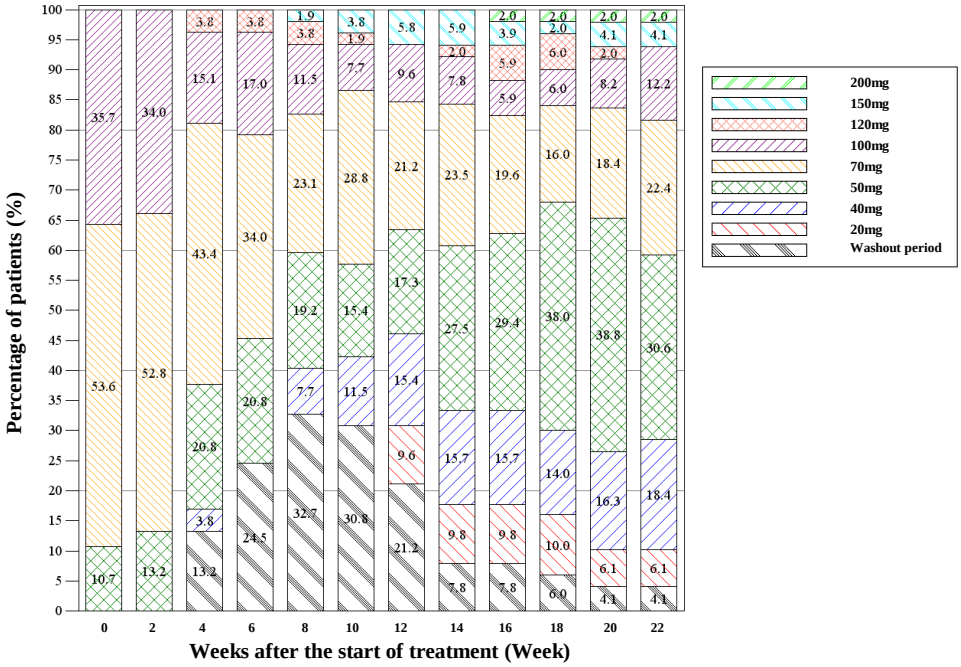


Figure 6. Time course of roxadustat dose levels (PD study, FAS)

There were no significant differences in the incidence of adverse events between PD and HD patients [see Section 7.R.2.2].

Based on the above, the appropriate switching dose of roxadustat after converting from ESA is 70 or 100 mg according to the prior dose of ESA.

PMDA's view:

There are no particular problems with the switching dose of roxadustat 70 or 100 mg, which is to be administered orally 3 times weekly in PD patients after converting from ESA, based on the results from

the PD study. However, because Hb increased slightly in the roxadustat group after converting from ESA, change in Hb values requires attention after conversion.

7.R.4.4 Method of dose adjustment

The applicant's explanation about the method of dose adjustment:

Roxadustat is intended to be administered with appropriate dose adjustment so that the Hb values are maintained within the target range (10.0 to 12.0 g/dL). The method of dose adjustment was defined as in Table 36.

Figure 1 shows time course of mean Hb from the Japanese long-term study in HD patients who were receiving ESA. The values were successfully maintained within the target range up to Week 52 with dose adjustment according to the adjustment method depending on Hb values. Figure 7 shows the change in the dose levels of roxadustat over time. The dose levels widely ranged from 20 to 250 mg.

