Report on the Deliberation Results

September 3, 2020
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Enaroy Tablets 2 mg, Enaroy Tablets 4 mg
Non-proprietary Name	Enarodustat (JAN*)
Applicant	Japan Tobacco Inc.
Date of Application	November 29, 2019

Results of Deliberation

In its meeting held on August 27, 2020, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Condition

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

**Japanese Accepted Name (modified INN)*

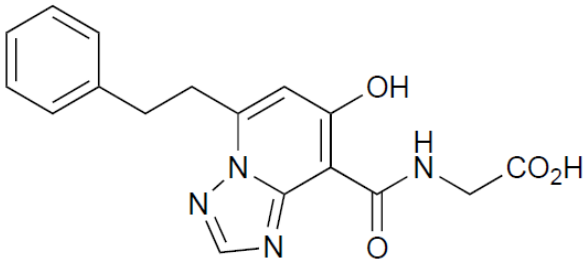
Review Report

August 6, 2020
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Enaroy Tablets 2 mg, Enaroy Tablets 4 mg
Non-proprietary Name	Enarodustat
Applicant	Japan Tobacco Inc.
Date of Application	November 29, 2019
Dosage Form/Strength	Film-coated tablets, each containing 2 or 4 mg of enarodustat
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{17}H_{16}N_4O_4$
Molecular weight: 340.33
Chemical name: *N*-[7-Hydroxy-5-(2-phenylethyl)[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonyl]glycine

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

Results of Review

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

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

Indication

Renal anemia

Dosage and Administration

1. Patients with chronic kidney disease not on dialysis and patients on peritoneal dialysis

   The usual adult starting dose of enarodustat is 2 mg administered orally once daily before a meal or at bedtime. Thereafter, the dose should be adjusted as appropriate according to the patient's condition. The maximum dose is 8 mg.

2. Patients on hemodialysis

   The usual adult starting dose of enarodustat is 4 mg administered orally once daily before a meal or at bedtime. Thereafter, the dose should be adjusted as appropriate according to the patient's condition. The maximum dose is 8 mg.

Approval Condition

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

Attachment

Review Report (1)

July 2, 2020

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

Product Submitted for Approval

Brand Name	Enaroy Tablets 2 mg, Enaroy Tablets 4 mg
Non-proprietary Name	Enarodustat
Applicant	Japan Tobacco Inc.
Date of Application	November 29, 2019
Dosage Form/Strength	Film-coated tablets, each containing 2 or 4 mg of enarodustat
Proposed Indication	Renal anemia

Proposed Dosage and Administration

- Patients with chronic kidney disease not on dialysis and patients on peritoneal dialysis

  For patients either naïve to or switching from an erythropoiesis-stimulating agent, the usual adult starting dose of enarodustat is 2 mg administered orally once daily before a meal or at bedtime. Thereafter, the dose should be adjusted as appropriate according to the severity of anemia, etc. The maximum dose is 8 mg.
- Patients on hemodialysis

  For patients either naïve to or switching from an erythropoiesis-stimulating agent, the usual adult starting dose of enarodustat is 4 mg administered orally once daily before a meal or at bedtime. Thereafter, the dose should be adjusted as appropriate according to the severity of anemia, etc. The maximum dose is 8 mg.

Table of Contents

List of Abbreviations

See Appendix.

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

Renal anemia is caused by impaired production of erythropoietin (EPO) due to renal impairment, and patients with renal anemia have shortness of breath, palpitations, fatiguability, anorexia, cardiac stress due to high cardiac output, etc. Although erythropoiesis-stimulating agents (ESAs) are mainly used as renal anemia drugs, ESAs are all injections, and the development of anti-EPO antibody-positive pure red cell aplasia has been reported ("Guideline for Renal Anemia in Chronic Kidney Disease 2015" Japanese Society for Dialysis Therapy ed.).

Enarodustat is an oral hypoxia-inducible factor (HIF)-prolyl hydroxylase (PH) inhibitor. The proposed product contains the active substance enarodustat discovered by the applicant. HIF is a transcription factor composed of 2 subunits (HIF-α and HIF-β). HIF is activated under hypoxic conditions and promotes erythropoiesis, etc., thereby inducing adaptive responses to hypoxia. Under normoxic conditions, HIF-α undergoes proteasome degradation after hydroxylation by HIF-PH (*Mol Cell*. 2008; 30: 393-402, *Cell Death Differ*. 2008; 15: 635-41, etc.). Enarodustat is expected to exert its therapeutic effects in the treatment of renal anemia because it promotes erythropoiesis through increased EPO production by inhibiting HIF-PH and activating the HIF pathway. Thus, the development of enarodustat was undertaken.

Claiming that Japanese clinical studies in patients with renal anemia demonstrated the efficacy and safety of enarodustat, the applicant has filed a marketing application for enarodustat.

As of June 2020, enarodustat has not been approved in any country or region.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder, and its description, solubility, hygroscopicity, melting point, dissociation constant, and partition coefficient have been determined. With respect to the crystalline forms of the drug substance, 5 [redacted] ([redacted]),1 [redacted], and 9 [redacted] have been identified during development, but the commercial process yields [redacted] only.

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

2.1.2 Manufacturing process

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

Quality by Design (QbD) approaches were utilized. Critical quality attributes (CQAs) were identified, and material attributes and process parameters that impact CQAs were characterized. Then a drug substance control strategy was developed (Table 1).

Table 1. Overview of drug substance control strategy

CQA	Method of control
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process
[redacted]	Manufacturing process
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process
[redacted]	Manufacturing process

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

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (IR, high performance liquid chromatography [HPLC]), purity (related substances [HPLC]), residue on ignition, particle size, and assay (HPLC). In the course of regulatory review, identification (HPLC) was added.

2.1.4 Stability of drug substance

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

Table 2. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	double polyethylene bags + polyethylene bottle	24 months
Accelerated	3 pilot-scale batches	40°C	75%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a re-test period of 36 months has been proposed for the drug substance when packaged in double polyethylene bags within a polyethylene drum and stored at room temperature. The long-term testing will be continued for [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet containing 2 or 4 mg of enarodustat and the following excipients: D-mannitol, low-substituted hydroxypropylcellulose, hypromellose, magnesium stearate, and hydroxypropylmethylcellulose 2910-titanium dioxide-Macrogol 400 mixture.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of blending/granulation/drying, size reduction, blending, tableting, coating, packaging/labeling, and testing/storage.

QbD approaches were utilized. CQAs were identified, and material attributes and process parameters that impact CQAs were characterized. Then a drug product control strategy was developed (Table 3).

Table 3. Overview of drug product control strategy

CQA	Method of control
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification
[redacted]	Manufacturing process, Specification

[redacted] has been defined as a critical step.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (HPLC), purity (degradation products [HPLC]), uniformity of dosage units (content uniformity testing [HPLC]), microbial limits, dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

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

Table 4. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 production batches	25°C	60%RH	Blister packs (polyvinyl chloride films/aluminum foils)	24 months
Accelerated	3 production batches	40°C	75%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a shelf-life of 36 months has been proposed for the drug product when packaged in blister packs (polyvinyl chloride films/aluminum foils) and stored at room temperature. The long-term testing will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

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

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

Primary pharmacodynamic studies were conducted to evaluate the inhibition of HIF-PH, induction of EPO production, induction of erythropoiesis, etc. by enarodustat. A secondary pharmacodynamic study was conducted to investigate the effects of enarodustat on enzymes other than HIF-PH and receptors. Safety pharmacology studies were performed to assess the effects of enarodustat on the central nervous, cardiovascular, and respiratory systems. Unless otherwise specified, dimethyl sulfoxide (DMSO) in *in vitro* studies and 0.5% methylcellulose in *in vivo* studies were used as vehicle.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Inhibition of HIF-PH (CTD 4.2.1.1-1)

Enarodustat was tested for its ability to inhibit the enzymatic reactions catalyzed by human recombinant HIF-PH1, HIF-PH2, and HIF-PH3. The Ki values of enarodustat for human HIF-PH1, HIF-PH2, and HIF-PH3 were 0.016, 0.061, and 0.101 μmol/L, respectively, and enarodustat inhibited all of HIF-PH1, HIF-PH2, and HIF-PH3. The mode of inhibition by enarodustat was competitive with a substrate of HIF-PH, α-ketoglutaric acid.

3.1.1.2 HIF stabilization (CTD 4.2.1.1-2)

Enarodustat 10 μmol/L was added to human hepatoma Hep3B cells, and the effects of enarodustat on the expression levels of HIF-1α, HIF-2α, and HIF-1β were analyzed by Western blotting. Enarodustat increased the expression of HIF-1α and HIF-2α compared with vehicle. On the other hand, enarodustat had no effect on the expression of HIF-1β.

3.1.1.3 Induction of EPO production (CTD 4.2.1.1-3)

Enarodustat 10 μmol/L was added to Hep3B cells, and the EPO concentration was measured at 1, 2, 4, 8, and 24 hours after addition. Enarodustat increased EPO production at 8 and 24 hours after addition. When enarodustat 0.1 to 10 μmol/L was added to Hep3B cells, and the EPO concentration was measured at 24 hours after addition, enarodustat increased the EPO concentration in a concentration-dependent manner, with an EC_{50} value of 4.7 μmol/L.

3.1.2 *In vivo* studies

3.1.2.1 Induction of EPO mRNA expression in rat liver and kidney (CTD 4.2.1.1-4)

A single oral dose of enarodustat 0.3, 1, or 3 mg/kg was administered to male rats (6/time point/group), and the EPO mRNA levels in the liver and kidney were measured at 1, 2, 4, 8, and 24 hours post-dose. Following administration of enarodustat 1 and 3 mg/kg, the EPO mRNA levels in the liver and kidney increased in a dose-dependent manner. The EPO mRNA levels in the liver and kidney peaked at 4 hours after administration of enarodustat and then decreased to levels comparable to those in the vehicle group by 24 hours post-dose.

3.1.2.2 Increased plasma EPO production in rat model of renal anemia (CTD 4.2.1.1-5)

A single oral dose of enarodustat 0.3, 1, or 3 mg/kg was administered to 5/6 nephrectomized rats (the renal anemia model) (6/group), and plasma EPO concentrations were measured at pre-dose and 2, 4, 8, and 24 hours post-dose. Enarodustat 3 mg/kg increased the plasma EPO concentration. The plasma EPO concentration in the enarodustat 3 mg/kg group peaked at 8 hours post-dose and then decreased to a level comparable to that in the vehicle group by 24 hours post-dose.

3.1.2.3 Induction of erythropoiesis in rat model of renal anemia (CTD 4.2.1.1-7)

Enarodustat 0.3, 1, or 3 mg/kg was administered orally once daily for 42 days to 5/6 nephrectomized rats (10-12/group). Blood was collected at pre-dose on Days 1, 8, 15, 22, 29, and 36 and on the following day of the

last dose of enarodustat (43 days from the start of dosing), and hemoglobin (Hb) levels were measured. Following administration of enarodustat 1 and 3 mg/kg, Hb levels increased in a dose-dependent manner.

3.1.2.4 Effect on iron availability in rats (CTD 4.2.1.1-8 and 4.2.1.1-9)

Enarodustat 3 mg/kg was administered orally once daily for 42 days, or recombinant human EPO (rHuEPO)[1)] 50 IU/kg was administered subcutaneously once daily for 42 days, to male rats (9/group). Blood was collected at pre-dose on Days 1, 8, 15, 22, 29, and 36 and on the following day of the last dose (43 days from the start of dosing), and Hb levels, serum iron levels, and transferrin saturation (TSAT) were measured. On the following day of the last dose, the livers were collected, and nonheme iron levels in the livers were measured. Enarodustat and rHuEPO caused comparable increases in Hb levels. On the other hand, rHuEPO reduced serum iron levels, TSAT, and nonheme iron levels in the livers, but enarodustat did not.

The effect of enarodustat on the expression of hepcidin, a protein that negatively regulates iron availability, was investigated. Male rats (9/group) received a single oral dose of enarodustat 3 mg/kg or a single subcutaneous dose of rHuEPO[1)] 50 IU/kg, and the hepcidin mRNA levels in the livers were measured at 8 hours post-dose. Enarodustat reduced the hepcidin mRNA levels in the livers, but rHuEPO did not.

The applicant's explanation:
Based on the above results, enarodustat promoted erythropoiesis without reducing iron availability as opposed to rHuEPO, and involvement of suppression of hepcidin production was suggested as its contributing factor.

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors and enzymes (CTD 4.2.1.2-1)

The effects of enarodustat on 23 receptors and 5 enzymes were investigated. The IC_{50} values of enarodustat for the receptors and enzymes tested were all higher than 10 μmol/L.

3.3 Safety pharmacology

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

Table 5. Summary of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Enarodustat dose	Method of administration	Findings	Attached document CTD
CNS	Rat (6 males/group)	Modified Irwin's test	3, 10, 30 mg/kg	Single, Oral	No effects at up to 30 mg/kg	4.2.1.3-1
Cardiovascular system	HEK293 cells (n = 5/group)	hERG current	10, 30, 100 μmol/L	*In vitro*	No effects at up to 100 μmol/L	4.2.1.3-2
	Dog (4 males/group)	blood pressure, heart rate, ECG	1, 3, 10 mg/kg	Single, Oral	No effects at up to 10 mg/kg	4.2.1.3-3
	Rat (6 males/group)	blood pressure, heart rate	3, 10, 30 mg/kg	Single, Oral	A decrease in blood pressure and an increase in heart rate at 30 mg/kg	4.2.1.3-4
Respiratory system	Dog (4 males/group)	respiratory rate, tidal volume, minute volume of ventilation	1, 3, 10 mg/kg	Single, Oral	No effects at up to 10 mg/kg	4.2.1.3-3

[1)] Saline was used as vehicle.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects

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

Enarodustat inhibits HIF-PH, which is involved in the degradation of HIF. HIF is a transcription factor composed of 2 subunits (HIF-α and HIF-β), and regulates responses to hypoxia (*J Clin Invest.* 2007; 117: 1926-32, *Kidney Int.* 2017; 92: 306-12, etc.). Under normoxic conditions, HIF-α undergoes proteasome degradation after hydroxylation by HIF-PH. Under hypoxic conditions, HIF-α is stabilized and dimerizes with HIF-β, resulting in the up-regulation of HIF-responsive genes (*Mol Pharmacol.* 2006; 70: 1469-80).

Renal anemia is considered the result of the diseased kidney being unable to adequately respond to hypoxia by inducing EPO production (*Nephrol Dial Transplant.* 2007; 22: 2900-8).

In primary pharmacodynamic studies, enarodustat inhibited human recombinant HIF-PH, induced EPO production, and increased Hb levels in the rat model of renal anemia. Thus, enarodustat is expected to exert its therapeutic effects in the treatment of renal anemia.

PMDA's view:

Based on the results of primary pharmacodynamic studies submitted and the applicant's discussion, enarodustat is considered to exert its therapeutic effects in the treatment of renal anemia by inhibiting HIF-PH and increasing Hb levels via activation of the HIF pathway.

3.R.2 Safety pharmacology studies

The applicant's explanation about the findings observed in safety pharmacology studies:

There were no relevant effects on the central nervous and respiratory systems.

There were no relevant effects on the cardiovascular system in a study that investigated the effect of enarodustat on hERG current and a safety pharmacology study in dogs. In a safety pharmacology study in rats, a decrease in systolic blood pressure and an increase in heart rate were observed in the enarodustat 30 mg/kg group at 4 and 8 hours post-dose, but resolved at 24 hours post-dose. These findings are considered related to the pharmacological effects of enarodustat because such findings are noted also under hypoxic conditions (*Annu Rev Physiol.* 2001; 63: 259-87, *Respir Physiol Neurobiol.* 2009; 165: 90-6). The C_{max} values (11.05 and 16.74 μg/mL) at the no-observed-effect-levels (NOELs) (10 mg/kg) in the safety pharmacology studies in rats and dogs were 9.6- and 14.6-fold, respectively, the estimated[2)] C_{max} at steady state (1.15 μg/mL) following administration of enarodustat at the maximum recommended clinical dose (8 mg).

Based on the above, enarodustat is unlikely to affect the central nervous, cardiovascular, and respiratory systems in clinical use.

[2)] Estimated based on enarodustat exposure following a single oral dose of enarodustat 15 mg in a Japanese phase I study in adult HD patients with renal anemia (Study MBX1-2) [see Section 6.2.4.1]. In a Japanese phase I study (Study MBX1-1), following single doses of enarodustat 1 to 200 mg, enarodustat exposure (C_{max} and $AUC_{0-\infty}$) increased in an approximately dose-proportional manner [see Section 6.2.1].

PMDA accepted the applicant's explanation.

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

Pharmacokinetics were studied in rats, dogs, and monkeys following administration of unlabeled enarodustat or [^{14}C]-enarodustat. Plasma concentrations of unchanged enarodustat were determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS), and the lower limits of quantification were 0.01 μg/mL for rat and dog plasma and 0.02 μg/mL for monkey plasma. [^{14}C]-enarodustat-derived radioactivity was determined using liquid scintillation counter or whole-body autoradiography.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1, 4.2.2.2-3, 4.2.2.2-5, 4.2.2.2-7, 4.2.2.2-8)

Table 6 shows the pharmacokinetic parameters of unchanged enarodustat following a single oral or intravenous administration of enarodustat in male rats, male dogs, and male monkeys under fasting or non-fasting conditions. In both rats and dogs, enarodustat exposure was lower in non-fasted than in fasted conditions. Following oral administration in dogs and monkeys under fasting conditions, the C_{max} and $AUC_{0-\infty}$ increased in an approximately dose-proportional manner.

Table 6. Plasma pharmacokinetic parameters of unchanged enarodustat following a single administration of enarodustat in rats, dogs, and monkeys

Species	Route of administration	Feeding condition	Enarodustat dose (mg/kg)	N	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	Bioavailability [a)] (%)
Rat	Oral	Fasting	1	3	2.69 ± 0.14	0.33 ± 0.14	5.09 ± 0.62	1.4 ± 0.1	74.5 ± 9.0
		Non-fasting		3	0.83 ± 0.19	0.42 ± 0.14	1.72 ± 0.27	1.4 ± 0.4	25.2 ± 4.0
	IV	—	0.3	3	—	—	2.05 ± 0.63	1.4 ± 0.1	—
Dog	Oral	Fasting	0.3	3	0.19 ± 0.00	0.58 ± 0.38	0.45 ± 0.06	1.9 ± 0.1	32.9 ± 4.4
			1	3	0.80 ± 0.22	0.33 ± 0.14	1.81 ± 0.36	1.7 ± 0.2	39.4 ± 7.9
			3	3	2.09 ± 0.38	0.42 ± 0.14	5.85 ± 1.66	2.9 ± 0.7	42.4 ± 12.0
		Non-fasting	1	3	0.09 ± 0.02	1.47 ± 2.19	0.53 ± 0.23	3.4 ± 2.4	11.6 ± 5.0
	IV	—	0.3	3	—	—	1.38 ± 0.17	1.2 ± 0.5	—
Monkey	Oral	Fasting	1	4	1.48 ± 0.61	0.8 ± 0.3	3.40 ± 1.20	1.8 ± 0.4	41.7 ± 14.7
			3	4	8.32 ± 2.92	0.9 ± 0.3	22.16 ± 13.20	2.8 ± 1.0	90.5 ± 53.9
			30	4	53.19 ± 15.22	1.3 ± 0.5	216.02 ± 25.97	2.8 ± 0.3	88.2 ± 10.6
	IV	—	0.3	3	—	—	2.45 ± 0.86	1.1 ± 0.2	—

Mean ± SD

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

4.1.2 Repeated-dose studies (CTD 4.2.3.2-6, 4.2.3.2-8, 4.2.3.2-11)

Toxicokinetics were evaluated in male and female rats following 6-month oral administration of enarodustat, and the plasma pharmacokinetic parameters of unchanged enarodustat are shown in Table 7. The C_{max} and AUC_{0-24h} increased in an approximately dose-proportional manner. The C_{max} and AUC_{0-24h} on Day 182 were higher than those on Day 1. The applicant explained that this was not due to accumulation after multiple dosing, but due to the timing of feeding (fasted from the evening on the day before Day 182) because the plasma concentration of unchanged enarodustat was near the lower limit of quantification at 24 hours after administration. There were no clear gender-related differences in the pharmacokinetics of enarodustat.

Table 7. Plasma pharmacokinetic parameters of unchanged enarodustat following 6-month oral administration of enarodustat in rats

Gender	Enarodustat dose (mg/kg/day)	Sampling day	C_{max} a) (μg/mL)	t_{max} (h)	AUC_{0-24h} (μg·h/mL)
Males	0.3	Day 1	0.15 ± 0.03	0.5	0.67
		Day 182	0.43 ± 0.13	0.5	1.15
	1	Day 1	0.49 ± 0.22	0.5	2.03
		Day 182	2.93 ± 0.12	0.5	6.18
	3	Day 1	2.01 ± 0.57	0.5	6.97
		Day 182	7.24 ± 3.22	0.5	15.27
Females	0.3	Day 1	0.15 ± 0.03	0.5	0.50
		Day 182	0.43 ± 0.10	0.5	1.05
	1	Day 1	0.83 ± 0.13	0.5	2.64
		Day 182	1.54 ± 0.45	0.5	4.50
	3	Day 1	2.85 ± 1.00	0.5	9.84
		Day 182	8.07 ± 3.18	0.5	19.52

Mean of 5 animals at each time point
a) Mean ± SD

Toxicokinetics were evaluated in male and female dogs following 3-month oral administration of enarodustat, and the plasma pharmacokinetics of unchanged enarodustat are shown in Table 8. The C_{max} and AUC_{0-24h} increased in an approximately dose-proportional manner, and there were no increases in exposure after multiple dosing. There were no clear gender-related differences in the pharmacokinetics of enarodustat.

Table 8. Plasma pharmacokinetic parameters of unchanged enarodustat following 3-month oral administration of enarodustat in dogs

Gender	Enarodustat dose (mg/kg/day)	Sampling day	N	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-24h} (μg·h/mL)
Males	0.3	Day 1	4	0.29 ± 0.09	1.1 ± 0.6	0.84 ± 0.28
		Day 91	4	0.29 ± 0.03	0.6 ± 0.3	0.66 ± 0.12
	1	Day 1	6	0.75 ± 0.12	0.8 ± 0.3	1.88 ± 0.75
		Day 91	6	1.07 ± 0.20	0.6 ± 0.2	2.05 ± 0.53
	3	Day 1	6	3.02 ± 0.46	0.7 ± 0.3	8.60 ± 1.94
		Day 91	6	4.22 ± 1.11	0.8 ± 0.3	13.89 ± 4.27
Females	0.3	Day 1	4	0.25 ± 0.01	0.9 ± 0.8	0.63 ± 0.18
		Day 91	4	0.29 ± 0.10	0.5 ± 0.0	0.57 ± 0.23
	1	Day 1	6	0.99 ± 0.20	0.9 ± 0.6	2.83 ± 0.39
		Day 91	6	1.09 ± 0.25	0.7 ± 0.3	2.52 ± 0.37
	3	Day 1	6	2.54 ± 0.28	1.0 ± 0.5	6.90 ± 1.59
		Day 91	6	3.24 ± 0.89	0.8 ± 0.3	10.82 ± 1.52

Mean ± SD

Toxicokinetics were evaluated in male and female monkeys following 9-month oral administration of enarodustat, and the plasma pharmacokinetics of unchanged enarodustat are shown in Table 9. Since the dose level was changed to 10 mg/kg/day for animals in the 30 mg/kg/day group during the study [see Section 5.2], no pharmacokinetic parameters beyond Day 49 in males and beyond Day 42 in females were obtained. Though the variability was high, the C_{max} and AUC_{0-24h} increased in an approximately dose-proportional manner, and there were no increases in exposure after multiple dosing. There were no clear gender-related differences in the pharmacokinetics of enarodustat.

Table 9. Plasma pharmacokinetic parameters of unchanged enarodustat following 9-month oral administration of enarodustat in monkeys

Gender	Enarodustat dose (mg/kg/day)	Sampling day	N	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)
Males	1	Day 1	4	1.48 ± 0.61	0.8 ± 0.3	3.73 ± 1.22
		Day 49	4	1.22 ± 0.68	0.6 ± 0.3	2.61 ± 0.71
		Day 273	4	1.33 ± 1.02	0.6 ± 0.3	3.29 ± 2.27
	3	Day 1	4	8.32 ± 2.92	0.9 ± 0.3	22.19 ± 12.98
		Day 49	4	5.40 ± 1.17	0.9 ± 0.3	17.06 ± 5.81
		Day 273	4	9.37 ± 1.27	0.8 ± 0.3	24.94 ± 6.04
	30	Day 1	4	53.19 ± 15.22	1.3 ± 0.5	215.17 ± 26.19
		Day 49	4	46.32 ± 4.13	4.0 ± 0.0	203.24 ± 17.73
		Day 273				
Females	1	Day 1	4	2.80 ± 1.46	0.8 ± 0.3	10.46 ± 9.13
		Day 42	4	1.59 ± 0.63	0.6 ± 0.3	6.02 ± 3.55
		Day 273	4	2.23 ± 0.66	0.5 ± 0.0	5.60 ± 1.89
	3	Day 1	4	8.41 ± 4.18	0.6 ± 0.3	21.97 ± 12.46
		Day 42	4	6.58 ± 2.39	0.5 ± 0.0	10.56 ± 2.22
		Day 273	4	5.49 ± 2.63	0.6 ± 0.3	22.70 ± 23.30
	30	Day 1	4	89.07 ± 27.66	1.5 ± 0.6	300.22 ± 90.50
		Day 42	4	70.63 ± 21.28	2.3 ± 1.3	344.99 ± 227.06
		Day 273				

Mean ± SD

4.2 Distribution

4.2.1 Tissue distribution in rats, dogs, and monkeys (CTD 4.2.2.3-1 to 4.2.2.3-3)

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in male rats, radioactivity concentrations in different tissues[3)] were determined at 1, 6, 24, and 168 hours post-dose. Maximum concentrations of radioactivity were measured in most tissues at 1 hour post-dose, and then the radioactivity concentrations declined over time. The radioactivity concentrations at 168 hours post-dose were all ≤5% of those at 1 hour post-dose. The distribution to the cerebrum, cerebellum, and eyeballs was low, and the radioactivity concentrations in these tissues at 1 hour post-dose were 0.01-, 0.02-, and 0.04-fold the plasma radioactivity concentration, respectively.