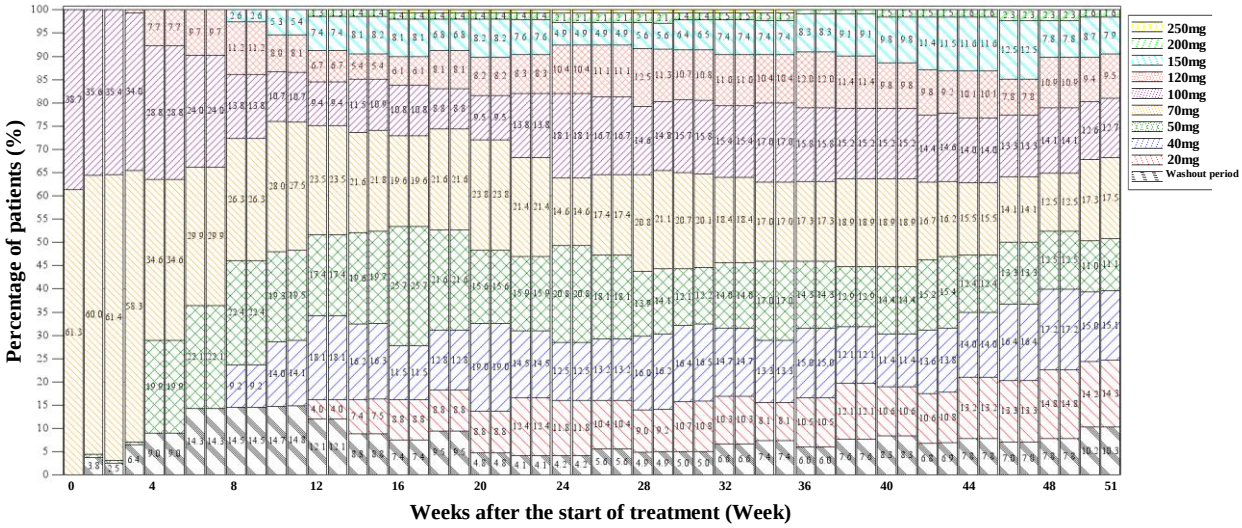


Figure 7. Time course of roxadustat dose levels (Japanese long-term study, FAS)

There were no trends toward increased incidence of adverse events as treatment duration increased [see Section 7.R.2.1.2].

In the anemia correction study in HD patients, conversion/maintenance study in HD patients, and PD study, Hb values were successfully maintained within the target range up to Week 24 by appropriate dose adjustment according to the Hb values [see Sections 7.R.4.1 through 7.R.4.3].

Based on the above, it was considered appropriate to define the dose adjustment method for roxadustat in Table 36 according to the Japanese phase III studies.

PMDA's view:

There are no particular problems in defining the dose adjustment method of for roxadustat according to the Japanese phase III studies in HD and PD patients, given that Hb values were successfully maintained

within the target range by appropriate dose adjustment in accordance with the prescribed dose adjustment method depending on the Hb values in the Japanese phase III studies.

7.R.4.5 Maximum dose

The applicant's explanation about the maximum dose:

The maximum dose in the Japanese phase III studies in HD and PD patients was 3.0 mg/kg, the safety of which was demonstrated in the 3 times weekly oral regimen in the Japanese phase I study. According to the roxadustat 20, 50, and 100 mg formulations, a dose adjustment table was created as a guide for dose selection in Japanese clinical studies. The specified formulations of the study drug were 20, 50, and 100 mg. The preferable number of tablets per dose is 1 to 3 tablets from the standpoint of medication adherence. Furthermore, roxadustat therapy requires Hb-level-based dose adjustment within a reasonable dose range of 1.2 to 1.4-fold. Accordingly, the dose adjustment table was prepared as per Table 36. Because there is no mention of body weight in the inclusion criteria for the Japanese phase III studies, the dose adjustment table shows dose adjustment range up to 300 mg to allow dose adjustment for patients weighing around 100 kg.

The dose levels of roxadustat at Weeks 12 to 23 widely ranged from 20 to 250 mg in the pooled data from the studies in HD patients (the anemia correction study in HD patients, conversion/maintenance study in HD patients, and long-term study), and ≥95% of patients received 20 to 150 mg. In the PD study, the dose levels of roxadustat at Weeks 16 to 22 ranged from 20 to 200 mg, and ≥95% of patients received 20 to 150 mg.

Table 64 shows the incidence of adverse events and adverse drug reactions in pooled data from the Japanese phase III studies in HD patients and PD patients (the anemia correction study in HD patients, conversion/maintenance study in HD patients, long-term study, and PD study). Only a few patients received 200 or 250 mg, and no patients received 300 mg, precluding safety evaluation at 200 to 300 mg. There were no significant differences in the incidence of adverse events or adverse drug reactions among other dose levels.