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in male dogs and male monkeys, radioactivity concentrations in different tissues[4)] were determined at 168 hours post-dose only. In dogs, the radioactivity concentrations in the adrenal glands and testes were higher than that in plasma, but were <0.1% of the administered radioactivity. In monkeys, the radioactivity concentrations in all tissues were similar to or lower than the plasma radioactivity concentration at 168 hours post-dose.

4.2.2 Whole-body autoradiography (CTD 4.2.2.3-1)

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in rats, radioactivity in different tissues was measured by autoradiograms at 1, 6, 24, and 168 hours post-dose. After administration, radioactivity was distributed into the whole body with high concentrations in the intestinal contents, gastric contents, kidneys, etc. Radioactivity

[3)] Plasma, blood, cerebrum, cerebellum, pituitary gland, eyeballs, Harderian glands, thyroid gland, submandibular glands, trachea, thymus, heart, lungs, liver, kidneys, adrenal glands, spleen, pancreas, white fat, brown fat, skeletal muscle, white skin, bone marrow, artery, mesenteric lymph nodes, testes, epididymides, prostate, seminal vesicle, stomach, small intestine, cecum, large intestine, urinary bladder

[4)] Dogs: plasma, blood, cerebrum, cerebellum, pituitary gland, eyeballs, thyroid gland, submandibular glands, trachea, thymus, heart, lungs, liver, kidneys, adrenal glands, spleen, pancreas, white fat, brown fat, skeletal muscle, white skin, pigmented skin, bone marrow, artery, mesenteric lymph nodes, testes, epididymides, prostate, stomach, small intestine, cecum, large intestine, and urinary bladder

Monkeys: plasma, blood, cerebrum, cerebellum, pituitary gland, eyeballs, thyroid gland, submandibular glands, trachea, thymus, heart, lungs, liver, kidneys, adrenal glands, spleen, pancreas, white fat, brown fat, skeletal muscle, pigmented skin, bone marrow, artery, mesenteric lymph nodes, testes, epididymides, prostate, seminal vesicle, stomach, small intestine, cecum, large intestine, and urinary bladder

in different tissues declined over time, and radioactivity was undetectable in almost all tissues at 168 hours post-dose.

4.2.3 Protein binding (CTD 4.2.2.3-4 to 4.2.2.3-6)

Using the plasma from mouse, rat, dog, monkey, and human, the protein binding of enarodustat (mouse, 1 and 10 μg/mL; other species, 1-300 μg/mL) was determined. The protein binding of enarodustat was 91.1% to 92.2%, 94.6% to 98.4%, 91.3% to 96.7%, 97.7% to 99.0%, and 97.9% to 99.5%, respectively.

When enarodustat (1 and 10 μg/mL) was added to human serum albumin solution or α_1-acid glycoprotein solution, the binding of enarodustat to human serum albumin and α_1-acid glycoprotein was 98.7% to 98.8% and 15.1% to 69.1%, respectively. The applicant explained that enarodustat binds primarily to albumin in human plasma.

4.2.4 Distribution in blood cells (CTD 4.2.2.3-8 and 4.2.2.3-9)

Using the blood from rat, dog, monkey, and human, the distribution of [^{14}C]-enarodustat (1-300 μg/mL) in blood cells was determined. The distribution in blood cells was 1.8% to 8.7%, 3.6% to 18.8%, 1.7% to 4.8%, and 2.5% to 6.8%, respectively, and the blood to plasma radioactivity concentration ratio was 0.63 to 0.68, 0.52 to 0.61, 0.58 to 0.59, and 0.56 to 0.59, respectively. The applicant explained that there is low distribution of enarodustat into blood cells.

4.2.5 Placental transfer to fetus (CTD 4.2.2.3-10)

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in pregnant rats on gestation day 18, concentrations of radioactivity in maternal and fetal tissues[5)] were determined up to 24 hours post-dose. Maximum concentrations of radioactivity were measured in almost all maternal tissues and fetal blood at 1 hour post-dose and in fetal tissues at 6 hours post-dose, and then the radioactivity concentrations declined over time. Since radioactivity was detected in fetal tissues, enarodustat was shown to cross the placenta into the fetus.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 4.2.2.4-6 to 4.2.2.4-8)

Using rat, dog, monkey, and human liver microsomes, the metabolism of [^{14}C]-enarodustat was studied. When enarodustat was incubated with liver microsomes for 2 hours in the presence of nicotinamide adenine dinucleotide phosphate (NADPH), 2 metabolites were detected in rat, monkey, and human liver microsomes, but the both metabolites were minor compared with unchanged enarodustat. No metabolites were detected in dog liver microsomes.

[5)] Maternal tissues: plasma, blood, cerebrum, cerebellum, pituitary gland, eyeballs, Harderian glands, thyroid gland, submandibular glands, trachea, thymus, heart, lungs, liver, kidneys, adrenal glands, spleen, pancreas, white fat, brown fat, skeletal muscle, skin, bone marrow, artery, mesenteric lymph nodes, uterus, ovaries, mammary gland, placenta, amnion, amniotic fluid, stomach, small intestine, cecum, large intestine, and urinary bladder
Fetal tissues: whole body, blood, plasma, brain, heart, lungs, liver, kidneys, digestive tract, skin, and muscle

Using rat, dog, monkey, and human hepatocytes, the metabolism of [^{14}C]-enarodustat was studied. One metabolite in rat hepatocytes, 4 metabolites in monkey hepatocytes, and 2 metabolites in human hepatocytes were detected, but all of these metabolites were minor compared with unchanged enarodustat. No metabolites were detected in dog hepatocytes.

4.3.2 Percentages of unchanged enarodustat and metabolites in plasma, urine, feces, and bile (CTD 4.2.2.4-2 and 4.2.2.4-5)

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in male rats, the percentages of unchanged enarodustat and metabolites in plasma, urine, and feces were determined. In the plasma collected up to 6 hours post-dose, unchanged enarodustat was the predominant component (accounting for 91.2% of the total radioactivity in plasma at 6 hours post-dose). In the urine collected up to 48 hours post-dose, 43.5% of the total radioactivity administered was excreted. The predominant component was unchanged enarodustat (accounting for 60.8% of the total radioactivity in urine), and 5 metabolites (3.6%-10.5% of the total radioactivity in urine) were also detected. In the feces collected up to 48 hours post-dose, 49.8% of the total radioactivity administered was excreted. The predominant component was unchanged enarodustat (accounting for 69.7% of the total radioactivity in feces), and 3 metabolites (1.6%-8.7% of the total radioactivity in feces) were also detected.

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in bile duct cannulated male rats, 68.2% of the total radioactivity administered was excreted in the bile up to 24 hours post-dose. The predominant component was unchanged enarodustat (accounting for 81.8% of the total radioactivity in bile), and 5 metabolites (0.6%-2.2% of the total radioactivity in feces) were also detected.

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in male dogs, the percentages of unchanged enarodustat and metabolites in plasma, urine, and feces were determined. In the plasma collected up to 6 hours post-dose, unchanged enarodustat was the predominant component (accounting for 92.4% of the total radioactivity in plasma at 6 hours post-dose). In the urine collected up to 48 hours post-dose, 8.2% of the total radioactivity administered was excreted. The predominant component was unchanged enarodustat (accounting for 81.2% of the total radioactivity in urine), and 2 metabolites (accounting for 6.0%-9.4% of the total radioactivity in urine) were also detected. In the feces collected up to 48 hours post-dose, 84.9% of the total radioactivity administered was excreted. The predominant component was unchanged enarodustat (accounting for 89.8% of the total radioactivity in feces), and 1 metabolite (accounting for 0.6% of the total radioactivity in feces) was also detected.

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in male monkeys, the percentages of unchanged enarodustat and metabolites in plasma, urine, and feces were determined. In the plasma collected up to 6 hours post-dose, unchanged enarodustat was the predominant component (accounting for 91.1% of the total radioactivity in plasma at 6 hours post-dose). In the urine collected up to 96 hours post-dose, 23.0% of the total radioactivity administered was excreted, and unchanged enarodustat (accounting for 34.5% of the total radioactivity in urine) and 4 metabolites (accounting for 3.2%-29.1% of the total radioactivity in urine) were detected. In the feces collected up to 96 hours post-dose, 68.9% of the total radioactivity administered

was excreted. The predominant component was unchanged enarodustat (accounting for 77.6% of the total radioactivity in feces), and 1 metabolite (accounting for 13.1% of the total radioactivity in feces) was also detected.

4.4 Excretion

4.4.1 Excretion in urine, feces, expired air, and bile in rats (CTD 4.2.2.5-1)

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in male rats, 43.7% and 50.0% of the administered radioactivity were recovered in urine and feces, respectively, up to 168 hours post-dose, and 2.8% of the administered radioactivity was recovered in expired air up to 72 hours post-dose. Following a single intravenous dose of [^{14}C]-enarodustat 0.3 mg/kg in male rats, 30.1% and 64.3% of the administered radioactivity were recovered in urine and feces, respectively, up to 168 hours post-dose, and 2.7% of the administered radioactivity was recovered in expired air up to 72 hours post-dose.

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in bile duct cannulated male rats, 15.5%, 10.7%, and 70.0% of the administered radioactivity were recovered in urine, feces, and bile, respectively, up to 48 hours post-dose. When bile collected up to 24 hours post-dose was intraduodenally administered to bile duct cannulated recipient male rats, 10.5%, 28.9%, and 53.9% of the administered radioactivity were recovered in urine, feces, and bile, respectively, up to 48 hours post-dose.

The applicant explained that the above results indicated that enarodustat is excreted predominantly in feces via bile in rats, and that a fraction of enarodustat excreted into bile is reabsorbed.

4.4.2 Urinary and fecal excretion in dogs and monkeys (CTD 4.2.2.5-2 and 4.2.2.5-3)

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in male dogs, 8.5% and 87.6% of the administered radioactivity were recovered in urine and feces, respectively, up to 168 hours post-dose. Following a single intravenous dose of [^{14}C]-enarodustat 0.3 mg/kg in male rats, 14.4% and 83.0% of radioactivity were recovered in urine and feces, respectively, up to 168 hours post-dose.

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in male monkeys, 23.3% and 70.3% of the administered radioactivity were recovered in urine and feces, respectively, up to 168 hours post-dose. Following a single intravenous dose of [^{14}C]-enarodustat 0.267 mg/kg in male rats, 45.6% and 49.9% of the administered radioactivity were recovered in urine and feces, respectively, up to 168 hours post-dose.

Based on the above, the applicant explained that in dogs and monkeys, enarodustat is excreted predominantly in feces with some urinary excretion.

4.4.3 Excretion into milk (CTD 4.2.2.3-10)

Following a single oral dose of [^{14}C]-enarodustat 1 mg/kg in female rats on lactation day 10, excretion in milk up to 24 hours post-dose was studied. The C_{max} of radioactivity in milk was 1.34 μg eq./mL ($t_{max,}$ 5.3 hours), and the radioactivity concentration in milk decreased to 0.20 μg eq./mL at 24 hours post-dose. The milk/plasma

$AUC_{0-\infty}$ ratio of radioactivity at 24 hours post-dose was approximately 7, which showed that enarodustat is excreted in milk.

4.R Outline of the review conducted by PMDA

PMDA considers that there are no particular problems with the non-clinical pharmacokinetics of enarodustat.

5. Toxicity and Outline of the Review Conducted by PMDA

Toxicity studies of enarodustat, namely single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity (a photosafety study) studies, were conducted. Unless otherwise specified, 0.5% methylcellulose solution was used as vehicle in *in vivo* studies.

5.1 Single-dose toxicity

Single oral dose toxicity studies were conducted in rats and dogs (Table 10).

Table 10. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Principal findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male rat (SD)	Oral	0, 125, 250, 500, 1,000, 2,000	Deaths or moribund sacrifices: 1,000 (4 of 4 animals), 2,000 (4 of 4 animals) no feces, urogenital staining/staining around the nose, edema in the hindlimb, reddish urine, discoloration of the forelimb/hindlimb and tail (dark red), discoloration of the eyeball/pinna (pale), reddish lacrimal fluid, lacrimation, small thymus, reddish focus/striation in the glandular stomach, dark reddish contents in the small intestine, reddish discoloration of the mesenteric lymph nodes/testis, subcutaneous reddish focus/reddish focus in the lung, subcutaneous congestion, discoloration of the liver (pale), etc. ≥250：soft stool, decreases in body weight/food consumption ≥500: hypothermia, decreased locomotor activity, decreases in the amount of feces, tachypnea	1,000	Reference data 4.2.3.1-2
Male dog (Beagle)	Oral	1, 3, 10, 30	≥1: increases in hematocrit/reticulocyte count/mean corpuscular volume/platelet count, increased blood EPO 30: decreases in body weight/food consumption, no feces, decreases in the amount of feces, deterioration of animal's physical condition, increases in RBC count/Hb/white blood cell count/neutrophil count	>30	Reference data 4.2.3.1-5

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies were conducted in rats (1, 3, and 6 months), dogs (1 and 3 months), and monkeys (1, 3, and 9 months) (Table 11). The principal findings were increased erythropoiesis (including increased erythroid hematopoiesis in the bone marrow and increased extramedullary hematopoiesis in the spleen), thrombus formation, congestion, and hemorrhage in multiple organs, centrilobular hepatocellular atrophy in the liver, increases in blood triglycerides, and decreases in blood glucose (rats, dogs, and monkeys), fatty changes of periportal hepatocytes in the liver, erosion in the stomach mucosa, decreases in platelet count, blood total cholesterol, and phospholipids, and effects on hemostasis parameters (rats and monkeys), and fatty changes of the renal tubular epithelium (rats and dogs). In addition, tubular regeneration, distal tubule dilatation, inflammatory changes, and papillary fibrosis in the kidney, and proliferation of osteoblasts and irregular

trabecular bone formation in the femur in rats, atrophy of the outer nuclear layer of the retina in dogs, and atrophy of acinar cells of the pancreas, etc. in monkeys were observed. These findings were all considered related to the induction of erythropoiesis or HIF-PH inhibition by enarodustat. Enarodustat exposure (C_{max} was 1.54-2.93 μg/mL and $AUC_{0\text{-}24h}$ was 4.50-6.18 μg·h/mL in rats; C_{max} was 5.49-9.37 μg/mL and $AUC_{0\text{-}24h}$ was 22.70-24.94 μg·h/mL in monkeys) at the no-observed-adverse-effect-levels (NOAELs) in the rat 6-month and monkey 9-month repeated oral dose toxicity studies (1 mg/kg/day in rats, 3 mg/kg/day in monkeys) were 1.3- to 2.5-fold (based on C_{max}) and 0.4- to 0.6-fold (based on $AUC_{0\text{-}24h}$) in rats and 4.8- to 8.1-fold (based on C_{max}) and 2.2- to 2.4-fold (based on $AUC_{0\text{-}24h}$) in monkeys, compared to the estimated human exposure following repeated oral administration of enarodustat at the maximum recommended clinical dose of 8 mg/day in hemodialysis (HD) patients (C_{max}, 1.15 μg/mL; AUC_{τ}, 10.30 μg·h/mL).

Table 11. Repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (mg/kg)	Principal findings	NOAEL (mg/kg)	Attached document CTD
Male and female rats (SD)	Oral	1 month (once daily) + 1-month recovery period	0, 3, 10, 30	≥3: increased erythropoiesis, increases in TIBC, decreases in platelet count, fatty changes of periportal hepatocytes[a)] ≥10: increases in blood AST/LDH/creatine kinase/indirect bilirubin/triglycerides/UIBC, decreases in blood total cholesterol/phospholipids/calcium/iron, decreases in bone marrow M/E ratio, reddish colored skin/chorioretina, increases in the weights of the heart/lung/spleen, decreased liver weight, large spleen/increased extramedullary hematopoiesis in the spleen, hepatocellular atrophy associated with centrilobular sinusoidal dilatation, erosion in the glandular mucosa of the stomach, increased erythroid hematopoiesis in the bone marrow, fatty changes of the proximal tubular epithelium 30: increases in blood potassium, decreases in blood inorganic phosphate/glucose, prolongation of PT, increases in urine bilirubin/urobilinogen, hemosiderin deposit in the renal tubule, hemorrhage/thrombus formation in the lung, proliferation of osteoblasts/irregular trabecular bone formation in the femur These findings were reversible (After the recovery period, positive urine occult blood, increases in the weights of the heart/lung/adrenal gland, hemosiderin deposit in the spleen/kidney, congestion in the spleen, etc. were observed).	3	4.2.3.2-3

Table 11. Repeated-dose toxicity studies

Male and female rats (SD)	**Oral**	**3 months (once daily) + 1-month recovery period**	**0, 1, 3, 6**	**Deaths or moribund sacrifices: 6 (5 of 20 males) Thrombus formation in the heart/lung/kidney, etc.** **≥1: increased erythropoiesis, decreases in platelet count** **≥3: reddish colored skin/chorioretina, increases in reticulocyte count/basophil count/monocyte count, increases in blood AST/LDH/creatine kinase/TIBC/UIBC/guanase/total bilirubin, decreases in blood total protein/albumin/total cholesterol/phospholipids/calcium/fibrinogen, increases in the weights of the heart/lung/kidney/spleen, decreases in the weights of the liver/seminal vesicle, congestion in multiple organs, large spleen/increased extramedullary hematopoiesis/decreased hemosiderin deposits in the spleen, increased erythroid hematopoiesis in the bone marrow, erosion in the glandular mucosa of the stomach, fatty changes of periportal hepatocytes, hyperplasia of osteoblasts/mesenchymal cells in the femur** **6: decreases in eosinophil count, decreases in bone marrow M/E ratio, increases in blood potassium/urea nitrogen/triglycerides/D-dimer, decreases in blood iron, prolongation of PT/APTT, positive urine occult blood, increases in urine bilirubin/protein, small liver, thrombus formation in the femoral bone marrow, colliquation necrosis in the brain, hepatocellular atrophy associated with centrilobular sinusoidal dilatation, increased tubular regeneration/erythrocyte casts in the kidney, irregular trabecular bone formation in the femur** **These findings were reversible (After the recovery period, increased lung weight, colliquation necrosis in the brain, decreased number of erythroblastic cells in the bone marrow, increased incidence and severity of hemosiderin deposit in the spleen/the femoral bone marrow/Kupffer cells in the liver/the proximal tubular epithelium, etc. were observed).**	**1**	**4.2.3.2-4**
Male and female rats (SD)	**Oral**	**6 months (once daily)**	**0, 0.3, 1, 3**	**≥1: increases in blood EPO/TIBC/PAI-1, decreases in blood total cholesterol/phospholipids/fibrinogen** **3: increased erythropoiesis, decreases in platelet count, increases in basophil count, increases in blood UIBC, decreases in blood iron, prolongation of PT/APTT, increased spleen weight/increased extramedullary hematopoiesis in the spleen, increased erythroid hematopoiesis in the bone marrow, decreases in bone marrow M/E ratio, increases in blood guanase/potassium, decreases in blood total protein/albumin/glucose, increases in urine Kim-1, increases in the weights of the kidney/adrenal gland/lung, decreased liver weight, tubular regeneration/distal tubular dilatation/inflammatory cell infiltration/papillary fibrosis/collecting duct dilatation in the kidney, centrilobular congestion/hepatocellular atrophy in the liver, organized thrombus in the heart, swelling/edema/granulation tissue/inflammatory cell infiltration in the hindlimb**	**1**	**4.2.3.2-6**

Table 11. Repeated-dose toxicity studies

Male and female dogs (Beagle)	**Oral**	**1 month (once daily)**	**0, 1, 3, 10[b)]**	**≥1: increased erythropoiesis, increases in platelet count, increases in blood EPO/TIBC/UIBC, decreases in blood iron/TSAT, increased erythroid hematopoiesis in the bone marrow, increased spleen weight, hepatocellular atrophy associated with centrilobular sinusoidal dilatation,[c)] fatty changes of the gallbladder epithelium[d)]** **≥3: decreased food consumption, decreased body weight gain, increases in white blood cell count, increases in blood triglycerides, decreases in blood glucose, increases in urine bilirubin, increased lung weight, increased extramedullary hematopoiesis in the spleen, reddish discoloration of the bone marrow/decreased adipocytes in the bone marrow, centrilobular inflammatory cell infiltration in the liver, thrombus formation in the lung, fatty changes of the proximal tubular epithelium,** **10: decreased body weight, dehydration, increases in blood total cholesterol/phospholipids/lactic acid/endothelin-1/CRP, reddish focus/hemorrhage in the heart/lung, increased extramedullary hematopoiesis in the liver, proliferation of choroid endothelial cells and fibroblasts/atrophy of the outer nuclear layer of the retina in the eyeball**	**1**	**4.2.3.2-7**
Male and female dogs (Beagle)	**Oral**	**3 months (once daily) + 12-week recovery period**	**0, 0.3, 1, 3**	**≥1: increased erythropoiesis, increases in blood EPO/TIBC, hemosiderin deposit in Kupffer cells/hepatocytes in the liver** **3: decreases in food consumption/body weight, increases in basophil/platelet counts, large platelets, increases in blood bilirubin/UIBC/VEGF, decreases in blood glucose/iron/TSAT, increases in urine bilirubin, increased spleen weight, rough surface of the liver, increased extramedullary hematopoiesis/congestion in the spleen, increased erythroid hematopoiesis in the bone marrow, changes in erythrocyte morphology, centrilobular congestion/single cell necrosis of hepatocytes/hepatocellular atrophy/lipofuscin deposition in Kupffer cells/bile deposition/inflammatory cell infiltration/bile duct proliferation/fibrosis in the liver** **These findings were reversible.**	**1**	**4.2.3.2-8**

Table 11. Repeated-dose toxicity studies

Male and female cynomolgus monkeys	**Oral**	**3 months (once daily) + 1-month recovery period**	**0, 3, 10, 30**	**≥3: increased erythropoiesis, increases in blood EPO/iron/TIBC/PAI-1, decreases in blood UIBC** **≥10: decreases in blood total cholesterol/phospholipids/fibrinogen, prolongation of PT/APTT, increases in D-dimer/PIC, decreases in heart rate, prolongation of PR interval, increased erythroid hematopoiesis in the bone marrow, decreases in bone marrow M/E ratio, changes in erythrocyte morphology, hemosiderin deposit in the tubular epithelium, congestion in the lung/stomach/jejunum/kidney/brain/spinal cord/pituitary gland/adrenal gland, centrilobular congestion/hepatocellular atrophy in the liver** **30: reddening skin/reddish conjunctiva, decreases in platelet count, increases in blood ALT/AST/LDH/triglycerides/creatinine/bilirubin/ guanase, decreases in blood glucose, positive urine occult blood, conjunctival hyperemia, increased heart weight, hemorrhage in the heart (coronary adipose tissue)/lung/stomach/jejunum, organized thrombus/inflammatory cell infiltration in coronary adipose tissue in the heart, atrophy of acinar cells of the pancreas, erosion/inflammatory cell infiltration in the mucosa of the stomach/jejunum** **These findings were reversible (After the recovery period, conjunctival hyperemia, decreases in heart rate, prolongation of PR interval, changes in iron-related parameters, and increases in bone marrow M/E ratio were observed).**	**3**	**4.2.3.2-10**
Male and female cynomolgus monkeys	**Oral**	**9 months (once daily)**	**0, 1, 3, 30/10[e)]**	**≥1: increases in blood iron** **≥3: increased erythropoiesis, increases in blood EPO/bilirubin/LDH/guanase/PAI-1** **30/10: decreases in platelet count, increases in blood ALT/AST/potassium/D-dimer/PIC, decreases in blood total cholesterol/phospholipids/glucose/fibrinogen, prolongation of PT/APTT, increased erythroid hematopoiesis in the bone marrow, decreases in bone marrow M/E ratio, reddening skin/reddish oral mucosa/reddish conjunctiva, conjunctival hyperemia, hemosiderin deposit in periportal hepatocytes/centrilobular congestion/hepatocellular atrophy/lipofuscin deposition/fatty changes of midzonal to periportal hepatocytes in the liver, atrophy of acinar cells of the pancreas**	**3**	**4.2.3.2-11**

a) The finding was considered of little toxicological significance because this was not associated with histological changes suggestive of organ injuries such as cellular degeneration and necrosis, etc.

b) Since all males and females in the 10 mg/kg group had physical deterioration by Day 6, the test article was not administered from Day 7 to Day 23.

c) These changes occurred in 1 female only, without injurious changes such as inflammatory cellular infiltration, degeneration, and necrosis. Thus, these changes were considered of little toxicological significance.

d) The finding was considered of little toxicological significance because the severity of fatty changes showed no clear dose-dependence, and no injurious changes were noted.

e) Due to deterioration of physical condition at 30 mg/kg, dosing was withheld from Day 56 in 2 males and from Day 80 in all males and females. Then, dosing was resumed at a dose of 10 mg/kg/day on Day 113.

5.3 Genotoxicity

As *in vitro* studies, a bacterial reverse mutation test and chromosomal aberration tests in Chinese hamster lung (CHL) cells and human peripheral blood lymphocytes were performed. As *in vivo* studies, a chromosomal aberration test in rat bone marrow cells, and a comet assay using rat liver and peripheral blood were performed (Table 12).

Although the frequency of cells with structural chromosome aberrations was increased after 24-hour treatment without S9 mix in the chromosomal aberration test in CHL cells, as the chromosomal aberration test in human peripheral blood lymphocytes, the chromosomal aberration test in rat bone marrow cells, and the comet assay using rat liver and peripheral blood produced negative results, etc., enarodustat was considered to have little genotoxic potential.

Table 12. Genotoxicity studies

Type of study		Test system	S9 (Treatment)	Concentration (μg/plate or μg/mL) Dose (mg/kg/day)	Test result	Attached document CTD
In vitro	Bacterial reverse mutation test (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537	−/+	TA98, S9−: 0, 94, 188, 375, 750, 1,500 TA98, S9+: 0, 188, 375, 750, 1,500, 3,000 TA100/TA1535/TA1537, S9−: 0, 47, 94, 188, 375, 750 TA100/TA1535/TA1537, S9+: 0, 94, 188, 375, 750, 1,500 WP2*uvrA*, S9−: 0, 188, 375, 750, 1,500, 3,000 WP2*uvrA*, S9+: 0, 375, 750, 1,500, 3,000, 5,000	Negative	4.2.3.3.1-1
		Escherichia coli: WP2*uvrA*				
	Chromosomal aberration tests in cultured mammalian cells	CHL cells	− (6 hours)	0, 300, 350, 450	Negative	4.2.3.3.1-2
			− (24 hours)	0, 50, 100, 150	Positive (≥100)	
			+ (6 hours)	0, 300, 350, 450	Negative	
		Human peripheral blood lymphocytes	− (3 hours)	0, 160, 240, 280, 360	Negative	4.2.3.3.1-3
			− (24 hours)	0, 1.25, 5, 10, 15	Negative	
			+ (3 hours)	0, 160, 200, 240, 320	Negative	
In vivo	Rodent chromosomal aberration test	Male rats (SD) Bone marrow		0, 62.5, 125, 250 (oral, single dose)	Negative	4.2.3.3.2-1
	Comet assay	Male rats (SD) Liver, Peripheral blood		0, 62.5, 125, 250 (oral, two doses, 21 hours apart)	Negative	4.2.3.3.2-2

5.4 Carcinogenicity

Carcinogenicity studies were conducted in rasH2 transgenic mice and rats (Table 13). Enarodustat was considered to have no carcinogenic potential.

Table 13. Carcinogenicity studies

Test system	Route of administration	Duration of dosing	Principal findings						NOEL for carcinogenesis (mg/kg)	Attached document CTD
Male and female mice (rasH2 Tg)	Oral	6 months (once daily)	Lesion	Gender	Dose (mg/kg)[a]				6	4.2.3.4.2-3
					0	0.6	2	6		
			Neoplastic lesion	Male Female	None					
			Non-neoplastic lesion		increased erythropoiesis, decreases in platelet count, increases in the weights of the spleen/kidney, congestion in the kidney, spleen swelling/increased extramedullary hematopoiesis in the spleen					
Male and female rats (SD)	Oral	24 months (once daily)	Lesion	Gender	Dose (mg/kg)[b]				1	4.2.3.4.1-1
					0	0.1	0.3	1		
			Neoplastic lesion	Male Female	None					
			Non-neoplastic lesion		increased erythropoiesis					

a) 25/sex/group
b) 65/sex/group

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in male and female rats, embryo-fetal development studies in rats and rabbits, and a rat study for effects on pre- and postnatal development, including maternal function, were conducted (Table 14). In the study of fertility and early embryonic development to implantation in female rats, decreased implantation index and increased total post-implantation loss were observed. Although increased total post-implantation loss and retarded ossification in the embryo-fetal development study in rats and increased post-implantation loss and abortion in the embryo-fetal development study in rabbits were observed, these studies showed no teratogenicity. In the rat study for effects on pre- and postnatal development, including maternal function, findings suggestive of the delayed development of F1 pups were observed, but there were no effects on functional development or reproductive function. Enarodustat exposure (C_{max} was 16.52 μg/mL and $AUC_{0\text{-}24h}$ was 59.01 μg·h/mL in rats; C_{max} was 10.44 μg/mL and $AUC_{0\text{-}24h}$ was 39.23 μg·h/mL in rabbits) at the NOAELs in the embryo-fetal development studies in rats and rabbits (10 and 60 mg/kg/day, respectively) were 14.3-fold (based on C_{max}) and 5.7-fold (based on $AUC_{0\text{-}24h}$) in rats and 9.0-fold (based on C_{max}) and 3.8-fold (based on $AUC_{0\text{-}24h}$) in rabbits, compared to the estimated exposure following repeated oral administration of enarodustat at the maximum recommended clinical dose of 8 mg/day in HD patients (C_{max}, 1.15 μg/mL; AUC_{τ}, 10.30 μg·h/mL).

Table 14. Reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Dose (mg/kg)	Principal findings	NOAEL (mg/kg)	Attached document CTD
Fertility and early embryonic development to implantation	Female rats (SD)	Oral	from 14 days prior to mating, through mating to gestation day 7 (once daily)	0, 3, 10, 30	Death: 30 (1 of 20 animals) decreased body weight, dark reddish discoloration of the lung/adrenal gland, enlargement of the lung ≥10：reddish-colored skin, increased weights of the spleen/heart/lung, blackish focus in the lung, vaginal bleeding, increased number of dead embryos and fetuses/increased total post-implantation loss, decreased number of live fetuses 30：decreased food consumption, decreased body weight gain, large spleen, dark reddish discoloration of the liver, whitish focus in the kidney, decreased number of implantation sites and decreased implantation index	Females General toxicity: 3 Fertility: 30 Implantation: 10 Early embryonic development: 3	4.2.3.5.1-1
	Male rats (SD)	Oral	for 21 or 28 days, beginning 14 days before mating (once daily)	0, 3, 10, 30	≥10: reddish colored skin, increased weights of the spleen/heart/lung 30: decreased body weight gain, decreased food consumption, decreased locomotor activity, decreased seminal vesicle weight, enlargement of the spleen, dark red focus in the lung/cecum, white focus in the liver No effects on reproductive performance or early embryonic development	Males General toxicity: 3 Male fertility: 30 Early embryonic development: 30	4.2.3.5.1-2
Embryo-fetal development	Female rats (SD)	Oral	Gestation days 7-17 (once daily) Caesarean section: gestation day 20	0, 3, 10, 30	Dams ≥10: increased spleen weight 30: decreased body weight gain, decreased food consumption, reddish colored skin, increased weights of the heart/lung, large spleen Fetuses 30: increased total post-implantation loss, decreased body weights of live fetuses, increased placental weights, increased incidence of bipartite ossification of thoracic centrum, decreased number of ossification sites for sacral and coccygeal vertebrae/metacarpals	Dams (General toxicity): 10 Embryo-fetal development: 10	4.2.3.5.2-1

Table 14. Reproductive and developmental toxicity studies

	Female rabbits (NZW)	**Oral**	**Gestation days 6-18 (once daily)** **Caesarean section: gestation day 28**	**0, 20, 60, 200**	**Deaths or moribund sacrifices: 200 (6 of 20 animals)** **Pale discoloration of the kidney, dark red focus in the stomach, fur ball retention in the stomach, retention of watery content in the cecum** **Dams** **≥60: decreased food consumption, decreases in the amount of feces, abortion** **200: decreased body weight** **Embryos/fetuses** **200: increased post-implantation loss, decreased number of live fetuses** **No effects on fetal morphology**	**Dams (General toxicity): 20** **Embryo-fetal development: 60**	**4.2.3.5.2-2**
Pre- and postnatal development, including maternal function	**Female rats (SD)**	**Oral**	**from gestation day 7 to lactation day 20 (once daily)**	**0, 1, 3, 10**	**Dams** **10: decreased food consumption, reddening of the skin, enlargement of the spleen, increased weights of the spleen/heart/lung** **F1 pups** **10: decreased body weight, delayed eyelid opening** **No effects on functional development/ reproductive function of F1 pups**	**Dams General toxicity: 3** **Physical development of F1 pups: 3** **Functional development/ reproductive function of F1 pups: 10**	**4.2.3.5.3-1**

5.6 Other toxicity studies

5.6.1 Photosafety

An *in vitro* phototoxicity study was conducted, and enarodustat was considered to have little phototoxic potential (Table 15).

Table 15. Photosafety study

Type of study	Test system	Test method	Principal findings	Attached document CTD
Phototoxicity	**Mouse fibroblast cells Balb/c 3T3**	**9.49, 13.3, 18.6, 26.0, 36.4, 51.0, 71.4, 100 μg/mL UVA irradiation**	**Not phototoxic (Mean photo effect, 0.101)**	**4.2.3.7.7-1**

5.R Outline of the review conducted by PMDA

5.R.1 Toxicological profile of enarodustat

The applicant's explanation about the toxicological profile of enarodustat:

The findings observed in enarodustat toxicity studies were all considered directly or secondarily related to HIF-PH inhibition or induction of erythropoiesis (pharmacological activity) by enarodustat, and most of these findings were reversible. In all animal species tested, along with increases in red blood cell-related parameters, changes related to increased erythropoiesis and erythrocytosis (increased extramedullary hematopoiesis in the spleen, increased erythroid hematopoiesis in the bone marrow, etc.), changes related to persistent polycythemia (centrilobular congestion and hepatocellular atrophy in the liver, etc.), changes due to circulatory disturbance

caused by persistent polycythemia (thrombus formation in multiple organs, etc.), changes considered related to increased EPO production (decreases in platelet count, blood total cholesterol, and phospholipids, etc.), etc. were observed. These findings have been reported also with the currently approved ESAs (*Journal of clinical therapeutics & medicine*. 1990; 6 Suppl 2: 97-116, "Review Report on Nesp 10 μg syringe for intravenous use and 6 products" [February 15, 2007]). In repeated-dose toxicity studies, changes suggestive of circulatory disturbance related to severe or persistent polycythemia occurred mainly at the high dose level. Meanwhile, at the low or mid dose level, polycythemia was mild in severity, and there was no clear increased severity of polycythemia or circulatory disturbance with prolonged treatment. The above results indicated that the risk of thrombus formation, circulatory disturbance, and other changes is low over the clinical dose range of enarodustat.

PMDA accepted the applicant's explanation (The findings observed in enarodustat toxicity studies were all considered related to the induction of erythropoiesis by enarodustat). While the ratios of enarodustat exposure at the NOAELs in enarodustat repeated-dose toxicity studies to the human exposure are not adequate, and the possibility that these findings occur in the clinical use of enarodustat cannot be ruled out, enarodustat is used with dose titration according to Hb levels in patients with renal anemia, and Hb is monitored regularly during treatment with enarodustat. Thus, PMDA concluded that these findings are unlikely to become a problem in clinical use. PMDA continues to assess safety in humans in Section 7.R.2.

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

The applicant's explanation:

Decreased number of implantation sites and decreased implantation index, increased number of dead embryos and fetuses and increased total post-implantation loss, and decreased number of live fetuses in a study of fertility and early embryonic development to implantation in female rats, increased total post-implantation loss (rats and rabbits), decreased fetal weights and changes suggestive of retarded ossification (rats), and abortion (rabbits) in embryo-fetal development studies in rats and rabbits, and decreased body weight and delayed eyelid opening of F1 pups in a rat study for effects on pre- and postnatal development, including maternal function, were observed. The NOAELs for early embryonic development in rats (increased number of dead embryos and fetuses/increased total post-implantation loss, and decreased number of live fetuses), abortion in rabbits, and the physical development of F1 pups in rats were 3, 20, and 3 mg/kg/day, respectively, and enarodustat exposure at these dose levels were 0.7-, 1.8-, and 0.7-fold, respectively, the estimated exposure following repeated oral administration of enarodustat at the maximum recommended clinical dose of 8 mg/day in HD patients (C_{max}, 1.15 μg/mL; AUC_{τ}, 10.30 μg·h/mL). The results from non-clinical studies indicated that enarodustat is unlikely to induce teratogenicity, but may affect the implantation index, and fetal growth and survival. Based on the above, the package insert, etc. will advise against the use of enarodustat in pregnant women or women who may be pregnant, and state that women of childbearing potential should be advised to use contraception during treatment with enarodustat and for a certain period of time after the last dose of enarodustat.

Since enarodustat was shown to be excreted in milk in rats [see Section 4.4.3], and findings suggestive of the delayed development of F1 pups were observed in the rat study for effects on pre- and postnatal development, including maternal function, the possibility that enarodustat affects the offspring directly via the mother's milk cannot be ruled out. Thus, the package insert, etc. will advise that nursing mothers should avoid breastfeeding during treatment with enarodustat and for a certain period of time after the last dose of enarodustat.

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

The 1-mg, 2-mg, and 4-mg film-coated tablets were used in phase III studies submitted in the present application (Study MBA4-1, Study MBA4-2, Study MBA4-3, Study MBA4-4, Study MBA4-5, Study MBA4-6). Dissolution testing demonstrated the bioequivalence between the different formulations. The formulations used in the phase III studies are identical to the proposed commercial formulations (the 2-mg tablet and the 4-mg tablet).

Plasma and urine concentrations of unchanged enarodustat and its metabolite (a benzylic hydroxylated metabolite[6)]) were determined by LC/MS/MS. The lower limits of quantification for unchanged enarodustat and its metabolite in plasma were 1 and 0.25 ng/mL, respectively, and the lower limit of quantification for unchanged enarodustat in urine was 5 ng/mL.

6.1.1 Japanese phase I study (Food effect) (CTD 5.3.3.1-1, Study MBX1-1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, single-blind study was conducted at 1 site in Japan to assess the effect of food, etc. on the pharmacokinetics of a single oral dose of enarodustat 100 mg in Japanese healthy adult male subjects (target sample size, 7 subjects [1 for placebo and 6 for enarodustat).

A single oral dose of enarodustat 100 mg or placebo was to be administered under fasting conditions or after a meal. All of 7 randomized subjects were included in the pharmacokinetic analysis population.

The geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of unchanged enarodustat in plasma for fed vs. fasted [90% confidence interval (CI)] were 0.53 [0.46, 0.61] and 0.74 [0.65, 0.84], respectively, and food decreased enarodustat exposure.

6.1.2 Studies using human biomaterials

6.1.2.1 *In vitro* metabolism (CTD 4.2.2.4-9)

[6)] (R)-enantiomer of a benzylic hydroxylated metabolite of enarodustat was measured.

[^{14}C]-enarodustat (10 μmol/L) was added to a human CYP expression system (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), and the metabolites of enarodustat were identified. A trace amount of a metabolite of enarodustat (a benzylic hydroxylated metabolite) was formed by CYP2C8, CYP2C9, and CYP3A4. Enarodustat was not metabolized by other CYP isoforms.

When [^{14}C]-enarodustat (10 μmol/L) and an inhibitor of each CYP isoform[7)] were added to human liver microsomes, CYP2C8, CYP2C9, and CYP3A4/5 inhibitors decreased formation of a metabolite (a benzylic hydroxylated metabolite) by up to 63.6%, 65.1%, and 32.5%, respectively.

Based on the above, the applicant explained that in humans, enarodustat is primarily metabolized by CYP2C8 and CYP2C9, and CYP3A4 is also involved.

6.1.2.2 Inhibition of human liver drug metabolizing enzymes by enarodustat (CTD 4.2.2.4-10)

Human liver microsomes were incubated with the substrates for CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5)[8)] in the presence of enarodustat (1-100 μmol/L) and NADPH, and the potential of enarodustat to inhibit CYP isoforms was assessed. Enarodustat 100 μmol/L inhibited the metabolism of CYP2B6, CYP2C8, and CYP2C9 substrates, and the remaining activities were 75.3%, 54.4%, and 83.4%, respectively. On the other hand, enarodustat did not inhibit the metabolism of the substrates for other CYP isoforms tested. Enarodustat was not a time-dependent inhibitor of any CYP isoform.

6.1.2.3 Induction of human liver drug metabolizing enzymes by enarodustat (CTD 4.2.2.4-11)

Human hepatocytes were incubated with enarodustat (0.1-100 μmol/L), and the mRNA expression levels of CYP1A2 and CYP3A4 were determined. Enarodustat concentration-dependently decreased the CYP1A2 and CYP3A4 mRNA levels. The applicant explained that HIF stabilization by enarodustat was considered to lead to decreases in the mRNA levels. For the effects of enarodustat on CYP enzyme activities, see Section 6.2.7.

6.1.2.4 Transporter-mediated transport (CTD 4.2.2.6-1 and 4.2.2.6-2)

P-glycoprotein (P-gp)- and breast cancer resistance protein (BCRP)-mediated transport of enarodustat (1-100 μmol/L) was investigated using human colonic adenocarcinoma cells (Caco-2 cells). Enarodustat was considered a substrate of BCRP.

Organic anion transporting polypeptide (OATP) 1B1- and OATP1B3-mediated transport of enarodustat (1-100 μmol/L) was investigated using human embryonic kidney 293 (HEK293) cells expressing OATP1B1 and OATP1B3. Enarodustat was not considered a substrate of OATP1B1 or OATP1B3.

[7)] The following inhibitors were used for assessment.
α-naphthoflavone for CYP1A; quercetin for CYP2C8; sulfaphenazole for CYP2C9; quinidine for CYP2D6; ketoconazole for CYP3A4/5

[8)] The following substrates were used for assessment.
phenacetin for CYP1A2; coumarin for CYP2A6; bupropion for CYP2B6; amodiaquine for CYP2C8; diclofenac for CYP2C9; S-(+)-mephenytoin for CYP2C19; (±)-bufuralol for CYP2D6; testosterone and midazolam for CYP3A4/5

Using mouse second portion of proximal tubule cells (S2 cells) expressing OAT1 and OAT3 or HEK293 cells expressing OCT2, multidrug and toxin extrusion (MATE) 1, and MATE2-K, OAT1-, OAT3-, OCT2-, MATE1-, and MATE2-K-mediated transport of enarodustat (1-100 μmol/L; 1-300 μmol/L for OAT1-mediated transport) was investigated. Enarodustat was considered a substrate of OAT1.

6.1.2.5 Inhibition of transporters (CTD 4.2.2.6-1 and 4.2.2.6-2)

Using Caco-2 cells, the effects of enarodustat (1-100 μmol/L) on the transport of the model substrates of P-gp and BCRP[9)] were investigated. Enarodustat inhibited BCRP with an IC_{50} value of 43.2 μmol/L.

Using HEK293 cells expressing OCT2, MATE1, MATE2-K, OATP1B1, and OATP1B3 or S2 cells expressing OAT1 and OAT3, the effects of enarodustat on the transport of the model substrates of these transporters[10)] were investigated. Enarodustat inhibited OATP1B1, OAT1, and OAT3 with IC_{50} values of 30.0, 0.96, and 1.67 μmol/L, respectively.

6.1.2.6 Clearance of enarodustat by dialysis membranes (CTD 4.2.2.7-1)

Enarodustat (0.1-10 μg/mL) was added to human plasma, which was dialyzed for 120 minutes by using various types of hemodialysis membranes (polysulfone, cellulose triacetate, polyethersulfone). The removal ratios of enarodustat at 0 to 120 minutes after the start of dialysis were determined.

At 120 minutes after the start of dialysis, the enarodustat removal ratios of the polysulfone, cellulose triacetate, and polyethersulfone membranes were 3.0% to 5.0%, 0.4% to 1.9%, and 3.0% to 5.1%, respectively. There was little clearance of enarodustat by these dialysis membranes.

6.2 Clinical pharmacology

6.2.1 Japanese phase I study (CTD 5.3.3.1-1, Study MBX1-1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

(1) Single dose administration

A placebo-controlled, randomized, single-blind study was conducted at 1 site in Japan to evaluate the pharmacokinetics, etc. of a single oral dose of enarodustat in healthy adult subjects (target sample size, 49 subjects [7 for placebo and 42 for enarodustat).

A single oral dose of placebo or enarodustat 1, 5, 15, 50, 100, or 200 mg was to be administered under fasting conditions.

Plasma pharmacokinetic parameters of unchanged enarodustat are shown in Table 16. The C_{max} and $AUC_{0-\infty}$ of unchanged enarodustat increased in an approximately dose-proportional manner. The mean fraction of systemically available drug excreted into the urine over the entire collection interval was 26.8% to 61.0%.

[9)] digoxin for P-gp; estrone-3-sulfate for BCRP

[10)] The following model substrates were used.
estradiol-17β-D-glucuronide for OATP1B1; estradiol-17β-D-glucuronide for OATP1B3; *p*-aminohippuric acid for OAT1; estrone-3-sulfate for OAT3; metformin for OCT2; metformin for MATE1; metformin for MATE2-K

Table 16. Plasma pharmacokinetic parameters of unchanged drug following a single oral dose of enarodustat

Enarodustat dose	N	C_{max} (μg/mL)	t_{max} [a)] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)
1 mg	6	0.16 ± 0.03	0.5 (0.5, 1.0)	0.82 ± 0.26	8.4 ± 1.9
5 mg	6	0.72 ± 0.13	1.0 (0.5, 1.5)	4.23 ± 1.49	8.7 ± 0.8
15 mg	6	2.27 ± 0.56	1.3 (0.5, 1.5)	11.61 ± 1.72	8.2 ± 0.8
50 mg	6	7.41 ± 0.94	1.5 (1.0, 3.0)	37.57 ± 10.47	9.1 ± 1.7
100 mg	6	11.34 ± 1.46	2.5 (1.0, 3.0)	59.79 ± 13.98	8.4 ± 0.7
200 mg	6	23.48 ± 7.65	1.5 (0.5, 4.0)	111.90 ± 22.23	7.7 ± 0.5

Mean ± SD
a) Median (Min., Max.)

Regarding safety, adverse events occurred in 16.7% (1 of 6) of subjects treated with placebo, 16.7% (1 of 6) of subjects treated with 1 mg of enarodustat, 16.7% (1 of 6) of subjects treated with 100 mg of enarodustat, and 33.3% (2 of 6) of subjects treated with 200 mg of enarodustat, and all those events except for the event reported with placebo were classified as adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to discontinuation.

(2) Multiple dose administration

A placebo-controlled, randomized, single-blind study was conducted to evaluate the pharmacokinetics, etc. of multiple oral doses of enarodustat in healthy adult subjects (target sample size, 36 subjects [9 for placebo and 27 for enarodustat).

Placebo or enarodustat 25, 50, or 100 mg was to be administered orally once daily before breakfast for 7 days. Since 4 subjects treated with enarodustat 100 mg discontinued at predose of Day 7 (the reasons for discontinuations were "the occurrence of adverse events" [3 subjects] and "the subject's request" [1 subject]), all subjects treated with enarodustat 100 mg discontinued at predose of Day 7 in the judgment of the investigator.

Plasma pharmacokinetic parameters of unchanged enarodustat are shown in Table 17. The C_{max} and AUC_{τ} of unchanged enarodustat increased in an approximately dose-proportional manner, and there was no evident accumulation after once daily administration of enarodustat 25 to 100 mg. The mean fraction of systemically available drug excreted into the urine during a dosing interval on Day 7 was 28.9% following administration of enarodustat 25 mg and 23.5% following administration of enarodustat 50 mg.

Table 17. Plasma pharmacokinetic parameters of unchanged drug following multiple oral doses of enarodustat

Enarodustat dose	Time point	N	C_{max} (μg/mL)	t_{max} [a)] (h)	AUC_{τ} (μg·h/mL)	$t_{1/2}$ (h)
25 mg	Day 1	9	3.44 ± 0.58	1.0 (0.5, 1.0)	13.67 ± 2.87	−
	Day 7	9	3.37 ± 0.98	1.0 (0.5, 1.0)	14.45 ± 3.16	8.0 ± 1.1
50 mg	Day 1	9	4.77 ± 1.64	1.0 (0.5, 1.5)	23.01 ± 4.35	−
	Day 7	8	6.97 ± 2.29	1.0 (0.5, 1.0)	34.25 ± 9.70	7.9 ± 0.8
100 mg	Day 1	9	11.00 ± 2.90	1.0 (1.0, 1.5)	50.26 ± 23.57	−
	Day 7 [b)]	−	−	−	−	−

Mean ± SD, −: Not calculated
a) Median (Min., Max.)
b) Pharmacokinetic parameters were not calculated because all subjects treated with enarodustat 100 mg discontinued at predose of Day 7.

Regarding safety, adverse events occurred in 55.6% (5 of 9) of subjects treated with placebo, 44.4% (4 of 9) of subjects treated with enarodustat 25 mg, 77.8% (7 of 9) of subjects treated with enarodustat 50 mg, and

100% (9 of 9) of subjects treated with enarodustat 100 mg, and adverse drug reactions occurred in 22.2% (2 of 9) of subjects treated with enarodustat 25 mg, 77.8% (7 of 9) of subjects treated with enarodustat 50 mg, and 88.9% (8 of 9) of subjects treated with enarodustat 100 mg. The events reported by ≥3 subjects following any of the treatments were lipids decreased (3 subjects treated with enarodustat 50 mg), C-reactive protein increased (5 subjects treated with enarodustat 100 mg), decreased appetite (4 subjects treated with enarodustat 100 mg), headache (3 subjects treated with enarodustat 100 mg), abdominal distension (3 subjects treated with enarodustat 100 mg), and nausea (3 subjects treated with enarodustat 100 mg), all of which were classified as adverse drug reactions. There were 13 discontinuations, and the reasons for discontinuations were "the occurrence of adverse events" (4 subjects) (1 subject treated with enarodustat 50 mg and 3 subjects treated with enarodustat 100 mg), "the subject's request" (1 subject treated with enarodustat 100 mg), and "the physician's decision" (8 subjects) (3 subjects treated with placebo, 5 subjects treated with enarodustat 100 mg). There were no deaths or serious adverse events.

6.2.2 Foreign phase I study (Mass balance study) (CTD 5.3.3.2-3, Study AZ951-U-15-010 [May 2016 to September 2016] [Reference data])

An open-label study was conducted at 1 site overseas to characterize the mass balance, etc. of a single oral dose of [^{14}C]-enarodustat in non-Japanese HD patients (target sample size, 6 subjects).

A single oral dose of [^{14}C]-enarodustat 10 mg (oral solution) was to be administered.