Table 64. Incidence of adverse events and adverse drug reactions by dose level of roxadustat (pooled analysis data from the Japanese phase III studies)

	20 mg (n = 100)	40 mg (n = 177)	50 mg (n = 291)	70 mg (n = 391)	100 mg (n = 273)	120 mg (n = 118)	150 mg (n = 67)	200 mg (n = 11)	250 mg (n = 2)
Adverse event	**49.0 (49)**	**49.2 (87)**	**52.2 (152)**	**59.6 (233)**	**59.3 (162)**	**55.9 (66)**	**55.2 (37)**	**63.6 (7)**	**100 (2)**
Adverse drug reaction	**3.0 (3)**	**5.6 (10)**	**8.9 (26)**	**13.8 (54)**	**11.0 (30)**	**12.7 (15)**	**7.5 (5)**	**9.1 (1)**	**0 (0)**

MedDRA ver.19.0; incidence, % (number of subjects)

As discussed above, taking into account that the majority of patients received 20 to 150 mg, the dose of roxadustat should usually be adjusted within the range of 20 to 150 mg after starting treatment. When there is no adequate response, dose may be administered up to the lower of 300 mg or 3.0 mg/kg.

PMDA's view:

After the start of treatment, the majority of patients received 20 to 150 mg and only few patients received ≥200 mg in the Japanese phase III studies in HD patients and PD patients. The applicant therefore explained that the normal dose range is 20 to 150 mg. However, there were no particular safety problems noted in patients receiving roxadustat 200 or 250 mg in these studies. Although it should be noted that only 11 patients received 200 mg and 2 received 250 mg, the normal dose range after the start of treatment need not be specified as 20 to 150 mg.

The maximum dose of roxadustat 3.0 mg/kg determined based on the Japanese phase III studies and referring to the dose adjustment table prepared based on the Japanese phase III studies is acceptable. However, due to the paucity of patients who received ≥200 mg of roxadustat, the collection of safety data of the maximum dose levels (≥200 mg) should be continued in the post-marketing setting for further investigation.

7.R.5 Post-marketing investigations

The applicant plans to conduct a specified use-results survey as summarized in Table 65 as part of post-marketing surveillance.

Table 65. Outline of specified use-results survey (draft)

Objective	**To assess the long-term safety of roxadustat and other aspects in clinical use in dialysis patients with renal anemia**
Survey method	**Central registration system**
Population	**Dialysis patients with renal anemia**
Planned sample size	**1000 patients (as analysis samples)**
Survey period	**2 years (registration period, 1 year)**
Observation period	**Maximum of 2 years**
Main survey items	• **Patient characteristics (e.g., age, sex, dialysis history, underlying illness requiring dialysis, prior renal anemia treatment, complications, medical history)** • **Dialysis (e.g., type, any change)** • **Details in treatment with roxadustat (e.g., daily dose, duration, reasons for discontinuation)** • **Concomitant drugs (e.g., names, route of administration, reason for use)** • **Laboratory values (Hb)** • **Adverse events (e.g., onset date, seriousness, outcome, a causal relationship to roxadustat, treatment)**

PMDA's view:

In view of the discussions presented in Sections 6.R, 7.R.2, and 7.R.4, the following post-marketing information should be gathered to assess the need for any cautionary advice, etc. The details of the post-marketing surveillance plan will be finalized taking into account the comments from the Expert Discussion.

- Occurrence of thromboembolism, hypertension, hepatic dysfunction, and other events
- Safety and efficacy of conversion from ESA to roxadustat
- Safety of roxadustat at higher doses (≥200 mg)

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 5.3.5.1-1, CTD 5.3.5.1-2, CTD 5.3.5.2-1, CTD 5.3.5.2-2, and CTD 5.3.5.2-3) 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. The results of inspection demonstrated that overall, the study was conducted in accordance with GCP. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. Meanwhile, the following error was noted at the sponsor, albeit with no major impact on the overall study evaluation. The matter was notified to the sponsor to request corrective actions.

Finding requiring corrective actions

Sponsor

- Part of information on serious and unexpected adverse drug reactions was not notified to the investigator or the head of the study site appropriately.

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

On the basis of the data submitted, PMDA has concluded that roxadustat has efficacy in the treatment of renal anemia, and that roxadustat has acceptable safety in view of its benefits. PMDA has concluded that roxadustat may be approved if efficacy, safety, indication, dosage and administration, and post-marketing investigations are not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 9, 2019

Product Submitted for Approval

Brand Name	Evrenzo Tablets 20 mg
	Evrenzo Tablets 50 mg
	Evrenzo Tablets 100 mg
Non-proprietary Name	Roxadustat
Applicant	Astellas Pharma Inc.
Date of Application	September 28, 2018

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 Safety

At the Expert Discussion, the expert advisors basically supported PMDA's conclusion on Section "7.R.2 Safety" in Review Report (1) while the following issue was raised by the expert advisors regarding the risk of thromboembolism:

- Although a causal relationship to roxadustat was ruled out, one death due to acute myocardial infarction occurred in the conversion/maintenance study in HD patients. Furthermore, the incidence of thromboembolism was higher in the roxadustat group as compared with the DA group. In addition, cerebral infarction, acute myocardial infarction, etc. were reported as serious adverse events [see Section 7.R.2.5.1]. Therefore, adequate attention should be paid to the risk of thromboembolism during roxadustat therapy, and this should be clearly communicated via the package insert.