Pharmacokinetic parameters of unchanged enarodustat and its metabolite (a benzylic hydroxylated metabolite) are shown in Table 18. The $AUC_{0-\infty}$ of unchanged enarodustat and its metabolite (a benzylic hydroxylated metabolite) accounted for 62.7% and 2.9%, respectively, of the total radioactivity in plasma, and unchanged enarodustat was the predominant component in plasma.

Table 18. Plasma pharmacokinetic parameters following a single oral dose of [^{14}C]-enarodustat in non-Japanese HD patients under fasting conditions

Enarodustat dose	N	Analyte	C_{max} (μg/mL)	t_{max} a) (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)
10 mg	6	Unchanged enarodustat	0.99 ± 0.29	0.5 (0.3, 2.0)	7.33 ± 1.65	25.9 ± 21.7
	6	Benzylic hydroxylated metabolite	0.025 ± 0.007	3.0 (2.0, 4.0)	0.36 ± 0.15	10.6 ± 1.9

Mean ± SD
a) Median (Min., Max.)

Up to 792 hours post-dose, 10.9% and 77.1% of the administered radioactivity were recovered in urine and feces, respectively, and fecal excretion was the major route of elimination of enarodustat in HD patients. In both urine and feces, the predominant analyte was unchanged enarodustat.

6.2.3 Japanese phase II study in patients with non-dialysis-dependent CKD (CTD 5.3.5.2-1, Study MBA2-2 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Following multiple oral administration of enarodustat in adult anemic patients with non-dialysis-dependent CKD (target sample size, 20 subjects), plasma concentrations of unchanged enarodustat were determined.

Enarodustat was to be started at 1 mg/day and escalated every 2 weeks to 3 and 5 mg/day. If a Hb level of ≥11 g/dL was reached, enarodustat was allowed to be continued at the same dose without escalation. Enarodustat was to be administered orally once daily before breakfast for 6 weeks.

As to pharmacokinetics, plasma trough concentrations after 2 weeks of treatment at each dose level are shown in Table 19, and the plasma trough concentration of unchanged enarodustat increased in a dose-proportional manner.

Table 19. Plasma trough concentrations of unchanged drug following multiple oral administration of enarodustat in patients with non-dialysis-dependent CKD (ng/mL)

Enarodustat dose	N	After 2 weeks of treatment
1 mg	16	11.43 ± 6.44
3 mg	17	36.17 ± 20.63
5 mg	14	56.84 ± 34.23

Mean ± SD

Regarding safety, adverse events occurred in 54.5% (12 of 22) of subjects, and those reported by ≥2 subjects were nasopharyngitis (5 subjects); fibrin D dimer increased (3 subjects); and back pain; and blood phosphorus increased (2 subjects each). Adverse drug reactions occurred in 18.2% (4 of 22) of subjects (diarrhoea; vomiting; thirst; fibrin D dimer increased; and interstitial lung disease [1 subject each] [some subjects had more than 1 event]).

No deaths were reported. Serious adverse events occurred in 4 subjects (interstitial lung disease; congestive cardiac failure; cardiac failure; and vomiting [1 subject each]), and those 3 events other than cardiac failure led to treatment discontinuation. Interstitial lung disease; and vomiting (1 subject each) were classified as adverse drug reactions, and the case of vomiting had an outcome of "resolved" and the case of interstitial lung disease had an outcome of "resolved with sequelae." There were no other adverse events leading to treatment discontinuation.

6.2.4 Clinical studies in HD patients

6.2.4.1 Japanese phase I study (CTD 5.3.3.2-1, Study MBX1-2 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Following a single oral dose of enarodustat in adult HD patients with renal anemia (target sample size, 6 subjects), plasma concentrations of unchanged enarodustat were determined.

A single oral dose of enarodustat 15 mg was to be administered under fasting conditions.

Pharmacokinetic parameters of unchanged enarodustat are shown in Table 20.

Table 20. Plasma pharmacokinetic parameters of unchanged drug following a single oral dose of enarodustat in HD patients

Treatment group	N	C_{max} (μg/mL)	t_{max} [a)] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)
15 mg	6	2.17 ± 0.38	1.2 (1.0, 2.0)	19.32 ± 4.42	11.3 ± 2.6

Mean ± SD
a) Median (Min., Max.)

6.2.4.2 Japanese phase II study (CTD 5.3.5.2-2, Study MBA2-1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Following multiple oral administration of enarodustat in adult HD patients with renal anemia (target sample size, 36 subjects [12 per group]), plasma concentrations of unchanged enarodustat were determined.

Enarodustat was to be administered at doses presented in Table 21 orally once daily before breakfast for 8 weeks. Since a foreign phase I study in HD patients (Study AZ951-U-13-005)[11] etc. showed that hemodialysis has no effect on the pharmacokinetics of enarodustat, enarodustat was to be administered without regard to dialysis in this study.

Table 21. Enarodustat dose

Treatment group	Weeks 0-2	Weeks 2-4	Weeks 4-8
1 mg	1 mg		
3 mg	1 mg	3 mg	
5 mg	1 mg	3 mg	5 mg

As to pharmacokinetics, plasma trough concentrations in the treatment groups are shown in Table 22, and the plasma trough concentration of unchanged enarodustat increased in a dose-proportional manner.

Table 22. Plasma trough concentrations of unchanged drug following multiple oral administration of enarodustat in HD patients (ng/mL)

Treatment group	N	Week 2	Week 4	Week 6	Week 8
1 mg	8	14.22 ± 11.32	17.02 ± 16.22	14.45 ± 9.91	20.76 ± 23.84
3 mg	9	13.17 ± 8.00	32.85 ± 29.95	33.98 ± 20.23	36.76 ± 22.30
5 mg	8	12.33 ± 4.74 a)	41.31 ± 37.65	49.15 ± 29.68	46.65 ± 34.11

Mean ± SD
a) N = 7

Regarding safety, adverse events occurred in 35.7% (5 of 14) of subjects in the 1 mg group, 84.6% (11 of 13) of subjects in the 3 mg group, and 69.2% (9 of 13) of subjects in the 5 mg group, and those reported by ≥2 subjects in any group are shown in Table 23. No adverse drug reactions were reported.

Table 23. Adverse events reported by ≥2 subjects in any group (Safety population)

	1 mg (N = 14)	3 mg (N = 13)	5 mg (N = 13)
Any adverse event	35.7 (5)	84.6 (11)	69.2 (9)
Nasopharyngitis	21.4 (3)	23.1 (3)	38.5 (5)
Stomatitis	0 (0)	0 (0)	15.4 (2)
Headache	0 (0)	15.4 (2)	0 (0)
Pruritus	0 (0)	15.4 (2)	0 (0)

MedDRA/J ver.16.0; Incidence % (n)

There were no deaths or serious adverse events. Adverse events leading to treatment discontinuation occurred in 1 subject in the 1 mg group (contusion, anaemia), and a causal relationship to study drug was denied for both events.

6.2.5 Foreign phase I study (Drug interaction study with sevelamer carbonate) (CTD 5.3.3.4-1, Study AZ951-U-[redacted]-002 [[redacted] 20[redacted] to [redacted] 20[redacted]] [Reference data])

One study was conducted in non-Japanese healthy adult subjects (target sample size, 12 subjects) to evaluate the effect of sevelamer carbonate on the pharmacokinetics of enarodustat.

[11] A single oral dose of enarodustat 5 mg was administered to non-Japanese HD patients 2 hours prior to or 2 hours after hemodialysis.

The geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of enarodustat for enarodustat + sevelamer carbonate vs. enarodustat are shown in Table 24. Sevelamer carbonate administered simultaneously with enarodustat decreased the C_{max} and $AUC_{0-\infty}$ of enarodustat.

Table 24. Geometric mean ratios of plasma pharmacokinetic parameters of unchanged enarodustat for enarodustat + sevelamer carbonate vs. enarodustat

Enarodustat dose	Concomitant drug (oral administration)	Timing of administration of enarodustat	N	C_{max}	$AUC_{0-\infty}$
25 mg	Sevelamer carbonate 2,400 mg 3 times daily[a)]	Simultaneously with sevelamer carbonate	12	0.47 [0.38, 0.58]	0.55 [0.49, 0.61]
		3 hours after administration of sevelamer carbonate	12	0.89 [0.72, 1.10]	0.94 [0.84, 1.06]
		1 hour prior to administration of sevelamer carbonate	12	0.92 [0.74, 1.14]	0.80 [0.71, 0.89]

Geometric mean ratio [90% CI]

a) The study consisted of treatment periods 1 to 4. On Day 1 of these treatment periods, enarodustat 25 mg alone was administered, enarodustat 25 mg was administered simultaneously with sevelamer carbonate 2,400 mg, enarodustat 25 mg was administered 3 hours after administration of sevelamer carbonate 2,400 mg, or enarodustat 25 mg was administered 1 hour prior to administration of sevelamer carbonate 2,400 mg.

Geometric mean ratio: C_{max} or $AUC_{0-\infty}$ with sevelamer carbonate/C_{max} or $AUC_{0-\infty}$ without sevelamer carbonate

6.2.6 Foreign phase I study (Drug interaction study with lapatinib) (CTD 5.3.3.4-3, Study AZ951-U-15-009 [November 2015 to March 2016] [Reference data])

Since an *in vitro* study using Caco-2 cells suggested that enarodustat is a substrate of BCRP [see Section 6.1.2.4], 1 study was conducted in non-Japanese HD patients (target sample size, 12 subjects) to evaluate the effect of lapatinib, a BCRP inhibitor, on the pharmacokinetics of enarodustat.

The geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of enarodustat for enarodustat + lapatinib vs. enarodustat are shown in Table 25. Coadministration with lapatinib increased the C_{max} and $AUC_{0-\infty}$ of enarodustat.

Table 25. Geometric mean ratios of plasma pharmacokinetic parameters of unchanged enarodustat for enarodustat + lapatinib vs. enarodustat

Enarodustat dose	Coadministered drug (oral administration)	N	C_{max}	$AUC_{0-\infty}$
5 mg	Lapatinib 250 mg [a)]	10	1.29 [1.11, 1.49]	1.32 [1.22, 1.43]

Geometric mean ratio [90% CI]

a) Enarodustat 5 mg was administered orally on Day 1, and enarodustat 5 mg was coadministered with lapatinib 250 mg on Day 5.

Geometric man ratio: C_{max} or $AUC_{0-\infty}$ with lapatinib/C_{max} or $AUC_{0-\infty}$ without lapatinib

6.2.7 Foreign phase I study (Drug interaction study with CYP substrates) (CTD 5.3.3.1-3, Study AZ951-U-[redacted]-003 [[redacted] 20[redacted] to [redacted] 20[redacted]] [Reference data])

An *in vitro* study using human liver microsomes suggested that enarodustat inhibits CYP2B6, CYP2C8, and CYP2C9 [see Section 6.1.2.2], and in an *in vitro* study using human hepatocytes, enarodustat decreased the CYP1A2 and CYP3A4 mRNA levels [see Section 6.1.2.3]. One study was conducted in non-Japanese healthy adult subjects to evaluate the effect of enarodustat on CYP activities, using a cocktail of CYP probe substrates.

The geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of each CYP substrate for with vs. without enarodustat are shown in Tables 26 and 27. Coadministration with enarodustat altered the C_{max} and $AUC_{0-\infty}$ of each CYP substrate.

Table 26. Geometric mean ratios (CYP substrate + enarodustat / CYP substrate alone) of plasma pharmacokinetic parameters of CYP substrates [90% CI]

Enarodustat dose	CYP isoform	Coadministered drug (oral administration)[a)]	N	Analyte	C_{max}	$AUC_{0-\infty}$
25 mg	1A2	Caffeine 200 mg	9	Caffeine	0.99 [0.88, 1.11]	1.61 [1.48, 1.75]
				1,7-dimethylxanthine[b)]	0.94 [0.89, 0.99]	1.40 [1.29, 1.51]
	2C9	Tolbutamide 500 mg		Tolbutamide	1.07 [0.96, 1.20]	1.07 [1.01, 1.14]
				Carboxytolbutamide[c)]	1.02 [0.94, 1.09]	1.05 [1.00, 1.10]
				4-hydroxytolbutamide[c)]	1.00 [0.93, 1.08]	1.04 [0.99, 1.09]
	2C19	Omeprazole 20 mg		Omeprazole	1.78 [1.14, 2.80]	0.92 [0.75, 1.14]
				5-hydroxy omeprazole[d)]	1.59 [1.16, 2.17]	1.11 [1.04, 1.19]
	2D6	Dextromethorphan 30 mg		Dextromethorphan	1.23 [0.98, 1.55]	1.21 [1.01, 1.44]
				Dextrorphan[e)]	0.90 [0.83, 0.99]	1.02 [0.97, 1.07]
	3A4	Midazolam 3 mg		Midazolam	1.43 [1.30, 1.57]	1.42 [1.24, 1.63]
				1-hydroxy midazolam[f)]	1.22 [1.04, 1.42]	1.36 [1.17, 1.58]

a) CYP substrate alone was administered on Day−3, and enarodustat 25 mg was administered on Days 1-15 with CYP substrate on Day 15. Geometric mean ratio (CYP substrate + enarodustat / CYP substrate alone) of C_{max} and $AUC_{0-\infty}$ of CYP substrates
b) A metabolite of caffeine
c) A metabolite of tolbutamide
d) A metabolite of omeprazole
e) A metabolite of dextromethorphan
f) A metabolite of midazolam

Table 27. Geometric mean ratios (CYP substrate + enarodustat / CYP substrate alone) of plasma pharmacokinetic parameters of CYP substrates [90% CI]

Enarodustat dose	CYP isoform	Coadministered drug (oral administration)[a)]	N	Analyte	C_{max}	$AUC_{0-\infty}$
50 mg	1A2	Caffeine 200 mg	8	Caffeine	1.06 [0.93, 1.20]	1.63 [1.49, 1.78]
				1,7-dimethylxanthine[b)]	0.92 [0.87, 0.97]	1.43 [1.32, 1.54]
	2C9	Tolbutamide 500 mg		Tolbutamide	0.98 [0.87, 1.10]	1.03 [0.96, 1.09]
				Carboxytolbutamide[c)]	1.06 [0.98, 1.14]	1.12 [1.07, 1.17]
				4-hydroxytolbutamide[c)]	1.06 [0.97, 1.15]	1.20 [1.14, 1.27]
	2C19	Omeprazole 20 mg		Omeprazole	1.03 [0.64, 1.66]	0.71 [0.52, 0.98]
				5-hydroxy omeprazole[d)]	1.09 [0.79, 1.52]	1.15 [1.07, 1.23]
	2D6	Dextromethorphan 30 mg		Dextromethorphan	1.89 [1.50, 2.37]	1.72 [1.44, 2.06]
				Dextrorphan[e)]	0.83 [0.76, 0.90]	1.04 [0.99, 1.09]
	3A4	Midazolam 3 mg		Midazolam	1.42 [1.28, 1.57]	1.63 [1.39, 1.90]
				1-hydroxy midazolam[f)]	1.23 [1.05, 1.45]	1.39 [1.17, 1.64]

a) CYP substrate alone was administered on Day−3, and enarodustat 50 mg was administered on Days 1-15 with CYP substrate on Day 15. Geometric mean ratio (CYP substrate + enarodustat / CYP substrate alone) of C_{max} and $AUC_{0-\infty}$ of CYP substrates
b) A metabolite of caffeine
c) A metabolite of tolbutamide
d) A metabolite of omeprazole
e) A metabolite of dextromethorphan
f) A metabolite of midazolam

6.2.8 QT/QTc evaluation study (CTD 5.3.4.1-1, Study AZ951-U-[redacted]-011 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo- and active-controlled, randomized, double-blind, 4-treatment, 4-period, crossover study was conducted in non-Japanese healthy adult subjects (target sample size, 52 subjects) to evaluate the effect of a single oral dose of enarodustat on ventricular repolarization.

A single oral dose of placebo, enarodustat 20 or 150 mg, or moxifloxacin 400 mg (positive control) was to be administered under fasting conditions. A 7-day washout period was included between periods.

The upper limit of the two-sided 90% confidence interval for the difference in individual-corrected QT interval (QTcI) change from baseline between enarodustat 20 or 150 mg and placebo (ΔΔQTcI) was 3.7 or 4.4 ms, respectively, which was below 10 ms. As the lower limit of the two-sided 90% confidence interval for ΔΔQTcI at 1 to 4 hours post-dose for moxifloxacin was above 5 ms, the study was considered to have assay sensitivity.

Plasma pharmacokinetic parameters of enarodustat following a single oral dose of enarodustat are shown in Table 28.

Table 28. Plasma pharmacokinetic parameters of unchanged drug following a single oral dose of enarodustat

Enarodustat dose	N	C_{max} (μg/mL)	t_{max}[a)] (h)	$AUC_{0-\infty}$ (μg·h/mL)
20 mg	51	2.07 ± 0.49	1.5 (0.5, 4.0)	10.80 ± 3.21[b)]
150 mg	52	14.80 ± 3.92	1.0 (0.5, 6.0)	71.50 ± 28.70[c)]

Mean ± SD
a) Median (Min., Max.); b) N = 49; c) N = 50

Regarding safety, adverse events occurred in 10.0% (5 of 50) of subjects in the placebo treatment period, 9.8% (5 of 51) of subjects in the 20 mg treatment period, 28.8% (15 of 52) of subjects in the 150 mg treatment period, and 18.8% (9 of 48) of subjects in the moxifloxacin treatment period. Those reported by ≥3 subjects in any treatment period are shown in Table 29. Adverse events leading to study discontinuation occurred in 4.0% (2 of 50) of subjects in the placebo treatment period (headache; and urticaria [1 subject each]) and 1.9% (1 of 52) of subjects in the 150 mg treatment period (orthostatic hypotension [1 subject]), and urticaria and orthostatic hypotension (1 subject each) were classified as adverse drug reactions. There were no deaths or serious adverse events.

Table 29. Adverse events reported by ≥3 subjects in any treatment period

	20 mg treatment period (N = 51)	150 mg treatment period (N = 52)	Placebo treatment period (N = 50)	Moxifloxacin treatment period (N = 48)
Any adverse event	**9.8 (5)**	**28.8 (15)**	**10.0 (5)**	**18.8 (9)**
Headache	**2.0 (1)**	**15.4 (8)**	**4.0 (2)**	**8.3 (4)**
Nausea	**0 (0)**	**9.6 (5)**	**2.0 (1)**	**4.2 (2)**

MedDRA/J ver.19.0; Incidence % (n)

6.R Outline of the review conducted by PMDA

6.R.1 Effects of other drugs on pharmacokinetics of enarodustat

The applicant's explanation about the effect of a BCRP inhibitor on the pharmacokinetics of enarodustat:

Study AZ951-U-15-009 showed that coadministration with a BCRP inhibitor, lapatinib, increased the C_{max} and $AUC_{0-\infty}$ of enarodustat by 28.5% and 32.1%, respectively [see Section 6.2.6]. A multiple-dose study in healthy adult subjects demonstrated the safety of enarodustat 25 mg [see Section 6.2.1]. Given the estimated exposure following multiple oral administration of enarodustat at the maximum recommended clinical dose of 8 mg/day in HD patients (C_{max}, 1.15 μg/mL; AUC_{τ}, 10.30 μg·h/mL), increased enarodustat exposure resulting from coadministration with a BCRP inhibitor was not considered to exceed enarodustat exposure following repeated administration of enarodustat 25 mg that has been demonstrated to be safe (C_{max}, 3.37 μg/mL; AUC_{τ}, 14.45 μg·h/mL). In addition, based on the data from clinical studies, the effect of concomitant BCRP inhibitors such as cyclosporine and eltrombopag (patient characteristics) on safety was assessed. Though only 3 patients received concomitant BCRP inhibitor, there were no clear safety concerns in these patients. Based on the above, the extent of increase in enarodustat exposure in the drug interaction study with lapatinib is insignificant. Enarodustat is used with dose titration according to Hb levels while monitoring Hb levels regularly. Given these points, there is no particular problem with coadministration of enarodustat and a BCRP inhibitor at present, and a relevant precautionary statement in the package insert is unnecessary.

In Study AZ951-U-[redacted]-002, when administered simultaneously with enarodustat, sevelamer carbonate decreased the C_{max} and $AUC_{0-\infty}$ of enarodustat by 53% and 45%, respectively. Meanwhile, when enarodustat was administered 3 hours after or 1 hour prior to administration of sevelamer carbonate, the effect of sevelamer carbonate on the pharmacokinetics of enarodustat was small. Interactions between enarodustat and sevelamer carbonate are thought to occur due to the ionic binding of the ionized carboxylic acid of enarodustat to sevelamer, and the possibility that, when administered simultaneously with enarodustat,

phosphate binders other than sevelamer carbonate also affect the pharmacokinetic of enarodustat cannot be ruled out. However, phosphate binders such as sevelamer carbonate are administered immediately before or after a meal, and will not be taken simultaneously with enarodustat, which is administered before a meal or at bedtime. Thus, as the effects of phosphate binders on the pharmacokinetics of enarodustat can be avoided, a relevant precautionary statement in the package insert is unnecessary.

PMDA's view:
There is no problem with the applicant's decision not to include a precautionary statement regarding coadministration of enarodustat and a BCRP inhibitor in the package insert. On the other hand, in the clinical use of enarodustat and phosphate binders such as sevelamer carbonate, the possibility that the administration of the two drugs in a short interval results in interactions cannot be ruled out. Thus, the package insert should advise that an appropriate interval is required between administration of enarodustat and phosphate binders such as sevelamer carbonate.

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

The applicant's explanation about the effects of enarodustat on the pharmacokinetics of CYP substrates:
Although coadministration with enarodustat affected the C_{max} and $AUC_{0-\infty}$ of each CYP substrate in Study AZ951-U-[redacted]-003 using a cocktail of CYP probe substrates, the IC_{50} values of enarodustat for CYP isoforms were all ≥100 μmol/L, and enarodustat was not a time-dependent inhibitor in an *in vitro* study using human liver microsomes [see Section 6.1.2.2]. Thus, there should be little concern about drug interactions in a clinical setting. Furthermore, as the study was conducted at higher dose levels (25 and 50 mg) compared with the clinical doses of enarodustat (1-8 mg) etc., the effects of enarodustat on CYP enzyme activities should be smaller at the clinical doses. Based on the above, at present, the effects of enarodustat on exposure of CYP substrates are small, posing little safety concern about coadministration with CYP substrates, and a relevant precautionary statement in the package insert is unnecessary.

PMDA accepted the applicant's explanation.

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

The applicant submitted the main efficacy and safety evaluation data, in the form of the results from 9 Japanese clinical studies (Table 30).

Table 30. Overview of main efficacy and safety evaluation data

Phase	Study ID	Study population	Study design	Duration of treatment	Treatment group: Number of subjects treated
II	MBA3-1	Patients with non-dialysis-dependent CKD	Part 1 (until Week 6) Randomized Double-blind Placebo-controlled Parallel-group Part 2 (Weeks 6-30) Open-label Uncontrolled	30 weeks	Part 1 Correction group Placebo group: 23 2 mg group: 24 4 mg group: 24 6 mg group: 23 Conversion group Placebo group: 26 2 mg group: 26 4 mg group: 27 6 mg group: 27 Part 2 Correction group Enarodustat: 77 Conversion group Enarodustat: 90
II	MBA3-2	HD patients off ESAs	Part 1 (until Week 6) Randomized Double-blind Parallel-group Part 2 (Weeks 6-30) Open-label Uncontrolled	30 weeks	Part 1 2 mg group: 24 4 mg group: 24 6 mg group: 23 Part 2 Enarodustat: 50
II	MBA3-3	HD patients with prior use of ESA	Part 1 (until Week 6) Randomized Double-blind Placebo-controlled Parallel-group Part 2 (Weeks 6-30) Open-label Uncontrolled	30 weeks	Part 1 Placebo group: 22 2 mg group: 21 4 mg group: 20 6 mg group: 22 Part 2 Enarodustat: 63
III	MBA4-4	Patients with non-dialysis-dependent CKD	Randomized Open-label Active-controlled Parallel-group	24 weeks	Enarodustat group: 107 DA group: 109
III	MBA4-1	Patients with non-dialysis-dependent CKD	Open-label Uncontrolled	52 weeks	Enarodustat: 132
III	MBA4-5	HD patients with prior use of ESA	Randomized Double-blind Active-controlled Parallel-group	24 weeks	Enarodustat group: 87 DA group: 86
III	MBA4-6	HD patients without prior use of ESA	Open-label Uncontrolled	24 weeks	Enarodustat: 34
III	MBA4-2	HD patients with prior use of ESA	Open-label Uncontrolled	52 weeks	Enarodustat: 136
III	MBA4-3	PD patients	Open-label Uncontrolled	52 weeks	Enarodustat: 42

7.1 Phase II studies

7.1.1 Phase II study in patients with non-dialysis-dependent CKD (CTD 5.3.5.1-1, Study MBA3-1 [May 2015 to September 2016])

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 54 sites in Japan to evaluate the dose response and safety of enarodustat in adult anemic non-dialysis-dependent CKD patients (Table 31) (target sample size, 160 subjects [20 per group]).

Table 31. Key inclusion and exclusion criteria

[Key inclusion criteria] **· ≥20 years of age; patients with non-dialysis-dependent CKD (eGFR at screening <60 mL/min/1.73 m^2) unlikely to require dialysis or renal transplantation from screening through the end of study** **· TSAT >20% or serum ferritin >50 ng/mL** **[Correction group]** **· ESA not received for ≥12 weeks before screening; mean of Hb levels at screening and 2 weeks later of ≥8.0 g/dL and ≤10.5 g/dL, with a difference in Hb between the 2 time points ≤1.0 g/dL. If mean Hb was not in the range of ≥8.0 g/dL and ≤10.5 g/dL, the difference in Hb between screening and 2 weeks later ≤1.0 g/dL, and mean of Hb levels at screening, 2 weeks later, and Week 0 of ≥8.0 g/dL and ≤10.5 g/dL, with differences among the 3 measurements ≤1.0 g/dL** **[Conversion group]** **· Stable ESA treatment for ≥8 weeks before screening at a dosing interval of 2 or 4 weeks; the last 2 doses before screening being the same** **· Mean of Hb levels at screening and 2 weeks later of ≥9.5 g/dL and ≤12.0 g/dL, with a difference in Hb between the 2 time points ≤1.0 g/dL. If mean Hb was not in the range of ≥9.5 g/dL and ≤12.0 g/dL, the difference in Hb between screening and 2 weeks later ≤1.0 g/dL, and mean of Hb levels at screening, 2 weeks later, and Week 0 of ≥9.5 g/dL and ≤12.0 g/dL, with differences among the 3 measurements ≤1.0 g/dL** **[Key exclusion criteria]** **· Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening** **· Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.**

The study consisted of Part 1 (a randomized, double-blind, parallel-group study during the first 6 weeks of the treatment period) and Part 2 (an open-label, uncontrolled study in the subsequent 24 weeks), and subjects were divided into 2 groups (the correction group, subjects without prior use of ESA; the conversion group, subjects with prior use of ESA).

In both groups, in Part 1, placebo or enarodustat 2, 4, or 6 mg was to be administered orally once daily before a meal or at bedtime. In Part 2, subjects in the placebo group were to be switched to receive enarodustat, and the starting dose of enarodustat was 4 mg/day (for Hb levels at Week 6 of ≥8.0 g/dL and ≤12.0 g/dL) or 2 mg/day (for Hb levels at Week 6 of >12.0 g/dL and <13.0 g/dL), with dose adjustment decisions made from Week 10 onward, and every 4 weeks thereafter, to maintain Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL). The doses of enarodustat were to be adjusted in 2 mg increments or decrements within the range of 2 to 8 mg/day, referring to Table 32.

Table 32. Dose titration algorithm

Hb level (g/dL)	Dose adjustment
≥13.0	**Interrupt dose until Hb decreases to ≤12.0 g/dL, and then resume enarodustat at 1 dose level lower. If already on the lowest dose, discontinue enarodustat.**
>12.0 and <13.0	**Reduce dose by 1 level.** **If already on the lowest dose, maintain the same dose.**
≥10.0 and ≤12.0 (Target range)	**Maintain the same dose.** **If Hb changes by more than ±1.0 g/dL in 4 weeks, dose may be changed, taking account of time course of Hb levels, etc.**
<10.0	**Increase dose by 1 level.** **If Hb increases by ≥1.0 g/dL in 4 weeks, maintain the same dose.**

In the correction group, all of 94 randomized subjects (23 in the placebo group, 24 in the 2 mg group, 24 in the 4 mg group, 23 in the 6 mg group) received study drug and were included in the safety population and the full analysis set (FAS) of Part 1. The FAS was used as the primary efficacy population. In Part 1, there were 17 discontinuations (3 in the 2 mg group, 2 in the 4 mg group, 12 in the 6 mg group), and the reasons for discontinuations were "the occurrence of adverse events" (1 subject in the 2 mg group), "Hb rise >2.0 g/dL in 4 weeks" (15 subjects [2 in the 2 mg group, 2 in the 4 mg group, 11 in the 6 mg group]), and "the physician's decision" (1 subject in the 6 mg group). All of 77 subjects who completed Part 1 entered Part 2,

and were included in the safety population of Part 2. In Part 2, there were 11 discontinuations, and the reasons for discontinuations were "the occurrence of adverse events" (2 subjects), "Hb level ≥13.0 g/dL and Hb level at the next visit >12 g/dL" (4 subjects), "maintenance dialysis or renal transplantation required" (2 subjects), and "the physician's decision" (3 subjects).

In Part 1, the primary efficacy endpoint of the rate of Hb rise per week during the first 6 weeks of treatment is shown in Table 33. The rate of Hb rise showed a dose response relationship of enarodustat ($P < 0.0001$, a trend test, one-sided significance level of 2.5%).

Table 33. Rate of Hb rise per week in Part 1 (FAS)

	Placebo (N = 23)	2 mg (N = 24)	4 mg (N = 24)	6 mg (N = 23)	*P*-value[a)]
Rate of Hb rise (g/dL/week) (Least-squares mean ± SE)	−0.023 ± 0.034	0.137 ± 0.034	0.193 ± 0.034	0.440 ± 0.037	*P* < 0.0001

a) A trend test for monotonic increase using a mixed effect model with treatment arm and treatment arm-by-time interaction as fixed effects and intercept and time as random effects, Contrast coefficients of (−3, −1, 1, 3), One-sided significance level of 2.5%

Regarding safety in Part 1, adverse events occurred in 34.8% (8 of 23) of subjects in the placebo group, 50.0% (12 of 24) of subjects in the 2 mg group, 33.3% (8 of 24) of subjects in the 4 mg group, and 56.5% (13 of 23) of subjects in the 6 mg group, and those reported by ≥2 subjects in any group are shown in Table 34. Adverse drug reactions occurred in 12.5% (3 of 24) of subjects in the 2 mg group (abdominal discomfort; diarrhoea; face oedema; blood cholesterol decreased; and rash [1 subject each] [some subjects had more than 1 event]), 12.5% (3 of 24) of subjects in the 4 mg group (blood pressure increased; hyperphosphataemia; and hypertension [1 subject each]), and 17.4% (4 of 23) of subjects in the 6 mg group (cardiac hypertrophy; blood parathyroid hormone increased; protein urine present; acne; and hypertension [1 subject each] [some subjects had more than 1 event]).

Table 34. Adverse events reported by ≥2 subjects in any group in Part 1 (Safety population)

	Placebo (N = 23)	2 mg (N = 24)	4 mg (N = 24)	6 mg (N = 23)
Any adverse event	34.8 (8)	50.0 (12)	33.3 (8)	56.5 (13)
Hypertension	0 (0)	0 (0)	4.2 (1)	13.0 (3)
Nasopharyngitis	4.3 (1)	16.7 (4)	12.5 (3)	0 (0)
Diarrhoea	0 (0)	8.3 (2)	0 (0)	0 (0)

MedDRA/J ver.18.0; Incidence % (n)

In Part 1, no deaths were reported. A serious adverse event occurred in 1 subject in the 4 mg group (peripheral arterial occlusive disease), but its causal relationship to study drug was denied, and its outcome was reported as "improved." Adverse events leading to treatment discontinuation occurred in 1 subject in the 2 mg group (rash, face oedema). Both events were classified as adverse drug reactions, but had an outcome of "resolved."

Among the 77 subjects who entered Part 2, throughout Part 1 and Part 2, the incidence of adverse events was 77.9% (60 of 77 subjects), and those reported by ≥5% of subjects are shown in Table 35. The incidence of adverse drug reactions was 18.2% (14 of 77 subjects). Adverse drug reactions reported by ≥2 subjects were retinal haemorrhage (2 subjects).

Table 35. Adverse events reported by ≥5% of subjects (Safety population)

	Subjects who entered Part 2 (N = 77)
Any adverse event	77.9 (60)
Nasopharyngitis	33.8 (26)
Hypertension	7.8 (6)
Constipation	6.5 (5)
Back pain	5.2 (4)
Arthralgia	5.2 (4)

MedDRA/J ver.18.0; Incidence % (n)

None of the subjects who entered Part 2 died. The incidence of serious adverse events was 6.5% (5 of 77 subjects) (peripheral arterial occlusive disease; inguinal hernia; aortic dissection; large intestine polyp; colon cancer; and congestive cardiac failure [1 subject each] [some subjects had more than 1 event]), and a causal relationship to study drug was denied for all those events. Among the serious adverse events, aortic dissection; and congestive cardiac failure (1 subject each) led to treatment discontinuation.

There were no other events leading to treatment discontinuation.

In the conversion group, among 107 randomized subjects (26 in the placebo group, 27 in the 2 mg group, 27 in the 4 mg group, 27 in the 6 mg group), 106 subjects (26 in the placebo group, 26 in the 2 mg group, 27 in the 4 mg group, 27 in the 6 mg group) after excluding 1 subject in the 2 mg group who discontinued the study before the start of study drug administration in the judgment of the physician, received study drug, and were included in the safety population of Part 1. Among the 106 subjects, 103 subjects (24 in the placebo group, 26 in the 2 mg group, 27 in the 4 mg group, 26 in the 6 mg group) after excluding 3 subjects who were assessed for efficacy less than twice (2 in the placebo group, 1 in the 6 mg group) were included in the FAS, which was used as the primary efficacy population. In Part 1, there were 9 discontinuations (2 in the placebo group, 2 in the 4 mg group, 5 in the 6 mg group), and the reasons for discontinuations were "the occurrence of adverse events" (1 subject in the placebo group), "medication non-compliance" (1 subject in the placebo group), "maintenance dialysis or renal transplantation required" (1 subject in the 4 mg group), "Hb rise >2.0 g/dL in 4 weeks" (3 subjects in the 6 mg group), "Hb level ≥13.0 g/dL" (1 subject in the 6 mg group), "the physician's decision" (1 subject in the 4 mg group), and "the subject's request" (1 subject in the 6 mg group). Among 97 subjects who completed Part 1, 90 entered Part 2 and were included in the safety population of Part 2. In Part 2, there were 13 discontinuations, and the reasons for discontinuations were "the occurrence of adverse events" (4 subjects), "Hb level ≥13.0 g/dL and Hb level at the next visit >12 g/dL" (1 subject), "Hb level <8.0 g/dL" (1 subject), "maintenance dialysis or renal transplantation required" (3 subjects), "the subject's request" (1 subject), and "the physician's decision" (3 subjects).

In Part 1, the primary efficacy endpoint of "the proportion of subjects with a mean of the Hb levels at the end of treatment and the previous time point within ± 1.0 g/dL of baseline" is shown in Table 36. There were no significant differences between any dose of enarodustat and placebo.

Table 36. Proportion of subjects with mean of Hb levels at the end of treatment and the previous time point within ± 1.0 g/dL of baseline (FAS)

		Placebo (N = 24)	2 mg (N = 26)	4 mg (N = 27)	6 mg (N = 26)
Mean Hb at baseline (g/dL)	Mean ± SD	10.73 ± 0.61	10.89 ± 0.57	10.73 ± 0.71	10.53 ± 0.63
Mean of Hb levels at end of treatment and previous time point (g/dL)	Mean ± SD	9.70 ± 0.86	10.48 ± 1.00	11.10 ± 1.15	11.40 ± 1.10
Proportion of subjects with mean Hb within ± 1.0 g/dL of baseline	% (n)	54.2 (13)	80.8 (21)	70.4 (19)	50.0 (13)
P-value[a)]		—	0.0619	0.2331	0.8239

a) Fisher's exact test, One-sided significance level of 2.5%, Permutation based multiplicity adjustment

Regarding safety in Part 1, the incidences of adverse events were 19.2% (5 of 26 subjects) in the placebo group, 19.2% (5 of 26 subjects) in the 2 mg group, 18.5% (5 of 27 subjects) in the 4 mg group, and 40.7% (11 of 27 subjects) in the 6 mg group. Those reported by ≥2 subjects in any group are shown in Table 37. Adverse drug reactions occurred in 3.8% (1 of 26) of subjects in the placebo group (generalized pruritus), 3.8% (1 of 26) of subjects in the 2 mg group (abdominal discomfort; and decreased appetite [1 subject each] [the subject had more than 1 event]), 7.4% (2 of 27) of subjects in the 4 mg group (cardiomegaly; back pain; pruritus; and hypertension [1 subject each] [some subjects had more than 1 event]), and 7.4% (2 of 27) of subjects in the 6 mg group (constipation; nausea; and prothrombin time prolonged [1 subject] [one subject had more than 1 event]).

Table 37. Adverse events reported by ≥2 subjects in any group in Part 1 (Safety population)

	Placebo (N = 26)	2 mg (N = 26)	4 mg (N = 27)	6 mg (N = 27)
Any adverse event	19.2 (5)	19.2 (5)	18.5 (5)	40.7 (11)
Nasopharyngitis	0 (0)	3.8 (1)	0 (0)	18.5 (5)
Nausea	3.8 (1)	0 (0)	0 (0)	11.1 (3)
Constipation	0 (0)	0 (0)	0 (0)	7.4 (2)

MedDRA/J ver.18.0; Incidence % (n)

In Part 1, no deaths were reported. Serious adverse events occurred in 1 subject in the placebo group (sinus arrest, renal failure, cardiac failure), 1 subject in the 2 mg group (bronchitis), and 2 subjects in the 4 mg group (retinal detachment; and renal cyst infection), but a causal relationship to study drug was denied for all those events. Among the serious adverse events, sinus arrest in the placebo group led to treatment discontinuation.

There were no other events leading to treatment discontinuation.

Among the 90 subjects who entered Part 2, throughout Part 1 and Part 2, the incidence of adverse events was 80.0% (72 of 90 subjects), and those reported by ≥5% of subjects were nasopharyngitis (26.7% [24 of 90 subjects]), hyperkalaemia (6.7% [6 of 90 subjects]), and hypertension (5.6% [5 of 90 subjects]). The incidence of adverse drug reactions was 17.8% (16 of 90 subjects). Those reported by ≥2 subjects were hypertension; and fibrin D dimer increased (3 subjects each); and cardiomegaly (2 subjects).

None of the subjects who entered Part 2 died. Serious adverse events occurred in 12.2% (11 of 90) of subjects (pyelonephritis; sepsis; postrenal failure; deep vein thrombosis; retinal detachment; meniscus injury; bone cancer; bacterial bronchitis; peripheral oedema; acute pancreatitis; loss of consciousness; complete atrioventricular block; sarcoidosis; and enterocolitis (1 subject each [some subjects had more than 1 event]).

Deep vein thrombosis and bone cancer were classified as adverse drug reactions, and deep vein thrombosis had an outcome of "resolved" and bone cancer had an outcome of "unresolved." Among the serious adverse events, deep vein thrombosis led to treatment discontinuation.

Other events leading to treatment discontinuation occurred in 3 subjects (macular oedema; peripheral oedema; and neovascular age-related macular degeneration), and peripheral oedema and neovascular age-related macular degeneration were classified as adverse drug reactions. Both events had an outcome of "resolved."

7.1.2 Phase II study in HD patients off ESAs (CTD 5.3.5.2-3, Study MBA3-2 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multicenter, randomized, double-blind, parallel-group study was conducted at 16 sites in Japan to evaluate the dose response and safety of enarodustat in adult HD patients with renal anemia who were previously treated with ESAs and off ESAs for a certain period of time (Table 38) (target sample size, 60 subjects [20 per group]).

Table 38. Key inclusion and exclusion criteria

[Key inclusion criteria]
· ≥20 years of age; CKD patients on stable HD 3 times weekly for ≥12 weeks before screening
· ESA received within 8 weeks before screening; pre-dialysis Hb at screening of ≥9.5 g/dL and ≤12.5 g/dL; predialysis Hb of ≥8.5 g/dL and <10.0 g/dL and of ≥0.5 g/dL below Hb at screening, when off ESAs for ≥7 days
· TSAT >20% or serum ferritin >75 ng/mL
[Key exclusion criteria]
· Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening
· Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.

The study consisted of Part 1 (a randomized, double-blind, parallel-group study during the first 6 weeks of the treatment period) and Part 2 (an open-label, uncontrolled study in the subsequent 24 weeks).

In Part 1, enarodustat 2, 4, or 6 mg was to be administered orally once daily before a meal or at bedtime. In Part 2, the starting dose of enarodustat was 4 mg/day (for Hb levels at Week 6 of ≥8.0 g/dL and ≤12.0 g/dL) or 2 mg/day (for Hb levels at Week 6 of >12.0 g/dL and <13.0 g/dL), with dose adjustment decisions made from Week 10 onward, and every 4 weeks thereafter, to maintain Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL). The doses of enarodustat were to be adjusted in 2 mg increments or decrements within the range of 2 to 8 mg/day, referring to Table 32.

All of 71 randomized subjects (24 in the 2 mg group, 24 in the 4 mg group, 23 in the 6 mg group) received study drug, and were included in the safety population and the FAS of Part 1. The FAS was used as the primary efficacy population. In Part 1, there were 17 discontinuations (10 in the 2 mg group, 3 in the 4 mg group, 4 in the 6 mg group), and the reasons for discontinuations were "Hb level <8.0 g/dL" (10 subjects) (7 in the 2 mg group, 2 in the 4 mg group, 1 in the 6 mg group), "Hb rise >2.0 g/dL in 4 weeks" (3 subjects) (1 in the 4 mg group, 2 in the 6 mg group), "the physician's decision" (3 subjects) (2 in the 2 mg group, 1 in the 6 mg group), and "the subject's request" (1 subject in the 2 mg group). Among 54 subjects who completed Part 1, 50 entered Part 2. All of the 50 subjects who entered Part 2 were included in the safety population of Part 2.

In Part 2, there were 4 discontinuations, and the reasons for discontinuations were "the occurrence of adverse events" (2 subjects), "the subject's request" (1 subject), and "the physician's decision" (1 subject).

In Part 1, the primary efficacy endpoint of the rate of Hb rise per week during the first 6 weeks of treatment is shown in Table 39. The rate of Hb rise showed a dose response relationship of enarodustat ($P < 0.0001$, a trend test, one-sided significance level of 2.5%).

Table 39. Rate of Hb rise per week in Part 1 (FAS)

	2 mg (N = 24)	4 mg (N = 24)	6 mg (N = 23)	*P*-value[a)]
Rate of Hb rise (g/dL/week) (Least-squares mean ± SE)	**−0.168 ± 0.045**	**0.094 ± 0.044**	**0.158 ± 0.045**	***P* < 0.0001**

a) A trend test for monotonic increase using a mixed effect model with treatment arm and treatment arm-by-time interaction as fixed effects and intercept and time as random effects, Contrast coefficients of (−1, 0, 1), One-sided significance level of 2.5%

Regarding safety in Part 1, adverse events occurred in 41.7% (10 of 24) of subjects in the 2 mg group, 41.7% (10 of 24) of subjects in the 4 mg group, and 60.9% (14 of 23) of subjects in the 6 mg group, and those reported by ≥2 subjects in any group are shown in Table 40. Adverse drug reactions occurred in 8.3% (2 of 24) of subjects in the 2 mg group (constipation; and orthostatic hypotension [1 subject each]) and 4.3% (1 of 23) of subjects in the 6 mg group (constipation).

Table 40. Adverse events reported by ≥2 subjects in any group in Part 1 (Safety population)

	2 mg (N = 24)	4 mg (N = 24)	6 mg (N = 23)
Any adverse event	**41.7 (10)**	**41.7 (10)**	**60.9 (14)**
Nasopharyngitis	**16.7 (4)**	**12.5 (3)**	**13.0 (3)**
Diarrhoea	**0 (0)**	**8.3 (2)**	**4.3 (1)**
Vomiting	**0 (0)**	**8.3 (2)**	**4.3 (1)**
Puncture site swelling	**8.3 (2)**	**0 (0)**	**0 (0)**

MedDRA/J ver.18.0; Incidence % (n)

In Part 1, there were no deaths or adverse events leading to treatment discontinuation. A serious adverse event occurred in 1 subject in the 2 mg group (gastric cancer), but its causal relationship to study drug was denied.

Among the 50 subjects who entered Part 2, throughout Part 1 and Part 2, the incidence of adverse events was 88.0% (44 of 50 subjects), and those reported by ≥5% of subjects are shown in Table 41. The incidence of adverse drug reactions was 4.0% (2 of 50 subjects) (constipation; and fibrin D dimer increased [1 subject each]).

Table 41. Adverse events reported by ≥5% of subjects who entered Part 2 (Safety population)

	Subjects who entered Part 2 (N = 50)
Any adverse event	88.0 (44)
Nasopharyngitis	40.0 (20)
Vomiting	14.0 (7)
Contusion	12.0 (6)
Diarrhoea	12.0 (6)
Back pain	6.0 (3)
Abrasion	6.0 (3)
Fibrin D dimer increased	6.0 (3)
Hyperphosphataemia	6.0 (3)
Hypertension	6.0 (3)
Pain in extremity	6.0 (3)
Pruritus	6.0 (3)

MedDRA/J ver.18.0; Incidence % (n)

None of the subjects who entered Part 2 died. Serious adverse events occurred in 14.0% (7 of 50) of subjects (lumbar spinal stenosis; osteoarthritis; foot fracture; cardiac failure; large intestine polyp; rectosigmoid cancer; asthma; peripheral arterial occlusive disease; coronary artery stenosis; acute myocardial infarction; cerebral infarction; and complete atrioventricular block [1 subject each] [some subjects had more than 1 event]), and a causal relationship to study drug was denied for all those events. Among the serious adverse events, rectosigmoid cancer; and cerebral infarction (1 subject each) led to treatment discontinuation.

There were no other events leading to treatment discontinuation.

7.1.3 Phase II study in HD patients with prior use of ESA (CTD 5.3.5.1-3, Study MBA3-3 [May 2015 to June 2016])

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 16 sites in Japan to evaluate the dose response and safety of enarodustat in adult HD patients with renal anemia with prior use of ESA (Table 42) (target sample size, 80 subjects [20 per group]).

Table 42. Key inclusion and exclusion criteria

[Key inclusion criteria]
- **≥20 years of age; CKD patients on stable HD 3 times weekly for ≥12 weeks before screening**
- **Stable ESA treatment for ≥4 weeks before screening at a dosing interval of ≤2 weeks; the total weekly dose being stable**
- **Mean of predialysis Hb levels at screening and 2 weeks later of ≥9.5 g/dL and ≤12.0 g/dL, with a difference in Hb between the 2 time points ≤1.0 g/dL**
- **TSAT >20% or serum ferritin >75 ng/mL**

[Key exclusion criteria]
- **Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening**
- **Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.**

The study consisted of Part 1 (a randomized, double-blind, parallel-group study during the first 6 weeks of the treatment period) and Part 2 (an open-label, uncontrolled study in the subsequent 24 weeks).

In Part 1, placebo or enarodustat 2, 4, or 6 mg was to be administered orally once daily before a meal or at bedtime. In Part 2, subjects in the placebo group were to be switched to receive enarodustat, and the starting dose of enarodustat was 4 mg/day (for Hb levels at Week 6 of ≥8.0 g/dL and ≤12.0 g/dL) or 2 mg/day

(for Hb levels at Week 6 of >12.0 g/dL and <13.0 g/dL), with dose adjustment decisions made from Week 10 onward, and every 4 weeks thereafter, to maintain Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL). The doses of enarodustat were to be adjusted in 2 mg increments or decrements within the range of 2 to 8 mg/day, referring to Table 32.

All of 85 randomized subjects (22 in the placebo group, 21 in the 2 mg group, 20 in the 4 mg group, 22 in the 6 mg group) received study drug, and were included in the safety population of Part 1. After excluding 3 subjects who were assessed for efficacy less than twice (2 in the 2 mg group, 1 in the 6 mg group), 82 subjects (22 in the placebo group, 19 in the 2 mg group, 20 in the 4 mg group, 21 in the 6 mg group) were included in the FAS, which was used as the primary efficacy population. In Part 1, there were 17 discontinuations (5 in the placebo group, 4 in the 2 mg group, 1 in the 4 mg group, 7 in the 6 mg group), and the reasons for discontinuations were "the occurrence of adverse events" (3 subjects) (1 in the placebo group, 1 in the 2 mg group, 1 in the 6 mg group), "Hb level <8.0 g/dL" (3 subjects in the placebo group), "Hb rise >2.0 g/dL in 4 weeks" (4 subjects) (1 in the 2 mg group, 3 in the 6 mg group), "Hb level ≥13.0 g/dL" (2 subjects) (1 each in the 4 mg and 6 mg groups), "inappropriate as a study subject" (3 subjects) (2 in the 2 mg group, 1 in the 6 mg group), and "the physician's decision" (2 subjects) (1 in the placebo group, 1 in the 6 mg group). Among 68 subjects who completed Part 1, 63 entered Part 2. All of the 63 subjects who entered Part 2 were included in the safety population of Part 2. In Part 2, there were 8 discontinuations, and the reasons for discontinuations were "the occurrence of adverse events" (4 subjects), "Hb level <8.0 g/dL" (1 subject), "the subject's request" (1 subject), and "the physician's decision" (2 subjects).

In Part 1, the primary efficacy endpoint of "the proportion of subjects with a mean of the Hb levels at the end of treatment and the previous time point within ± 1.0 g/dL of baseline" is shown in Table 43. There were no significant differences between any dose of enarodustat and placebo.

Table 43. Proportion of subjects with mean of Hb levels at the end of treatment and the previous time point within ± 1.0 g/dL of baseline (FAS)

		Placebo (N = 22)	2 mg (N = 19)	4 mg (N = 20)	6 mg (N = 21)
Mean Hb at baseline (g/dL)	Mean ± SD	10.54 ± 0.64	10.39 ± 0.50	10.59 ± 0.65	10.48 ± 0.60
Mean of Hb levels at end of treatment and the previous time point (g/dL)	Mean ± SD	9.27 ± 1.23	9.77 ± 1.15	10.97 ± 1.15	11.37 ± 1.02
Proportion of subjects with mean Hb within ± 1.0 g/dL of baseline	% (n)	27.3 (6)	63.2 (12)	60.0 (12)	52.4 (11)
P-value[a)]		—	0.0311	0.0457	0.1189

a) Fisher's exact test, One-sided significance level of 2.5%, Permutation based multiplicity adjustment

Regarding safety in Part 1, adverse events occurred in 63.6% (14 of 22) of subjects in the placebo group, 33.3% (7 of 21) of subjects in the 2 mg group, 60.0% (12 of 20) of subjects in the 4 mg group, and 54.5% (12 of 22) of subjects in the 6 mg group. Those reported by ≥2 subjects in any group are shown in Table 44. Adverse drug reactions occurred in 18.2% (4 of 22) of subjects in the placebo group (nausea; oral discomfort; hepatic enzyme increased; and cerebral infarction [1 subject each]), 9.5% (2 of 21) of subjects in the 2 mg group (nausea; and pulmonary mass [1 subject each]), 5.0% (1 of 20) of subjects in the 4 mg group (pruritus), and 9.1% (2 of 22) of subjects in the 6 mg group (shunt occlusion; and fibrin D dimer increased [1 subject each]).