PMDA, in response to the discussions at the Expert Discussion on thromboembolism, requested the applicant to provide the following cautionary statement in the "WARNING" section of the package insert so that the risk of thromboembolism would be assessed to determine carefully whether to use roxadustat beforehand, and patients would be monitored carefully for any signs of thromboembolism and be provided with appropriate instructions. The applicant took appropriate measures, and PMDA accepted the measures.

Warning

Roxadustat therapy may cause serious thromboembolism including cerebral infarction, myocardial infarction, and pulmonary embolism, with a possible fatal outcome. Roxadustat therapy should be preceded by the assessment of risks of thromboembolism, such as current or past history of cerebral infarction, myocardial infarction, and pulmonary embolism, based on which whether to use roxadustat be carefully determined. During roxadustat therapy, patient condition should be closely monitored for any signs or symptoms suggestive of thromboembolism. Patients should be instructed to visit a medical institution immediately in case of such symptoms.

1.2 Efficacy, indication, dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions on Sections "7.R.1 Efficacy," "7.R.3 Indication and clinical positioning," and "7.R.4 Dosage and administration" in Review Report (1). The following issue was raised by the expert advisors in relation to Section "7.R.4 Dosage and administration."

- Roxadustat is administered orally 3 times weekly instead of every day. Patients should be provided with written guidance on medication adherence so that they do not miss a dose or overdose.

Based on the discussion at the Expert Discussion, PMDA accepted the description of the "INDICATION" section proposed by the applicant. PMDA requested the applicant to modify the "DOSAGE AND ADMINISTRATION" and "Precautions for Indication" and "Precautions for Dosage and Administration" of the package insert as shown below. The applicant responded appropriately and PMDA accepted the applicant's actions. In view of the "3 times weekly" regimen, the applicant explained that it will provide healthcare professionals and patients with explanatory materials to ensure medication adherence.

Indication

Renal anemia in patients on dialysis

Precautions for Indication

The rough standard for the initiation of treatment is a hemoglobin concentration of <10 g/dL in hemodialysis patients, and <11 g/dL in peritoneal dialysis patients.

Dosage and Administration

For patients naïve to erythropoiesis-stimulating agents:

The usual adult starting dosage is 50 mg of roxadustat administered orally 3 times weekly. The dose should be then adjusted according to the patient's condition. However, the maximum dose should not exceed 3.0 mg/kg.

For patients switching from an erythropoiesis-stimulating agent:

The usual adult starting dosage is 70 mg or 100 mg of roxadustat administered orally 3 times weekly. The dose should be then adjusted according to the patient's condition. However, the maximum dose should not exceed 3.0 mg/kg.

Precautions for Dosage and Administration

1. The starting dose for patients converting from an erythropoiesis-stimulating agent

Determine the dose of roxadustat based on the dose of erythropoiesis-stimulating agent previously taken, and then convert to roxadustat therapy at the dose determined.

Erythropoietin formulation (IU/week)	Darbepoetin alfa (μg/week)	Epoetin beta pegol (μg/4 weeks)	Roxadustat (mg/dose)
<4500	<20	≤100	70
≥4500	≥20	>100	100

2. Dose adjustment

When dose adjustments are required, increase or decrease the dose according to the "Dose increase/decrease table" and "Dose adjustment table" below. Once adjusted, maintain the dose level for ≥4 weeks. If the hemoglobin concentration increases rapidly (>2.0 g/dL) within 4 weeks of a dose increase, decrease the dose or suspend the treatment immediately [see Section 8.1].