Table 44. Adverse events reported by ≥2 subjects in any group in Part 1 (Safety population)

	Placebo (N = 22)	2 mg (N = 21)	4 mg (N = 20)	6 mg (N = 22)
Any adverse event	63.6 (14)	33.3 (7)	60.0 (12)	54.5 (12)
Nasopharyngitis	13.6 (3)	9.5 (2)	15.0 (3)	13.6 (3)
Constipation	4.5 (1)	9.5 (2)	5.0 (1)	0 (0)
Diarrhoea	0 (0)	0 (0)	10.0 (2)	0 (0)

MedDRA/J ver.18.0, Incidence % (n)

No deaths were reported. Serious adverse events occurred in 1 subject in the enarodustat 6 mg group (basal ganglia infarction, retinal vein occlusion), but their causal relationship to study drug was denied. Adverse events leading to treatment discontinuation occurred in 1 subject in the placebo group (cerebral infarction), 1 subject in the 2 mg group (nausea), and 1 subject in the 6 mg group (basal ganglia infarction). Cerebral infarction in the placebo group and nausea in the 2 mg group were classified as adverse drug reactions, both of which were mild in severity and had an outcome of "resolved."

Among the 63 subjects who entered Part 2, throughout Part 1 and Part 2, the incidence of adverse events was 95.2% (60 of 63 subjects), and those reported by ≥5% of subjects are shown in Table 45. Adverse drug reactions occurred in 11.1% (8 of 63) of subjects (coronary artery stenosis; chronic gastritis; constipation; fibrin D dimer increased; dysaesthesia; metrorrhagia; pruritus; and hypertension [1 subject each] [some subjects had more than 1 event]).

Table 45. Adverse events reported by ≥5% of subjects who entered Part 2 (Safety population)

	Subjects who entered Part 2 (N = 63)
Any adverse event	95.2 (60)
Nasopharyngitis	46.0 (29)
Upper respiratory tract infection	11.1 (7)
Constipation	11.1 (7)
Oropharyngeal pain	7.9 (5)
Pruritus	7.9 (5)
Diarrhoea	7.9 (5)
Abrasion	7.9 (5)
Arthralgia	6.3 (4)
Contusion	6.3 (4)
Wound	6.3 (4)

MedDRA/J ver.18.0; Incidence % (n)

None of the subjects who entered Part 2 died. Serious adverse events occurred in 9.5% (6 of 63) of subjects (pneumonia [2 subjects]; and tonsillitis; colon cancer; myelopathy; procedural hypertension; coronary artery stenosis; ventricular tachycardia; positional vertigo; subdural haematoma; cervical spinal cord injury; and cerebral haematoma [1 subject each] [some subjects had more than 1 event]). Coronary artery stenosis was classified as an adverse drug reaction, but had an outcome of "resolved." Among the serious adverse events, subdural haematoma; cervical spinal cord injury; cerebral haematoma; and colon cancer (1 subject each) led to treatment discontinuation.

Other adverse events leading to treatment discontinuation occurred in 2 subject (dysaesthesia; and metrorrhagia [1 subject each]), both of which were classified as adverse drug reactions, but had an outcome of "resolved."

7.2 Phase III studies

7.2.1 Phase III study in patients with non-dialysis-dependent CKD (CTD 5.3.5.1-2, Study MBA4-4 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multicenter, randomized, open-label, active-controlled, parallel-group study was conducted at 69 sites in Japan to evaluate the efficacy and safety of enarodustat in adult anemic non-dialysis-dependent CKD patients (Table 46) (target sample size, 200 subjects [100 per group]).

Table 46. Key inclusion and exclusion criteria

[Key inclusion criteria]
• ≥20 years of age; patients with non-dialysis-dependent CKD (eGFR at screening <60 ml/min/1.73 m^2) unlikely to require dialysis or renal transplantation from screening through the end of study
· TSAT >20% or serum ferritin >50 ng/mL
[Patients without prior use of ESA]
· ESA not received for ≥12 weeks before screening; Hb levels at screening and 2 weeks later of ≥8.0 g/dL and ≤10.5 g/dL, with an absolute difference in Hb between the 2 time points ≤1.0 g/dL
[Patients with prior use of ESA]
· Stable ESA treatment for ≥8 weeks before screening; the last 2 dosing intervals and the last 2 doses before screening being the same
· Hb levels at screening and 2 weeks later of ≥9.5 g/dL and ≤12.0 g/dL, with an absolute difference in Hb between the 2 time points ≤1.0 g/dL
[Key exclusion criteria]
· Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening
· Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.

Enarodustat or darbepoetin alfa (genetical recombination) (DA) was to be administered for 24 weeks, as per Table 47, to maintain Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL). Dose adjustment decisions were to be made from Week 4 onward, and every 4 weeks thereafter.

Table 47. Dosing regimen

<table>
<tr><th></th><th>Enarodustat group</th><th>DA group</th></tr>
<tr><td>Method of administration</td><td>Administered orally once daily before a meal or at bedtime</td><td>Administered subcutaneously every 2 or 4 weeks</td></tr>
<tr><td>Starting dose</td><td>2 mg</td><td>Patients without prior use of ESA: 30 μg/2 weeks
Patients with prior use of ESA:
In the case of prior ESA treatment with DA, the same dosing regimen was continued.
In the case of prior ESA treatment with rHuEPO or CERA, the starting dose was selected based on prior ESA dose as per the table below.
<table>
<tr><th>Prior ESA</th><th>Prior ESA dose</th><th>Starting dose of DA</th></tr>
<tr><td rowspan="3">rHuEPO</td><td>6,000 IU/2 weeks</td><td>30 μg/2 weeks</td></tr>
<tr><td>12,000 IU/4 weeks</td><td>30 μg/2 weeks</td></tr>
<tr><td>12,000 IU/2 weeks</td><td>60 μg/2 weeks</td></tr>
<tr><td rowspan="6">CERA</td><td>[redacted] μg/[redacted] weeks</td><td>[redacted] μg/[redacted] weeks</td></tr>
<tr><td>[redacted] μg/[redacted] weeks</td><td>[redacted] μg/[redacted] weeks</td></tr>
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<tr><td>Dose adjustment range</td><td>
<table>
<tr><th>Level</th><th>Dose (mg)</th></tr>
<tr><td>1</td><td>1</td></tr>
<tr><td>2</td><td>2</td></tr>
<tr><td>3</td><td>4</td></tr>
<tr><td>4</td><td>6</td></tr>
<tr><td>5</td><td>8</td></tr>
</table></td><td>
<table>
<tr><th>Level</th><th>Dose (μg)</th></tr>
<tr><td>1</td><td>15</td></tr>
<tr><td>2</td><td>30</td></tr>
<tr><td>3</td><td>60</td></tr>
<tr><td>4</td><td>90</td></tr>
<tr><td>5</td><td>120</td></tr>
<tr><td>6</td><td>180</td></tr>
</table></td></tr>
<tr><td>Target Hb levels</td><td colspan="2">≥10.0 g/dL and ≤12.0 g/dL</td></tr>
<tr><td>Dose titration algorithm (Reference information)</td><td colspan="2">
<table>
<tr><th rowspan="2">Hb level (g/dL)</th><th colspan="4">Hb change in 4 weeks (ΔHb)</th></tr>
<tr><th>≤−0.5</th><th>> −0.5 and ≤0</th><th>>0 and ≤2.0</th><th>>2.0</th></tr>
<tr><td>≥13.0</td><td colspan="3">Interrupt dose[a)]</td><td>Interrupt dose.[a)] If already on the lowest dose, discontinue.</td></tr>
<tr><td>>12.0 and <13.0</td><td>Maintain the same dose</td><td colspan="2">Reduce dose by 1 level</td><td rowspan="5">Reduce dose by 1 level. If already on the lowest dose, discontinue.</td></tr>
<tr><td>>11.5 and ≤12.0</td><td colspan="2">Maintain the same dose</td><td>Reduce dose by 1 level</td></tr>
<tr><td>≥10.5 and ≤11.5</td><td colspan="3">Maintain the same dose</td></tr>
<tr><td>≥10.0 and <10.5</td><td>Increase dose by 1 level</td><td colspan="2">Maintain the same dose</td></tr>
<tr><td><10.0[b)]</td><td colspan="2">Increase dose by 1 level</td><td>Maintain the same dose. If ΔHb is >0 and ≤0.5, increase dose by 1 level.</td></tr>
</table>
a) Interrupt dose until Hb decreases to <12.5 g/dL, and then resume at 1 dose level lower. If already on the lowest dose, interrupt dose until Hb decreases to <11.5 g/dL, and then resume at the lowest dose. In the DA group, resume at the same dosing interval.
b) If Hb is <8.0 g/dL even at the highest dose level, discontinue.</td></tr>
</table>

All of 216 randomized subjects (107 in the enarodustat group, 109 in the DA group) received study drug, and were included in the safety population. The number of patients with prior use of ESA was 114 (57 per group), and the number of patients without prior use of ESA was 102 (50 in the enarodustat group, 52 in the DA group). Among the 216 subjects who received study drug, 193 subjects (97 in the enarodustat group, 96 in the DA group) after excluding 23 subjects (10 in the enarodustat group, 13 in the DA group)[12)] were included in

[12)] Enarodustat group: Hb not measured at Week 20, 22, 24, or discontinuation (corresponding to Week 24) (10 subjects), red blood cell transfusion (1 subject), inclusion criteria not met (1 subject), and exclusion criteria violation (1 subject); DA group: Hb not measured at Week 20, 22, 24, or discontinuation (corresponding to Week 24) (13 subjects) and red blood cell transfusion (2 subjects) (some subjects had more than 1 reason)

the per protocol set (PPS), which was used as the primary efficacy population. There were 21 discontinuations (9 in the enarodustat group, 12 in the DA group), and the reasons for discontinuations were "the occurrence of adverse events" (9 subjects) (4 in the enarodustat group, 5 in the DA group), "Hb rise >2.0 g/dL at the lowest dose level" (1 subject in the DA group), "initiation of dialysis, etc." (4 subjects in the DA group), "the subject's request" (2 subjects) (1 per group), "protocol deviations" (3 subjects in the enarodustat group), and "the physician's decision" (2 subjects) (1 per group).

The primary efficacy endpoint of "the mean Hb during the evaluation period (Weeks 20-24)" is shown in Table 48. The lower limit of the 95% confidence interval for the treatment difference (enarodustat group − DA group) was above the pre-specified non-inferiority margin of −0.75 g/dL,[13] therefore establishing the non-inferiority of enarodustat to DA.[14]

Table 48. Mean Hb during evaluation period (Weeks 20-24) (g/dL) (PPS)

	Enarodustat (N = 96)[a]	DA (N = 96)
Mean Hb at baseline[b] (Mean ± SD)	10.17 ± 0.85	10.31 ± 0.92
Mean Hb during Weeks 20-24 (Mean [95% CI])	10.96 [10.84, 11.07]	10.87 [10.75, 10.99]
Treatment difference in mean Hb during Weeks 20-24 (Enarodustat group − DA group)[c] [95% CI]	0.09 [−0.07, 0.26]	

a) One subject was excluded from analysis because Hb measurement at Week 24 was missing due to coagulation, and Hb level during evaluation period could not be calculated.
b) Mean of Hb levels at screening 1, screening 2, and Week 0.
c) Analysis of covariance including treatment group as a factor and Hb at baseline as a covariate

Regarding safety, adverse events occurred in 65.4% (70 of 107) of subjects in the enarodustat group and 82.6% (90 of 109) of subjects in the DA group, and those reported by ≥2% of subjects in either group are shown in Table 49. Adverse drug reactions occurred in 10.3% (11 of 107) of subjects in the enarodustat group and 3.7% (4 of 109) of subjects in the DA group, and those reported by ≥2 subjects in either group were hyperkalaemia in the enarodustat group (2 subjects) only.

[13] Based on data from a Japanese clinical study of DA in patients with non-dialysis-dependent CKD, the difference in Hb between placebo and DA was estimated at around 1.5 g/dL, and a non-inferiority margin of 0.75 g/dL, i.e. the half of the difference, was chosen.
[14] The mean Hb during Weeks 20-24 in the enarodustat group [95% CI] was 10.96 [10.84, 11.07] (g/dL), and since the 95% confidence interval fell within the target range (≥10.0 g/dL and ≤12.0 g/dL), non-inferiority was tested.

Table 49. Adverse events reported by ≥2% of subjects in either group (Safety population)

	Enarodustat (N = 107)	DA (N = 109)
Any adverse event	65.4 (70)	82.6 (90)
Viral upper respiratory tract infection	17.8 (19)	22.9 (25)
Hyperkalaemia	4.7 (5)	3.7 (4)
Constipation	3.7 (4)	2.8 (3)
Blood pressure increased	3.7 (4)	1.8 (2)
Oedema	3.7 (4)	0.9 (1)
Diarrhoea	2.8 (3)	8.3 (9)
Malaise	2.8 (3)	0 (0)
Upper respiratory tract inflammation	1.9 (2)	6.4 (7)
Arthralgia	1.9 (2)	4.6 (5)
Chronic kidney disease	1.9 (2)	3.7 (4)
Cystitis	1.9 (2)	2.8 (3)
Pruritus	1.9 (2)	2.8 (3)
Contusion	0.9 (1)	5.5 (6)
Peripheral oedema	0.9 (1)	3.7 (4)
Hypertension	0.9 (1)	2.8 (3)
Muscle spasms	0.9 (1)	2.8 (3)

MedDRA/J ver.20.0; Incidence % (n)

Death occurred in 1 subject in the DA group (drowning[15)]), and its causal relationship to study drug was denied. Non-fatal serious adverse events occurred in 12.1% (13 of 107) of subjects in the enarodustat group and 10.1% (11 of 109) of subjects in the DA group, and Table 50 shows the breakdown of the non-fatal serious adverse events. Fluid retention; hyperkalaemia; oedema; and pneumonia (1 subject each) in the enarodustat group were classified as adverse drug reactions, and the outcomes of these events were all reported as "improved" or "resolved." Among the serious adverse events, fluid retention; and hyperkalaemia (1 subject each) in the enarodustat group and fracture; hypothermia; myocardial ischaemia; myelodysplastic syndrome; and malignant neoplasm of renal pelvis (1 subject each) in the DA group led to treatment discontinuation.

Table 50. Serious adverse events (Safety population)

Treatment group	No. of subjects with event	Event term
Enarodustat	2	pneumonia
	1	bacterial pneumonia, sciatica, large intestine polyp, bacterial prostatitis, fluid retention, hyperkalaemia, loss of consciousness, oedema, hypoglycaemia, cardiac failure, asphyxia, chronic kidney disease, gastric ulcer
DA	4	chronic kidney disease
	1	gastric cancer, fracture, hypothermia, myocardial ischaemia, myelodysplastic syndrome, malignant neoplasm of renal pelvis, pneumonia legionella, cellulitis, gastroenteritis, pneumonia

MedDRA/J ver.20.0

Other adverse events leading to treatment discontinuation occurred in 1.9% (2 of 107) of subjects in the enarodustat group (chest pain; and dyspnoea [1 subject each]) and 1.8% (2 of 109) of subjects in the DA group (contusion; and dementia [1 subject each]). Dyspnoea in the enarodustat group was classified as an adverse drug reaction, but had an outcome of "resolved."

[15)] A 7[redacted]-year-old man. After the completion of the follow-up visit following the end of study treatment, the patient died from drowning before scheduled follow-up of ongoing adverse events (blood pressure increased and peripheral oedema). Its causal relationship to study drug was denied.

7.2.2 Long-term treatment study in patients with non-dialysis-dependent CKD (CTD 5.3.5.2-6, Study MBA4-1 [20 to 20])

A multicenter, open-label, uncontrolled study was conducted at 40 sites in Japan to evaluate the long-term safety and efficacy of enarodustat in adult anemic non-dialysis-dependent CKD patients (Table 51) (target sample size, 125 subjects).

Table 51. Key inclusion and exclusion criteria

[Key inclusion criteria]
· ≥20 years of age; patients with non-dialysis-dependent CKD (eGFR at screening <60 mL/min/1.73 m^2) unlikely to require dialysis or renal transplantation from screening through the end of study
· TSAT >20% or serum ferritin >50 ng/mL
[Patients without prior use of ESA]
· ESA not received for ≥12 weeks before screening; Hb at screening of ≥8.0 g/dL and ≤10.5 g/dL
[Patients with prior use of ESA]
· ESA received within 8 weeks before screening; Hb at screening of ≥9.0 g/dL and ≤12.0 g/dL
[Key exclusion criteria]
· Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening
· Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.

The starting dose of enarodustat was 2 mg/day, with dose adjustment decisions made from Week 4 onward, and every 4 weeks thereafter, to maintain Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL). The doses of enarodustat were to be adjusted within the range of 1 to 8 mg/day as per the dose titration algorithm provided in Table 52. Enarodustat was to be administered orally once daily before a meal or at bedtime for 52 weeks.

Table 52. Dose titration algorithm

Hb level (g/dL)	Dose adjustment	
	Hb change in 4 weeks ≤ +2.0 g/dL	Hb change in 4 weeks > +2.0 g/dL
≥13.0	Interrupt dose[a), b)]	Interrupt dose.[a)] If already on the lowest dose, discontinue enarodustat.
>12.0 and <13.0	Reduce dose by 1 level. If already on the lowest dose, maintain the same dose. If Hb changes by ≤ −0.5 g/dL in 4 weeks, the same dose may be maintained.	Reduce dose by 1 level. If already on the lowest dose, discontinue enarodustat.
≥10.0 and ≤12.0 (Target range)	Maintain the same dose. Taking account of time course of Hb levels, dose may be increased or decreased by 1 level to maintain Hb levels within target range.	
<10.0	Increase dose by 1 level. If Hb changes by ≥ +0.5 g/dL in 4 weeks, maintain the same dose. Also if already on the highest dose, maintain the same dose. If Hb is <8.0 g/dL even at the highest dose level, discontinue enarodustat.	

a) Interrupt dose until Hb decreases to <12.5 g/dL, and then resume at 1 dose level lower.
b) If already on the lowest dose, interrupt dose until Hb decreases to ≤12.0 g/dL, and then resume at the lowest dose.

All of 132 subjects who received study drug were included in the safety population. The number of patients with prior use of ESA was 90, and the number of patients without prior use of ESA was 42. After excluding 2 subjects who were not assessed for efficacy at Week 4, 130 subjects were included in the FAS, which was used as the primary efficacy population. There were 40 discontinuations, and the reasons for discontinuations were "death" (2 subjects), "the occurrence of adverse events" (15 subjects), "Hb level <8.0 g/dL at the highest dose

level" (1 subject), "Hb rise >2.0 g/dL at the lowest dose level" (1 subject), "initiation of dialysis, etc." (10 subjects), "the subject's request" (4 subjects), "lost to follow up " (1 subject), and "the physician's decision" (6 subjects).

Regarding efficacy, the mean Hb levels at baseline and at or near the end of treatment[16] (Mean ± SD) in the FAS were 10.56 ± 1.04 and 10.74 ± 0.95 g/dL, respectively.

Regarding safety, adverse events occurred in 87.1% (115 of 132) of subjects, and those reported by ≥4% of subjects are shown in Table 53. Adverse drug reactions occurred in 13.6% (18 of 132) of subjects, and those reported by ≥2 subjects were hypertension (4 subjects); and blood pressure increased; and fibrin D dimer increased (2 subjects each).

Table 53. Adverse events reported by ≥4% of subjects (Safety population)

	Enarodustat-treated patients (N = 132)
Any adverse event	87.1 (115)
Viral upper respiratory tract infection	25.8 (34)
Chronic kidney disease	8.3 (11)
Hypertension	7.6 (10)
Constipation	6.1 (8)
Contusion	6.1 (8)
Diarrhoea	6.1 (8)
Dizziness	4.5 (6)
Eczema	4.5 (6)
Herpes zoster	4.5 (6)
Hyperkalaemia	4.5 (6)
Oedema	4.5 (6)
Renal impairment	4.5 (6)

MedDRA/J ver.20.0; Incidence % (n)

There were 4 deaths (subdural haematoma[17]; chronic kidney disease[18]; plasma cell myeloma[19]; and death [unspecified][20] [1 subject each]), and 1 case of death (unspecified) was classified as an adverse drug reaction. Non-fatal serious adverse events occurred in 27.3% (36 of 163) of subjects, and Table 54 shows the breakdown of the non-fatal serious adverse events. Renal impairment; and anti-neutrophil cytoplasmic antibody positive vasculitis (1 subject each) were classified as adverse drug reactions, and the outcome of anti-neutrophil cytoplasmic antibody positive vasculitis was reported as "unresolved." Among the serious adverse events, renal impairment (2 subjects); and ileus; anti-neutrophil cytoplasmic antibody positive vasculitis; congestive cardiac failure; drug eruption; and chronic kidney disease (1 subject each) led to treatment discontinuation.

[16] Mean of Hb levels at the end of treatment (at Week 52 or discontinuation) and the previous time point (if Hb was assessed twice after Week 4); Hb level at the end of treatment (at Week 52 or discontinuation) (if Hb was assessed once after Week 4)

[17] A 6[redacted]-year-old man. The patient developed subdural haemorrhage on Day 47, and died on Day 49. This event was traumatic, and its causal relationship to study drug was denied.

[18] A 8[redacted]-year-old woman. The primary disease causing CKD was nephrosclerosis, and the patient also had secondary hyperparathyroidism, hypertension, etc. The patient died of worsening of chronic renal failure on Day 363. Its causal relationship to study drug was denied because it was worsening of the primary disease, and renal function was aggravated during interruption of study drug.

[19] A 6[redacted]-year-old man. The patient developed plasma cell myeloma on Day 72, and died on Day 237. This event was considered to be preexisting prior to study drug administration, and its causal relationship to study drug was denied.

[20] A 6[redacted]-year-old man. The primary disease causing CKD was chronic glomerulonephritis, and the patient also had Brown-Sequard syndrome, hyperkalaemia, secondary hyperparathyroidism, hypertension, etc. On Day 185, the study site was notified of the subject's death. An attempt was made to find out the date and time of death, the cause of death, etc., but the details were unknown. This case was assessed by the investigator as "related to" study drug because the details were unknown.

Table 54. Serious adverse events (Safety population)

No. of subjects with event	Event term
7	chronic kidney disease
3	renal impairment
2	atrial fibrillation, congestive cardiac failure
1	pharyngitis, duodenitis, chronic cardiac failure, hyperkalaemia, spinal compression fracture, ureteric stenosis, retinal detachment, femoral neck fracture, lumbar spinal stenosis, large intestine polyp, ileus, upper gastrointestinal haemorrhage, anti-neutrophil cytoplasmic antibody positive vasculitis, hyponatraemia, cellulitis, cholangitis, septic shock, drug eruption, white blood cell count decreased, rheumatoid arthritis, dehydration, malnutrition, sinus node dysfunction, epilepsy, pyelonephritis, myelopathy, myocardial ischaemia, inguinal hernia, pericarditis, acute cardiac failure

MedDRA/J ver.20.0

Other adverse events leading to treatment discontinuation occurred in 6.1% (8 of 132) of subjects (chronic kidney disease; and diabetic retinopathy (2 subjects each); and congestive cardiac failure; hepatic function abnormal; pulmonary mass; hepatitis E; and depression (1 subject each [some subjects had more than 1 event]). One case of diabetic retinopathy was classified as an adverse drug reaction, but had an outcome of "resolved."

7.2.3 Phase III study in HD patients with prior use of ESA (CTD 5.3.5.1-4, Study MBA4-5 [20 to 20])

A multicenter, randomized, double-blind, active-controlled, parallel-group study was conducted at 45 sites in Japan to evaluate the efficacy and safety of enarodustat in adult HD patients with prior use of ESA (Table 55) (target sample size, 156 subjects [78 per group]).

Table 55. Key inclusion and exclusion criteria

[Key inclusion criteria]
- **≥20 years of age; patients with stable CKD on HD 3 times weekly for ≥12 weeks before screening**
- **Treatment with rHuEPO or DA for ≥4 weeks before screening; the total weekly dose being stable**
- **Pre-dialysis Hb levels at screening and 2 weeks later of ≥9.5 g/dL and <12.0 g/dL, with an absolute difference in Hb between the 2 time points ≤1.0 g/dL**
- **TSAT >20% or serum ferritin >75 ng/mL**

[Key exclusion criteria]
- **Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening**
- **Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.**

Enarodustat or DA was to be administered for 24 weeks, as per Table 56, to maintain pre-dialysis Hb levels within the target range (≥10.0 g/dL and <12.0 g/dL). Dose adjustment decisions were to be made from Week 4 onward, and every 4 weeks thereafter.

Table 56. Dosing regimen

<table>
<tr><th></th><th>Enarodustat group</th><th>DA group</th></tr>
<tr><td>Method of administration</td><td>Administered orally once daily before a meal or at bedtime</td><td>Administered intravenously once weekly</td></tr>
<tr><td>Staring dose</td><td>4 mg</td><td>The starting dose was selected based on ESA dose in screening period as per the table below.
<table>
<tr><th colspan="2">ESA dose in screening period</th><th rowspan="2">Starting dose of DA (μg)</th></tr>
<tr><th>rHuEPO (IU/week)</th><th>DA (μg/week)</th></tr>
<tr><td>≤2,250</td><td>10</td><td>10</td></tr>
<tr><td>>2,250 and ≤3,000</td><td>15</td><td>15</td></tr>
<tr><td>>3,000 and ≤4,500</td><td>20</td><td>20</td></tr>
<tr><td>>4,500 and ≤6,000</td><td>30</td><td>30</td></tr>
<tr><td>>6,000 and ≤9,000</td><td>40</td><td>40</td></tr>
</table></td></tr>
<tr><td>Dose adjustment range</td><td>
<table>
<tr><th>Level</th><th>Dose (mg)</th></tr>
<tr><td>1</td><td>1</td></tr>
<tr><td>2</td><td>2</td></tr>
<tr><td>3</td><td>4</td></tr>
<tr><td>4</td><td>6</td></tr>
<tr><td>5</td><td>8</td></tr>
</table></td><td>
<table>
<tr><th>Level</th><th colspan="5">Dose (μg)</th></tr>
<tr><td>1</td><td>Not administer</td><td>5</td><td>10</td><td>15</td><td>20</td></tr>
<tr><td>2</td><td>5</td><td>10</td><td>15</td><td>20</td><td>30</td></tr>
<tr><td>3 (Starting dose)</td><td>10</td><td>15</td><td>20</td><td>30</td><td>40</td></tr>
<tr><td>4</td><td>15</td><td>20</td><td>30</td><td>40</td><td>50</td></tr>
<tr><td>5</td><td>20</td><td>30</td><td>40</td><td>50</td><td>60</td></tr>
</table></td></tr>
<tr><td>Target Hb levels</td><td colspan="2">≥10.0 g/dL and <12.0 g/dL</td></tr>
<tr><td>Dose titration algorithm (Reference information)</td><td colspan="2">
<table>
<tr><th rowspan="2">Hb level (g/dL)</th><th colspan="4">Hb change in 4 weeks (ΔHb)</th></tr>
<tr><th>≤ −0.5</th><th>> −0.5 and ≤0</th><th>>0 and ≤2.0</th><th>>2.0</th></tr>
<tr><td>≥13.0</td><td colspan="3">Interrupt dose[a)]</td><td>Interrupt dose.[a)] If already on the lowest dose, discontinue.</td></tr>
<tr><td>≥12.0 and <13.0</td><td>Maintain the same dose</td><td colspan="2">Reduce dose by 1 level</td><td rowspan="5">Reduce dose by 1 level. If already on the lowest dose, discontinue.</td></tr>
<tr><td>>11.5 and <12.0</td><td colspan="2">Maintain the same dose</td><td>Reduce dose by 1 level</td></tr>
<tr><td>≥10.5 and ≤11.5</td><td colspan="3">Maintain the same dose</td></tr>
<tr><td>≥10.0 and <10.5</td><td>Increase dose by 1 level</td><td colspan="2">Maintain the same dose</td></tr>
<tr><td><10.0[b)]</td><td colspan="2">Increase dose by 1 level</td><td>Maintain the same dose. If ΔHb is >0 and <0.5, increase dose by 1 level.</td></tr>
</table>
a) Interrupt dose until Hb decreases to <12.0 g/dL, and then resume at 1 dose level lower. If already on the lowest dose, interrupt dose until Hb decreases to <10.5 g/dL, and then resume at the lowest dose. In either case, resume on the day of dialysis at the beginning of a week.
b) If Hb is <8.0 g/dL even at the highest dose level, discontinue.</td></tr>
</table>

All of 173 randomized subjects (87 in the enarodustat group, 86 in the DA group) received study drug, and were included in the safety population. Among the 173 subjects who received study drug, 158 subjects (78 in the enarodustat group, 80 in the DA group) after excluding 15 subjects (9 in the enarodustat group, 6 in the DA group)[21)] were included in the PPS, which was used as the primary efficacy population. There were 14 discontinuations (8 in the enarodustat group, 6 in the DA group), and the reasons for discontinuations were "the occurrence of adverse events" (7 subjects) (4 in the enarodustat group, 3 in the DA group), "Hb level <8.0 g/dL" (1 subject in the enarodustat group), "protocol deviations" (1 subject in the enarodustat group), and "the physician's decision" (5 subjects) (2 in the enarodustat group, 3 in the DA group).

[21)] Enarodustat group: study drug compliance rate <75% (1 subject), Hb not measured at Week 20, 22, 24, or discontinuation (corresponding to Week 24) (8 subjects), use of prohibited concomitant medications (4 subjects), and administration of the wrong study drug (the wrong drug number) (2 subjects); DA group: Hb not measured at Week 20, 22, 24, or discontinuation (corresponding to Week 24) (6 subjects) and use of prohibited concomitant medications (2 subjects) (some subjects had more than 1 reason)

The primary efficacy endpoint of "the mean Hb during the evaluation period (Weeks 20-24)" is shown in Table 57. The lower limit of the 95% confidence interval for the treatment difference (enarodustat group − DA group) was above the pre-specified non-inferiority margin of −1.0 g/dL,[22] therefore establishing the non-inferiority of enarodustat to DA.[23]

Table 57. Mean Hb during evaluation period (Weeks 20-24) (g/dL) (PPS)

	Enarodustat (N = 78)	DA (N = 80)
Mean Hb at baseline[a] (Mean ± SD)	10.79 ± 0.65	10.86 ± 0.70
Mean Hb during Weeks 20-24 (Mean [95% CI])	10.73 [10.56, 10.91]	10.85 [10.72, 10.98]
Treatment difference in mean Hb during Weeks 20-24 (Enarodustat group − DA group)[b] [95% CI]	−0.12 [−0.33, 0.10]	

a) Mean of Hb levels at screening 1, screening 2, and Week 0
b) Analysis of covariance including treatment group as a factor and Hb at baseline as a covariate

Regarding safety, adverse events occurred in 87.4% (76 of 87) of subjects in the enarodustat group and 83.7% (72 of 86) of subjects in the DA group, and those reported by ≥2% of subjects in either group are shown in Table 58. Adverse drug reactions occurred in 4.6% (4 of 87) of subjects in the enarodustat group (fibrin D dimer increased [2 subjects]; and retinal haemorrhage; and C-reactive protein increased [1 subject each]) and 3.5% (3 of 86) of subjects in the DA group (retinal haemorrhage [2 subjects]; and hepatic function abnormal [1 subject]).

[22] Based on data from a Japanese clinical study of DA in HD patients, the difference in Hb between placebo and DA was estimated at 2.5 g/dL, and a non-inferiority margin of 1.0 g/dL, i.e. the half of the difference, was chosen.
[23] The mean Hb during Weeks 20-24 [95% CI] in the enarodustat group was 10.73 [10.56, 10.91] (g/dL), and since the 95% confidence interval fell within the target range (≥10.0 g/dL and <12.0 g/dL), non-inferiority was tested.

Table 58. Adverse events reported by ≥2% of subjects in either group (Safety population)

	Enarodustat (N = 87)	DA (N = 86)		Enarodustat (N = 87)	DA (N = 86)
Any adverse event	87.4 (76)	83.7 (72)	Musculoskeletal pain	2.3 (2)	1.2 (1)
Viral upper respiratory tract infection	32.2 (28)	38.4 (33)	Periodontitis	2.3 (2)	1.2 (1)
Vomiting	10.3 (9)	2.3 (2)	Pyrexia	2.3 (2)	1.2 (1)
Influenza	9.2 (8)	5.8 (5)	Vertigo	2.3 (2)	1.2 (1)
Back pain	6.9 (6)	3.5 (3)	Haematuria	2.3 (2)	1.2 (1)
Shunt stenosis	5.7 (5)	10.5 (9)	Abdominal pain lower	2.3 (2)	0 (0)
Upper respiratory tract inflammation	5.7 (5)	7.0 (6)	Cerebral haemorrhage	2.3 (2)	0 (0)
Contusion	5.7 (5)	3.5 (3)	Dizziness	2.3 (2)	0 (0)
Gastroenteritis	5.7 (5)	0 (0)	Dry eye	2.3 (2)	0 (0)
Shunt occlusion	4.6 (4)	4.7 (4)	Muscle spasms	2.3 (2)	0 (0)
Pharyngitis	4.6 (4)	0 (0)	Rhinitis allergic	2.3 (2)	0 (0)
Procedural hypotension	3.4 (3)	4.7 (4)	Dermatitis contact	1.1 (1)	4.7 (4)
Retinal haemorrhage	3.4 (3)	3.5 (3)	Hyperkeratosis	1.1 (1)	3.5 (3)
Hypertension	3.4 (3)	2.3 (2)	Abdominal pain	1.1 (1)	2.3 (2)
Bronchitis	3.4 (3)	1.2 (1)	Arthritis	1.1 (1)	2.3 (2)
Constipation	3.4 (3)	1.2 (1)	Gastrooesophageal reflux disease	1.1 (1)	2.3 (2)
Large intestine polyp	3.4 (3)	1.2 (1)	Ligament sprain	1.1 (1)	2.3 (2)
Nausea	3.4 (3)	1.2 (1)	Periodontal disease	1.1 (1)	2.3 (2)
Skin exfoliation	3.4 (3)	1.2 (1)	Stomatitis	1.1 (1)	2.3 (2)
Pruritus	3.4 (3)	0 (0)	Thermal burn	1.1 (1)	2.3 (2)
Wound	3.4 (3)	0 (0)	Arthralgia	0 (0)	4.7 (4)
Diarrhoea	2.3 (2)	4.7 (4)	Eczema	0 (0)	3.5 (3)
Abrasion	2.3 (2)	4.7 (4)	Carnitine deficiency	0 (0)	2.3 (2)
Pain in extremity	2.3 (2)	4.7 (4)	Headache	0 (0)	2.3 (2)
C-reactive protein increased	2.3 (2)	2.3 (2)	Otitis externa	0 (0)	2.3 (2)
Cough	2.3 (2)	2.3 (2)	Paronychia	0 (0)	2.3 (2)
Enterocolitis	2.3 (2)	2.3 (2)	Rash	0 (0)	2.3 (2)
Epistaxis	2.3 (2)	1.2 (1)	Vessel puncture site pruritus	0 (0)	2.3 (2)
Fibrin D dimer increased	2.3 (2)	1.2 (1)			

MedDRA/J ver.20.0; Incidence % (n)

No deaths were reported. Serious adverse events occurred in 14.9% (13 of 87) of subjects in the enarodustat group and 14.0% (12 of 86) of subjects in the DA group, and Table 59 shows the breakdown of the serious adverse events. A causal relationship to study drug was denied for all those events. Among the serious adverse events, cerebral haemorrhage (2 subjects) in the enarodustat group and diabetic gangrene; and femur fracture (1 subject each) in the DA group led to treatment discontinuation.

Table 59. Serious adverse events (Safety population)

Treatment group	No. of subjects with event	Event term
Enarodustat	3	shunt occlusion
	2	shunt stenosis, cerebral haemorrhage
	1	febrile convulsion, colitis, mitral valve incompetence, acute myocardial infarction, pulmonary embolism, large intestine polyp, pseudomembranous colitis, vitreous haemorrhage, pyelonephritis, spinal osteoarthritis, spondylolisthesis
DA	2	shunt stenosis, shunt occlusion
	1	cataract, diabetic gangrene, angina pectoris, vertigo, appendicitis, congestive cardiac failure, arrhythmia, aphakia, malignant neoplasm of renal pelvis, femur fracture

MedDRA/J ver.20.0

Other adverse events leading to treatment discontinuation occurred in 2.3% (2 of 87) of subjects in the enarodustat group (renal cancer; and hepatic cirrhosis [1 subject each]) and 1.2% (1 of 86) of subjects in the DA group (hypertension [1 subject]). A causal relationship to study drug was denied for all those events.

7.2.4 Phase III study in HD patients without prior use of ESA (CTD 5.3.5.2-4, Study MBA4-6 [20 to 20])

A multicenter, open-label, uncontrolled study was conducted at 32 sites in Japan to evaluate the efficacy and safety of enarodustat in adult HD patients with renal anemia without prior use of ESA (Table 60) (target sample size, 26 subjects).

Table 60. Key inclusion and exclusion criteria

[Key inclusion criteria] **· ≥20 years of age; CKD patients who had initiated HD before screening and had been receiving HD 3 times weekly at Week 0** **· ESA not received for 8 weeks before screening (ESA not received since HD initiation if HD had been initiated within 8 weeks before screening)** **· Pre-dialysis Hb levels at screening and ≥2 weeks later (at the beginning of a week) of ≥8.0 g/dL and <10.0 g/dL, and change from screening of ≤1.0 g/dL if Hb rose during the screening period.** **· TSAT >20% or serum ferritin >50 ng/mL** **[Key exclusion criteria]** **· Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening** **· Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.**

The starting dose of enarodustat was 4 mg/day, with dose adjustment decisions made from Week 4 onward, and every 4 weeks thereafter, to maintain pre-dialysis Hb levels within the target range (≥10.0 g/dL and <12.0 g/dL). The doses of enarodustat were to be adjusted within the range of 1 to 8 mg/day as per the dose titration algorithm provided in Table 61. Enarodustat was to be administered orally once daily before a meal or at bedtime for 24 weeks.

Table 61. Dose titration algorithm

Hb level (g/dL)	Dose adjustment	
	Hb change in 4 weeks ≤ +2.0 g/dL	Hb change in 4 weeks > +2.0 g/dL
≥13.0	Interrupt dose[a), b)]	Interrupt dose.[a)] If already on the lowest dose, discontinue enarodustat.
≥12.0 and <13.0	Reduce dose by 1 level If already on the lowest dose, maintain the same dose. If Hb changes by ≤ −0.5 g/dL in 4 weeks, the same dose may be maintained.	Reduce dose by 1 level. If already on the lowest dose, discontinue enarodustat.
≥10.0 and <12.0 (Target range)	Maintain the same dose. Taking account of time course of Hb levels, dose may be increased or decreased by 1 level to maintain Hb levels within target range.	
<10.0	Increase dose by 1 level. If Hb changes by ≥ +0.5 g/dL in 4 weeks, maintain the same dose. Also if already on the highest dose, maintain the same dose. If Hb is <8.0 g/dL even at the highest dose level, discontinue enarodustat.	

a) Interrupt dose until Hb decreases to <12.0 g/dL, and then resume at 1 dose level lower.
b) If already on the lowest dose, resume at the lowest dose.

All of 34 subjects who received study drug were included in the safety population and in the FAS, and the FAS was the primary efficacy population. There was 1 discontinuation, and its reason was "the physician's decision."

The primary efficacy endpoint of "the rate of Hb rise during Weeks 0 to 4 (g/dL/week)" [95% CI] was estimated at 0.302 [0.239, 0.365].[24)]

Regarding safety, adverse events occurred in 85.3% (29 of 34) of subjects, and those reported by ≥2 subjects are shown in Table 62. Adverse drug reactions occurred in 5.9% (2 of 34) of subjects (posterior capsule opacification; and blood pressure increased [1 subject each]).

Table 62. Adverse events reported by ≥2 subjects (Safety population)

	Enarodustat-treated subjects (N = 34)
Any adverse event	85.3 (29)
Shunt stenosis	14.7 (5)
Viral upper respiratory tract infection	14.7 (5)
Gastroenteritis	8.8 (3)
Abdominal discomfort	5.9 (2)
Abdominal pain	5.9 (2)
Blood pressure increased	5.9 (2)
Bronchitis	5.9 (2)
C-reactive protein increased	5.9 (2)
Dehydration	5.9 (2)
Diarrhoea	5.9 (2)
Epistaxis	5.9 (2)
Gastrooesophageal reflux disease	5.9 (2)
Hyperphosphataemia	5.9 (2)
Pain in extremity	5.9 (2)
Periarthritis	5.9 (2)
Periodontitis	5.9 (2)
Pleurisy	5.9 (2)
Retinal haemorrhage	5.9 (2)
Shunt occlusion	5.9 (2)
Upper respiratory tract inflammation	5.9 (2)
Vomiting	5.9 (2)

MedDRA/J ver.20.0; Incidence % (n)

No deaths were reported. Serious adverse events occurred in 23.5% (8 of 34) of subjects (shunt stenosis [2 subjects]; and cataract; shunt infection; shunt occlusion; atrioventricular block; complication associated with device; dehydration; pericarditis; pleurisy; coronary artery stenosis; pulmonary congestion; and vertigo [1 subject each] [some subjects had more than 1 event]), but a causal relationship to enarodustat was denied for all those events. There were no adverse events leading to treatment discontinuation.

7.2.5 Long-term treatment study in HD patients with prior use of ESA (CTD 5.3.5.2-5, Study MBA4-2 [[redacted] to [redacted]])

A multicenter, open-label, uncontrolled study was conducted at 32 sites in Japan to evaluate the long-term safety and efficacy of enarodustat in adult HD patients with prior use of ESA (Table 63) (target sample size, 125 subjects).

[24)] Calculated using a mixed effect model with time as a fixed effect and subject as a random effect, assuming a variance components covariance structure within subjects.

Table 63. Key inclusion and exclusion criteria

[Key inclusion criteria] **· ≥20 years of age; CKD patients on stable HD 3 times weekly for ≥12 weeks before screening** **· Pre-dialysis Hb at screening of ≥9.0 g/dL and <12.0 g/dL** **· TSAT >20% or serum ferritin >75 ng/mL** **· ESA treatment for ≥4 weeks before screening; the last dosing interval of ESA was ≤4 weeks** **[Key exclusion criteria]** **· Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening** **· Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.**

The starting dose of enarodustat was 4 mg/day, with dose adjustment decisions made from Week 4 onward, and every 4 weeks thereafter, to maintain pre-dialysis Hb levels within the target range (≥10.0 g/dL and <12.0 g/dL). The doses of enarodustat were to be adjusted within the range of 1 to 8 mg/day as per the dose titration algorithm provided in Table 64. Enarodustat was to be administered orally once daily before a meal or at bedtime for 52 weeks.

Table 64. Dose titration algorithm

Hb level (g/dL)	Dose adjustment	
	Hb change in 4 weeks ≤ +2.0 g/dL	Hb change in 4 weeks > +2.0 g/dL
≥13.0	Interrupt dose[a), b)]	Interrupt dose.[a)] If already on the lowest dose, discontinue enarodustat.
≥12.0 and <13.0	Reduce dose by 1 level. If already on the lowest dose, maintain the same dose. If Hb changes by ≤ −0.5 g/dL in 4 weeks, the same dose may be maintained.	Reduce dose by 1 level. If already on the lowest dose, discontinue enarodustat.
≥10.0 and <12.0 (Target range)	Maintain the same dose. Taking account of time course of Hb levels, dose may be increased or decreased by 1 level to maintain Hb levels within the target range.	
<10.0	Increase dose by 1 level. If Hb changes by ≥ +0.5 g/dL in 4 weeks, maintain the same dose. Also if already on the highest dose, maintain the same dose. If Hb is <8.0 g/dL even at the highest dose level, discontinue enarodustat.	

a) Interrupt dose until Hb decreases to <12.0 g/dL, and then resume enarodustat at 1 dose level lower.
b) If already on the lowest dose, resume enarodustat at the lowest dose.

All of 136 subjects who received study drug were included in the safety population and in the FAS, and the FAS was the primary efficacy population. There were 18 discontinuations, and the reasons for discontinuations were "the occurrence of adverse events" (13 subjects), "the subject's request" (2 subjects), and "the physician's decision" (3 subjects).

Regarding efficacy, the mean Hb levels (Mean ± SD) at baseline and at or near the end of treatment [16)] in the FAS were 10.61 ± 0.80 and 10.72 ± 0.96 g/dL, respectively.

Regarding safety, adverse events occurred in 97.8% (133 of 136) of subjects, and those reported by ≥5% of subjects are shown in Table 65. Adverse drug reactions occurred in 8.8% (12 of 136) of subjects, and those reported by ≥2 subjects were hypertension (4 subjects); and eczema (2 subjects).

Table 65. Adverse events reported by ≥5% of subjects (Safety population)

	Enarodustat-treated patients (N = 136)
Any adverse event	97.8 (133)
Viral upper respiratory tract infection	49.3 (67)
Contusion	16.9 (23)
Diarrhoea	16.9 (23)
Shunt stenosis	14.7 (20)
Upper respiratory tract inflammation	12.5 (17)
Abrasion	8.8 (12)
Vomiting	8.8 (12)
Muscle spasms	8.1 (11)
Back pain	7.4 (10)
Eczema	7.4 (10)
Shunt occlusion	7.4 (10)
Influenza	6.6 (9)
Pharyngitis	6.6 (9)
Skin exfoliation	6.6 (9)
Gastroenteritis	5.9 (8)
Constipation	5.1 (7)
Dermatitis contact	5.1 (7)
Dry eye	5.1 (7)
Hypertension	5.1 (7)
Myalgia	5.1 (7)
Pain in extremity	5.1 (7)

MedDRA/J ver.20.0; Incidence % (n)

No deaths were reported. Serious adverse events occurred in 22.8% (31 of 136) of subjects, and Table 66 shows the breakdown of the serious adverse events. Peripheral arterial occlusive disease and brain stem infarction were classified as adverse drug reactions, but both had an outcome of "resolved." Among the serious adverse events, colon cancer; brain stem infarction; gastric cancer; gastric ulcer; and femoral neck fracture (1 subject each) led to treatment discontinuation.

Table 66. Serious adverse events (Safety population)

No. of subjects with event	Event term
6	shunt occlusion
5	pneumonia
3	angina pectoris, cholangitis
1	prostatitis, subcutaneous haematoma, colon cancer, glottis carcinoma, peripheral arterial occlusive disease, brain stem infarction, cerebral infarction, haematoma, gastrointestinal haemorrhage, large intestine polyp, humerus fracture, hypoglycaemia, endocarditis, pneumonia legionella, cataract, gastric cancer, gastric ulcer, macular hole, shunt malfunction, carpal tunnel syndrome, trigger finger, myocardial ischaemia, device dislocation, vitreous opacities, clavicle fracture, femoral neck fracture

MedDRA/J ver.20.0

Other adverse events leading to treatment discontinuation occurred in 5.9% (8 of 136) of subjects (dizziness; parosmia; disturbance in attention; transient ischaemic attack; somatic symptom disorder; anovulatory cycle; diabetic neuropathy; and eczema [1 subject each]). Dizziness and eczema were classified as adverse drug reactions, but both had an outcome of "resolved."

7.2.6 Phase III study in PD patients (CTD 5.3.5.2-7, Study MBA4-3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multicenter, open-label, uncontrolled study was conducted at 14 sites in Japan to evaluate the efficacy and safety of enarodustat in adult PD patients with renal anemia (Table 67) (target sample size, 30 subjects).

Table 67. Key inclusion and exclusion criteria

[Key inclusion criteria] **· ≥20 years of age; CKD patients on stable PD for ≥12 weeks before screening** **• TSAT >20% or serum ferritin >50 ng/mL** **[Patients without prior use of ESA]** **· ESA not received for 12 weeks before screening; Hb at screening of ≥8.0 g/dL and ≤10.5 g/dL** **[Patients with prior use of ESA]** **· ESA treatment for 8 weeks before screening; Hb at screening of ≥9.5 g/dL and ≤12.0 g/dL** **[Key exclusion criteria]** **· Development of myocardial infarction, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism within 24 weeks before screening** **· Patients scheduled to undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration, etc.**

The starting dose of enarodustat was 2 mg/day, with dose adjustment decisions made from Week 4 onward, and every 4 weeks thereafter, to maintain Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL). The doses of enarodustat were to be adjusted within the range of 1 to 8 mg/day as per the dose titration algorithm provided in Table 52. Enarodustat was to be administered orally once daily before a meal or at bedtime for 52 weeks.

All of 42 subjects who received study drug were included in the safety population. The number of patients with prior use of ESA was 41, and the number of patients without prior use of ESA was 1. Among the 42 subjects who received study drug, 41 subjects after excluding 1 subject who was not assessed for efficacy at Weeks 2 and 4 were included in the FAS, which was used as the primary efficacy population. There were 10 discontinuations, and the reasons for discontinuations were "death" (2 subjects), "the occurrence of adverse events" (5 subjects), "initiation of another type of dialysis" (2 subjects), and "the physician's decision" (1 subject).

Regarding efficacy, the mean Hb levels (Mean ± SD) at baseline and at or near the end of treatment[25)] in the FAS were 11.01 ± 0.81 and 10.78 ± 0.69 g/dL, respectively.

Regarding safety, adverse events occurred in 100% (42 of 42) of subjects, and those reported by ≥5% of subjects are shown in Table 68. Adverse drug reactions occurred in 16.7% (7 of 42) of subjects (pulmonary embolism; dry eye; macular oedema; retinal aneurysm; retinal haemorrhage; constipation; blood alkaline phosphatase increased; decreased appetite; dermatitis; rash; and hypertension [1 subject each] [some subjects had more than 1 event]).

[25)] Mean of Hb levels at the end of treatment (at Week 52 or discontinuation) and the previous time point

Table 68. Adverse events reported by ≥5% of subjects (Safety population)

	Enarodustat-treated patients (N = 42)
Any adverse event	100 (42)
Catheter site infection	26.2 (11)
Viral upper respiratory tract infection	19.0 (8)
Peritonitis	16.7 (7)
Back pain	14.3 (6)
Constipation	14.3 (6)
Device related infection	14.3 (6)
Hypertension	14.3 (6)
Contusion	11.9 (5)
Nausea	11.9 (5)
Diarrhoea	9.5 (4)
Insomnia	9.5 (4)
Bronchitis	7.1 (3)
Conjunctival haemorrhage	7.1 (3)
Muscle spasms	7.1 (3)
Musculoskeletal pain	7.1 (3)
Rash	7.1 (3)
Vomiting	7.1 (3)

MedDRA/J ver.20.0; Incidence % (n)

There were 3 deaths (pulmonary embolism,[26)] influenzal pneumonia,[27)] thalamus haemorrhage[28)]), and pulmonary embolism was classified as an adverse drug reaction. Non-fatal serious adverse events occurred in 42.9% (18 of 42) of subjects (peritonitis [7 subjects]; catheter site infection [3 subjects]; pneumonia; coronary artery stenosis; and congestive cardiac failure [2 subjects each]; and spinal compression fracture; cerebral infarction; peripheral arterial occlusive disease; fluid retention; aortic valve stenosis; renal cell carcinoma; nausea; contusion; renal cancer; cardiac failure; macular hole; cataract; dehydration; pyrexia; device related infection; viral upper respiratory tract infection; hyperkalaemia; and chronic cardiac failure [1 subject each] [some subjects had more than 1 event]), but a causal relationship to study drug was denied for all those events. Among the serious adverse events, renal cell carcinoma; congestive cardiac failure; renal cancer; dehydration; and pyrexia (1 subject each) led to treatment discontinuation.