Dose increase/decrease table

<table>
<tr><td rowspan="2">Change in Hb from 4 weeks before to the current week</td><td colspan="4">Current week Hb</td></tr>
<tr><td><10.5 g/dL</td><td>≥10.5 g/dL
≤11.5 g/dL</td><td>>11.5 g/dL
≤12.5 g/dL</td><td>>12.5 g/dL</td></tr>
<tr><td><−1.0 g/dL</td><td>Increase by 1 step</td><td>Increase by 1 step</td><td>No change</td><td rowspan="4">Suspend treatment until Hb decreases below 11.0 g/dL. Resume treatment at the dose 1 step lower than the pre-suspension dose.</td></tr>
<tr><td>≥−1.0 g/dL
≤1.0 g/dL</td><td>Increase by 1 step</td><td>No change</td><td>Decrease by 1 step</td></tr>
<tr><td>>1.0 g/dL
≤2.0 g/dL</td><td>No change</td><td>Decrease by 1 step</td><td>Decrease by 1 step</td></tr>
<tr><td>>2.0 g/dL</td><td colspan="3">Decrease by 1 step</td></tr>
</table>

Dose adjustment table

Step	1	2	3	4	5	6	7	8
Roxadustat dose(Note)	20 mg	40 mg	50 mg	70 mg	100 mg	120 mg	150 mg	200 mg

(Note) Each dose should not exceed3.0 mg/kg. A dose >200 mg should be increased by 50 mg.

3. Three times weekly regimen

Roxadustat should be administered 3 times weekly, once every 2 to 3 days (e.g., Monday/Wednesday/Friday or Tuesday/Thursday/Saturday).

4. Missed dose

When there is ≥24 hour interval until the next scheduled dosing time, take the missed dose immediately and follow the prescribed schedule for subsequent doses. If there is <24 hours until the next scheduled

dosing time, skip the missed dose, and take the next dose as scheduled. Do not take 2 doses on the same day.

1.3 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion on Section "7.R.5 Post-marketing investigations" in Review Report (1). The following issues were raised by the expert advisors:

- Unlike ESAs, roxadustat promotes angiogenesis via the activation of the HIF pathway, and may cause retinal haemorrhage, etc. associated with the proliferation of tumor cells and retinal blood vessels. Data on the incidence of malignant tumors or retinal haemorrhage should be collected via post-marketing surveillance for further investigation.
- Due to the paucity of PD patients investigated and no long-term safety data available, safety data in long-term treatment in PD patients should be collected via post-marketing surveillance for further investigation.

Based on the above discussion, PMDA has concluded that the risk management plan (draft) for roxadustat should include the safety and efficacy specifications presented in Table 66, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 67 and the specified use-results survey presented in Table 68.

Table 66. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
• **Thromboembolism** • **Hypertension**	• **Effect of drug-drug interaction with HMG-CoA reductase inhibitors** • **Hepatic dysfunction** • **Malignant tumors** • **Retinal haemorrhage**	• **Not applicable**
Efficacy specification		
• **Not applicable**		

Table 67. 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** • **Prepare and provide information materials for healthcare professionals** • **Prepare and provide a brochure for patients and their families**

Table 68. Outline of specified use-results survey (draft)

Objective	**To assess the long-term safety of roxadustat and other aspects in clinical use in dialysis patients with renal anemia**
Survey method	**Central registration system**
Population	**Dialysis patients with renal anemia**
Planned sample size	**1000 patients (as analysis samples, 900 HD patients, and 100 PD patients)**
Observation period	**2 years**
Main survey items	• **Patient characteristics (e.g., age, sex, dialysis history, underlying illness for initiating dialysis, prior renal anemia treatment, complications, past history)** • **Dialysis (e.g., type of, change in dialysis)** • **Treatment status with roxadustat (e.g., dose per administration, treatment duration, reasons for treatment discontinuation)** • **Use of concomitant drugs (e.g., name of drugs, route of administration, reason for use)** • **Laboratory values (Hb)** • **Adverse events (e.g., onset date, seriousness, outcome, a causal relationship to roxadustat, treatment)**

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration statements as shown below, with the following condition of approval. Since roxadustat is a drug with a new active ingredient, the re-examination period is 8 years. Roxadustat is not classified as a biological product or a specified biological product. Both the drug product and its drug substance are classified as poisonous drugs and powerful drugs.

Indication

Renal anemia in patients on dialysis

Dosage and Administration

For patients naïve to erythropoiesis-stimulating agents:

The usual adult starting dosage is 50 mg of roxadustat administered orally 3 times weekly. The dose should be then adjusted according to the patient’s condition. However, the maximum dose should not exceed 3.0 mg/kg.

For patients switching from an erythropoiesis-stimulating agent:

The usual adult starting dosage is 70 mg or 100 mg of roxadustat administered orally 3 times weekly. The dose should be then adjusted according to the patient's condition. However, the maximum dose should not exceed 3.0 mg/kg.

Condition of Approval

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

Appendix

List of Abbreviations

Adverse drug reaction	Adverse event for which a causal relationship with the study drug cannot be ruled out
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anemia correction study in HD patients	Japanese phase III study in ESA-naïve HD patients (CTD 5.3.5.2-2, Study 1517-CL-0308)
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-versus-time curve
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
^{14}C	Carbon-14
CCK_A	Cholecystokinin A
CERA	Epoetin beta pegol (genetical recombination)
CKD	Chronic kidney disease
CL/F	Oral clearance
C_{max}	Maximum concentration
Conversion/maintenance study in HD patients	Japanese phase III comparative study in HD patients on ESA treatment (CTD 5.3.5.1-2, Study 1517-CL-0307)
CPK	Creatine phosphokinase
CQA	Critical quality attribute
CTD	Common technical document
CYP	Cytochrome P450
DA	Darbepoetin alfa (genetical recombination)
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
FAS	Full analysis set
GCP	Good clinical practice
GLP	Good laboratory practice
Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia	"Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia" (Notification No. 0930-(1) of the Evaluation and Licensing Division, PFSB dated September 30, 2011)
2008 Guideline for Renal Anemia in Chronic Kidney Disease	"2008 Guideline for Renal Anemia in Chronic Kidney Disease," edited by Japanese Society for Dialysis Therapy
2015 Guideline for Renal Anemia in Chronic Kidney Disease	"2015 Guideline for Renal Anemia in Chronic Kidney Disease," edited by Japanese Society for Dialysis Therapy
Hb	Hemoglobin
Hct	Hematocrit
HD	Hemodialysis
HEK293 cell	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 Guidelines	Evaluation of stability data
ICR	Institute of Cancer Research
IL-1β	Interleukin-1β
IR	Infrared absorption spectrum
Japanese long-term study	Japanese phase III long-term study in HD patients on ESA therapy (CTD 5.3.5.2-3, Study 1517-CL-0312)
ka	Absorption rate constant
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LLC-PK1 cell	Lilly Laboratories Cell-Porcine Kidney 1 cell
MATE	Multidrug and toxic extrusion transporter
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDCK cell	Martin-Darby canine kidney cell
MDR	Multidrug resistance
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
mRNA	Messenger ribonucleic acid
MET1	4-*O*-β-glucuronidated roxadustat
MET3	Produced by sulfate conjugation of 4'-hydroxylated roxadustat
MET4	4'-hydroxylated roxadustat
MET11-1	hydroxylated roxadustat
MET12	Produced by sulfate conjugation of hydroxylated roxadustat)
MRP	Multidrug resistance protein
MS	Mass spectrometry
NA	Not applicable
NADPH	Nicotinamide adenine dinucleotide phosphate
NE	Norepinephrine
NMR	Nuclear magnetic resonance spectrum
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PD	Peritoneal dialysis
PD study	Japanese phase III study in PD patients (CTD 5.3.5.2-1, Study 1517-CL-0302)
P-gp	P-glycoprotein
PG-PS	Peptidoglycan-polysaccharide
PH	Prolyl hydroxylase
PHD	Prolyl hydroxylase domain enzyme
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population Pharmacokinetics
PPS	Per protocol set
PT	Prothrombin time
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
QTcI	Individual-corrected QT interval
RH	Relative humidity

rHuEPO	Recombinant human erythropoietin
RNA	Ribonucleic acid
SD	Sprague-Dawley
$t_{1/2}$	Elimination half life
TIBC	Total iron binding capacity
t_{max}	Time to reach maximum concentration
TNF-α	Tumor necrosis factor
TSAT	Transferrin saturation
UGT	Uridine diphosphate-glucuronosyltransferase
UIBC	Unsaturated iron binding capacity
UV/VIS	Ultraviolet-visible absorption spectroscopy
Vc/F	Apparent volume of central compartment
WBP	Whole body plethysmography