Other events leading to treatment discontinuation occurred in 1 subject (rash), which was classified as an adverse drug reaction. The event was mild in severity and had an outcome of "resolved."

[26)] A 5[redacted]-year-old woman. The patient had persistent nausea and vomiting from Day 236 onward and was hospitalized on Day 246. After the onset of nausea, the patient was on peritoneal dialysis every other day from Day 238 onward, and did not receive peritoneal dialysis during a 3-day period from Day 243 to hospitalization. After hospitalization, study drug and concomitant medications were interrupted due to difficulty in taking drugs, and peritoneal dialysis was resumed. Since nausea resolved on Day 250, concomitant medications excluding study drug were resumed. In the evening of the same day, the patient developed pulmonary embolism, and died on the next day. This case was assessed by the investigator as "related" to study drug for the following reason: Although thrombus formation occurred possibly due to the compound factors of inadequate dialysis, dehydration, etc., adverse drug reactions associated with ESA include pulmonary infarction, and pulmonary embolism is an expected adverse reaction to enarodustat.

[27)] A 6[redacted]-year-old woman. Due to the onset of dyspnoea on Day 312, the patient visited an emergency room and was hospitalized with diagnoses of pneumonia and congestive cardiac failure. The patient tested positive for influenza A on Day 314, and discontinued study drug on Day 316. The patient died of respiratory failure due to influenzal pneumonia on Day 324. Its causal relationship to study drug was denied.

[28)] A 5[redacted]-year-old man. The patient complained of numbness in the right hand on Day 11 and was transported via ambulance to hospital, but died of thalamus haemorrhage. Its causal relationship to study drug was denied because the patient had hypertension and was receiving concomitant anticoagulant and antiplatelet.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA's view:

Based on the considerations in Sections 7.R.1.1 to 7.R.1.3, the efficacy of enarodustat in patients with non-dialysis-dependent CKD and HD patients has been demonstrated, and the efficacy of enarodustat is expected also in PD patients.

7.R.1.1 Patients with non-dialysis-dependent CKD

The applicant's explanation about the efficacy of enarodustat in patients with non-dialysis-dependent CKD:

In a phase III study in patients with non-dialysis-dependent CKD (Study MBA4-4), the difference in the primary endpoint of the mean Hb during the evaluation period (Weeks 20-24) between the enarodustat and DA groups [95% CI] was 0.09 [−0.07, 0.26] g/dL, and the lower limit of the 95% confidence interval for the treatment difference was above the pre-specified non-inferiority margin of −0.75 g/dL, therefore establishing the non-inferiority of enarodustat to DA (Table 48). Based on the analysis in the FAS,[29)] the difference in the mean Hb at or near the end of treatment[30)] between the enarodustat and DA groups [95% CI] was 0.13 [−0.04, 0.30] g/dL, which showed a similar trend to the results of the primary analysis in the PPS.

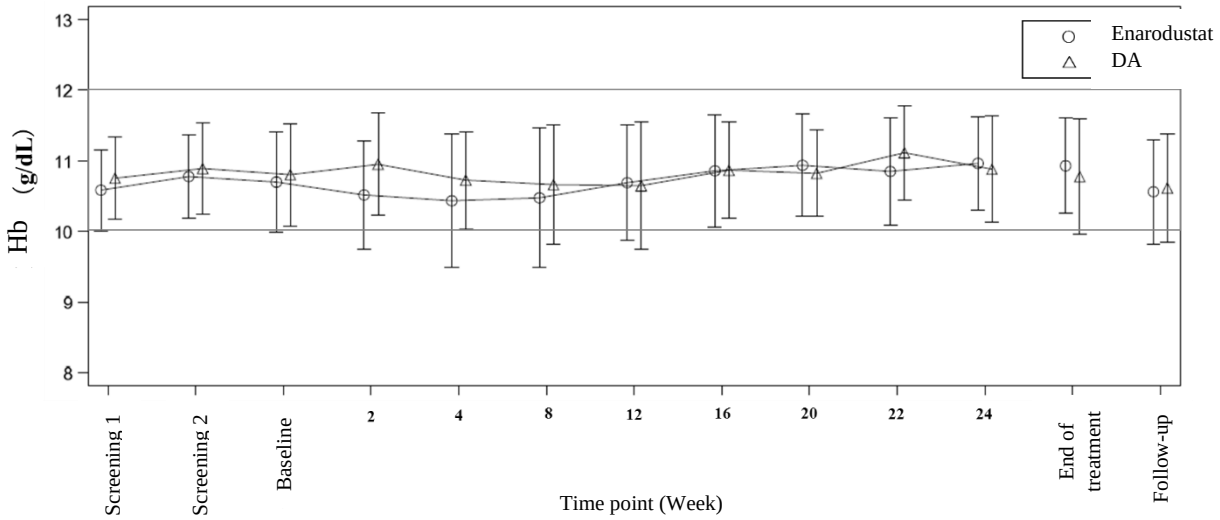
In Study MBA4-4, the efficacy of enarodustat was analyzed by prior ESA use status.[31)]

Among patients with prior use of ESA, the mean Hb levels up to Week 24 and the proportions of subjects with Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL) at different time points are shown in Figure 1 and Table 69, respectively. The mean Hb levels were maintained within the target range (≥10.0 g/dL and ≤12.0 g/dL) in both the enarodustat and DA groups. Among patients without prior use of ESA, the mean Hb levels rose after the start of treatment in both the enarodustat and DA groups, and were maintained within the target range (≥10.0 g/dL and ≤12.0 g/dL), after Week 2 in the DA group and after Week 8 in the enarodustat group (Figure 2 and Table 70).

[29)] Among 216 subjects who received study drug, 212 subjects (105 in the enarodustat group, 107 in the DA group) after excluding 4 subjects assessed for efficacy less than twice after Week 4 (2 each in the enarodustat and DA groups) were included in the FAS.

[30)] Mean of Hb levels at the end of treatment (at Week 24 or discontinuation) and the previous 2 time points (if Hb was assessed 3 times after Week 4); Mean of Hb levels at the end of treatment (at Week 24 or discontinuation) and the previous time point (if Hb was assessed twice after Week 4)

[31)] Prior ESA use status was a stratification factor for randomization.



Time point (Week)	Screening 1	Screening 2	Baseline	2	4	8	12	16	20	22	24	End of treatment	Follow-up
Enarodustat group (N)	57	57	57	56	57	56	55	54	53	53	53	57	53
DA group (N)	55	55	55	55	55	55	54	52	52	52	50	55	50

Follow-up: 2 weeks after the end of treatment

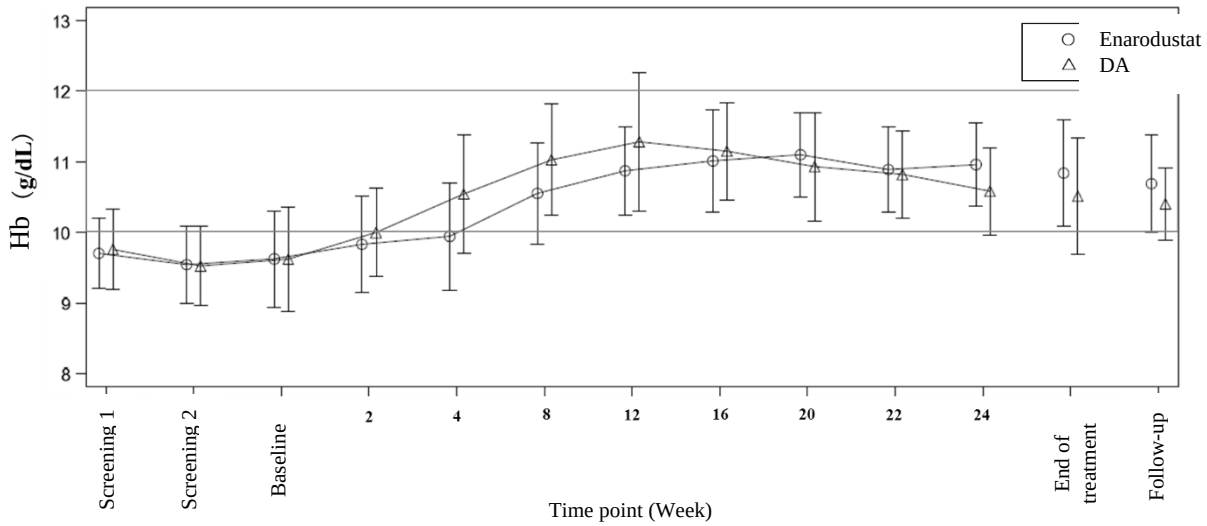
Figure 1. Time course of mean Hb levels (Mean ± SD) (Study MBA4-4, With prior use of ESA, FAS)

Table 69. Proportions of subjects with Hb levels within target range (≥10.0 g/dL and ≤12.0 g/dL) at different time points (%) (Study MBA4-4, With prior use of ESA, FAS)

Time point (Week)	Screening 1	Screening 2	Baseline	2	4	8	12	16	20
Enarodustat group	87.7 (50/57)	96.5 (55/57)	78.9 (45/57)	75.0 (42/56)	66.7 (38/57)	62.5 (35/56)	74.5 (41/55)	77.8 (42/54)	83.0 (44/53)
DA group	90.9 (50/55)	89.1 (49/55)	83.6 (46/55)	87.3 (48/55)	85.5 (47/55)	74.5 (41/55)	66.7 (36/54)	84.6 (44/52)	88.5 (46/52)

Time point (Week)	22	24	End of treatment	Follow-up
Enarodustat group	83.0 (44/53)	86.8 (46/53)	87.7 (50/57)	77.4 (41/53)
DA group	86.5 (45/52)	84.0 (42/50)	81.8 (45/55)	80.0 (40/50)

Proportion (%) (No. of subjects with Hb levels within target range/No. of subjects assessed at each time point)
Follow-up: 2 weeks after the end of treatment



Time point (Week)	Screening 1	Screening 2	Baseline	2	4	8	12	16	20	22	24	End of treatment	Follow-up
Enarodustat group (N)	48	48	48	48	47	48	47	47	46	45	45	48	45
DA group (N)	52	52	52	52	52	52	51	48	47	47	47	52	47

Follow-up: 2 weeks after the end of treatment

Figure 2. Time course of mean Hb levels (Mean ± SD) (Study MBA4-4, Without prior use of ESA, FAS)

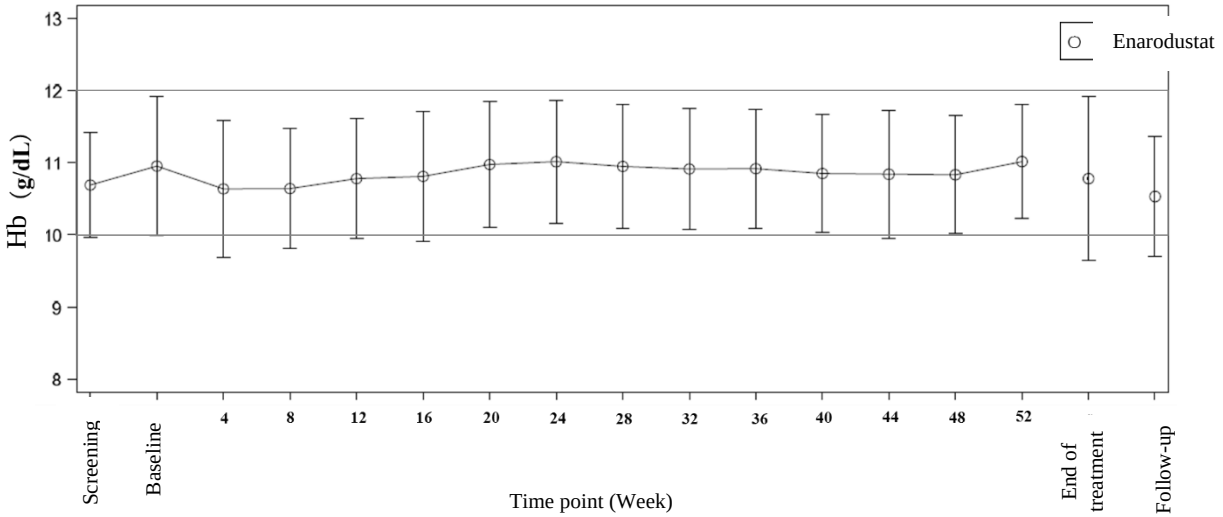
Table 70. Proportions of subjects with Hb levels within target range (≥10.0 g/dL and ≤12.0 g/dL) at different time points (%) (Study MBA4-4, Without prior use of ESA, FAS)

Time point (Week)	Screening 1	Screening 2	Baseline	2	4	8	12	16	20
Enarodustat group	33.3 (16/48)	25.0 (12/48)	29.2 (14/48)	43.8 (21/48)	48.9 (23/47)	81.3 (39/48)	85.1 (40/47)	87.2 (41/47)	89.1 (41/46)
DA group	46.2 (24/52)	19.2 (10/52)	30.8 (16/52)	57.7 (30/52)	75.0 (39/52)	82.7 (43/52)	74.5 (38/51)	87.5 (42/48)	85.1 (40/47)

Time point (Week)	22	24	End of treatment	Follow-up
Enarodustat group	95.6 (43/45)	93.3 (42/45)	87.5 (42/48)	82.2 (37/45)
DA group	93.6 (44/47)	83.0 (39/47)	76.9 (40/52)	83.0 (39/47)

Proportion (%) (No. of subjects with Hb levels within target range/No. of subjects assessed at each time point)
Follow-up: 2 weeks after the end of treatment

In a long-term treatment study in patients with non-dialysis-dependent CKD (Study MBA4-1), the time course of the mean Hb levels up to Week 52 and the proportions of subjects with Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL) at different time points are shown in Figure 3 and Table 71, respectively, for patients with prior use of ESA, and Figure 4 and Table 72, respectively, for patients without prior use of ESA. The mean Hb levels were maintained within the target range (≥10.0 g/dL and ≤12.0 g/dL), throughout the enarodustat treatment period in patients with prior use of ESA and after Week 4 in patients without prior use of ESA.



Time point (Week)	Screening	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52	End of treatment	Follow-up
Enarodustat-treated patients (N)	88	88	88	84	82	81	77	74	72	71	67	67	65	64	62	88	61

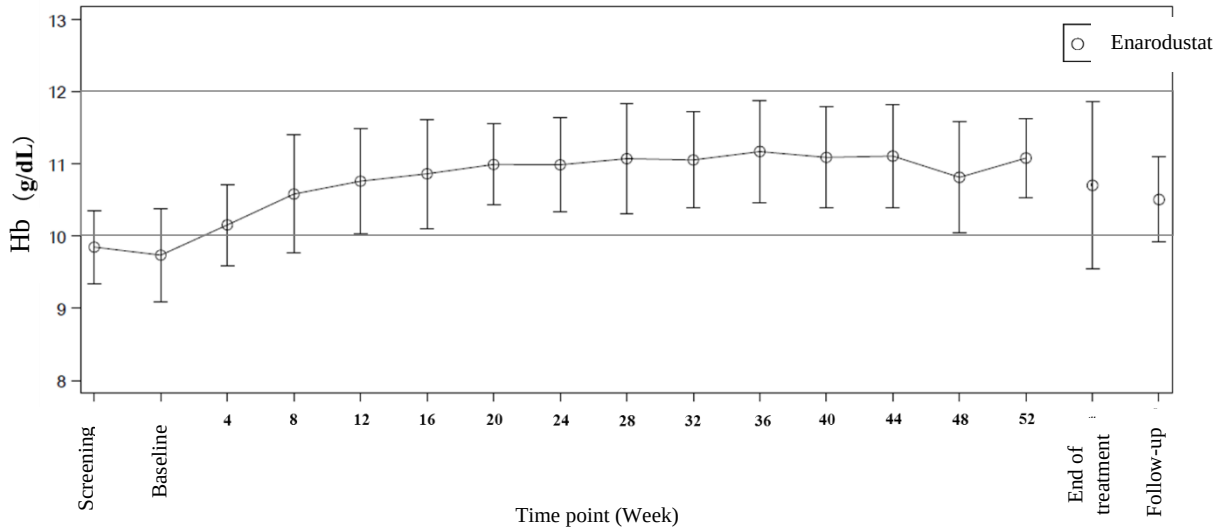
Follow-up: 2 weeks after the end of treatment

Figure 3. Time course of mean Hb levels (Mean ± SD) (Study MBA4-1, With prior use of ESA, FAS)

Table 71. Proportions of subjects with Hb levels within target range (≥10.0 g/dL and ≤12.0 g/dL) at different time points (%) (Study MBA4-1, With prior use of ESA, FAS)

Time point (Week)	**Screening**	**Baseline**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Enarodustat-treated patients	**80.7 (71/88)**	**73.9 (65/88)**	**69.3 (61/88)**	**77.4 (65/84)**	**79.3 (65/82)**	**77.8 (63/81)**	**84.4 (65/77)**	**78.4 (58/74)**	**77.8 (56/72)**
Time point (Week)	**32**	**36**	**40**	**44**	**48**	**52**	**End of treatment**	**Follow-up**	
Enarodustat-treated patients	**81.7 (58/71)**	**80.6 (54/67)**	**83.6 (56/67)**	**75.4 (49/65)**	**76.6 (49/64)**	**83.9 (52/62)**	**68.2 (60/88)**	**72.1 (44/61)**	

Proportion (%) (No. of subjects with Hb levels within target range/No. of subjects assessed at each time point)
Follow-up: 2 weeks after the end of treatment



Time point (Week)	Screening	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52	End of treatment	Follow-up
Enarodustat-treated patients (N)	42	42	42	40	40	40	39	39	36	35	34	34	32	32	31	42	31

Follow-up: 2 weeks after the end of treatment

Figure 4. Time course of mean Hb levels (Mean ± SD) (Study MBA4-1, Without prior use of ESA, FAS)

Table 72. Proportions of subjects with Hb levels within target range (≥10.0 g/dL and ≤12.0 g/dL) at different time points (%) (Study MBA4-1, Without prior use of ESA, FAS)

Time point (Week)	**Screening**	**Baseline**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Enarodustat-treated patients	**54.8 (23/42)**	**35.7 (15/42)**	**69.0 (29/42)**	**80.0 (32/40)**	**80.0 (32/40)**	**87.5 (35/40)**	**94.9 (37/39)**	**89.7 (35/39)**	**80.6 (29/36)**
Time point (Week)	**32**	**36**	**40**	**44**	**48**	**52**	**End of treatment**	**Follow-up**	
Enarodustat-treated patients	**88.6 (31/35)**	**85.3 (29/34)**	**88.2 (30/34)**	**93.8 (30/32)**	**81.3 (26/32)**	**90.3 (28/31)**	**81.0 (34/42)**	**87.1 (27/31)**	

Proportion (%) (No. of subjects with Hb levels within target range/No. of subjects assessed at each time point)
Follow-up: 2 weeks after the end of treatment

PMDA's view:

Study MBA4-4 demonstrated the non-inferiority of enarodustat to DA, and Studies MBA4-4 and MBA4-1 showed that the mean Hb levels were maintained within the target range (≥10.0 g/dL and ≤12.0 g/dL), regardless of prior use of ESA. Thus, the efficacy of enarodustat in patients with non-dialysis-dependent CKD was demonstrated.

7.R.1.2 HD patients

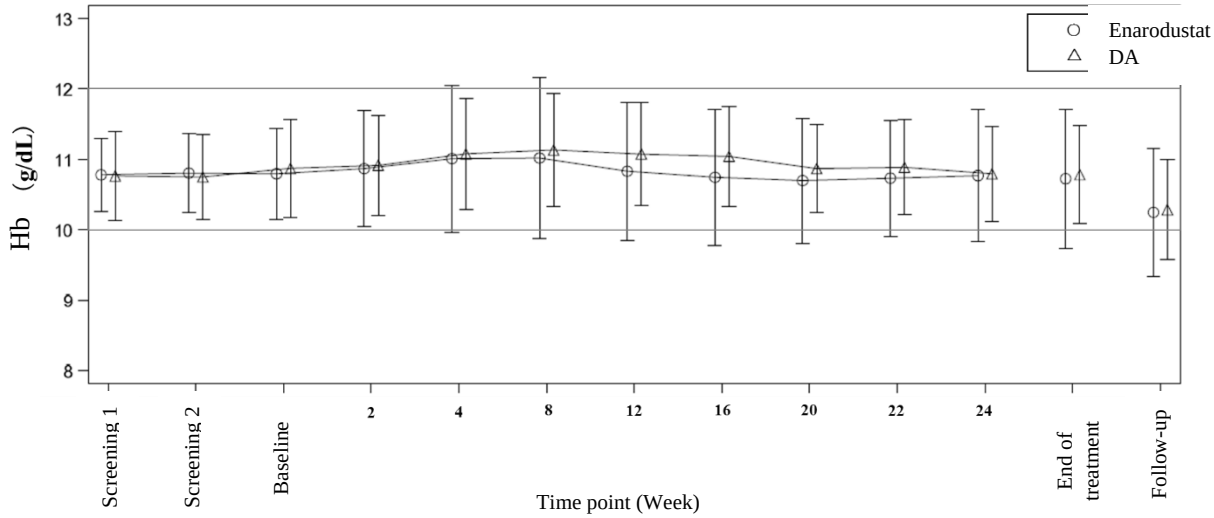
Based on the considerations in Sections 7.R.1.2.1 and 7.R.1.2.2, PMDA considers that the efficacy of enarodustat in HD patients was demonstrated.

7.R.1.2.1 HD patients with prior use of ESA

The applicant's explanation about the efficacy of enarodustat in HD patients with prior use of ESA:

In a phase III study in HD patients with prior use of ESA (Study MBA4-5), the difference in the primary endpoint of the mean Hb during the evaluation period (Weeks 20-24) between the enarodustat and DA groups [95% CI] was −0.12 [−0.33, 0.10] g/dL, and the lower limit of the 95% confidence interval for the treatment difference was above the pre-specified non-inferiority margin of −1.0 g/dL, therefore establishing the non-inferiority of enarodustat to DA (Table 57). Base on the analysis in the FAS,[32)] the difference in the mean Hb at or near the end of treatment[33)] between the enarodustat and DA groups [95% CI] was −0.14 [−0.36, 0.08] g/dL, which showed a similar trend to the results of the primary analysis in the PPS.

Among the secondary endpoints, the time course of the mean Hb levels up to Week 24 and the proportions of subjects with Hb levels within the target range (≥10.0 g/dL and <12.0 g/dL) at different time points are shown in Figure 5 and Table 73, respectively. The mean Hb levels were maintained within the target range (≥10.0 g/dL and <12.0 g/dL) in both the enarodustat and DA groups.



Time point (Week)	Screening 1	Screening 2	Baseline	2	4	8	12	16	20	22	24	End of treatment	Follow-up
Enarodustat group (N)	86	86	86	86	86	86	84	81	79	79	79	86	79
DA group (N)	86	86	86	86	86	85	85	84	82	80	80	86	80

Follow-up: 2 weeks after the end of treatment

Figure 5. Time course of mean Hb levels (Mean ± SD) (Study MBA4-5, FAS)

[32)] Among 173 subjects who received study drug, 172 subjects after excluding 1 subject assessed for efficacy less than twice after Week 4 in the enarodustat group were included in the FAS (86 in the enarodustat group, 86 in the DA group).

[33)] Mean of Hb levels at the end of treatment (at Week 24 or discontinuation) and the previous 2 time points (if Hb was assessed 3 times after Week 4); Mean of Hb levels at the end of treatment (at Week 24 or discontinuation) and the previous time point (if Hb was assessed twice after Week 4)

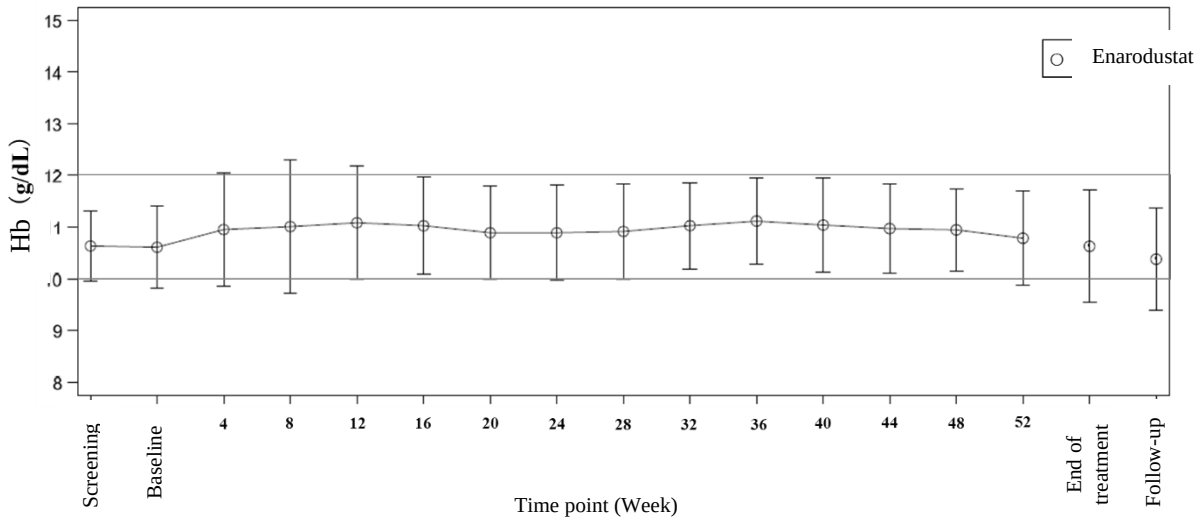
Table 73. Proportions of subjects with Hb levels within target range (≥10.0 g/dL and <12.0 g/dL) at different time points (%) (Study MBA4-5, FAS)

Time point (Week)	Screening 1	Screening 2	Baseline	2	4	8	12	16	20
Enarodustat group	90.7 (78/86)	95.3 (82/86)	87.2 (75/86)	77.9 (67/86)	65.1 (56/86)	62.8 (54/86)	75.0 (63/84)	71.6 (58/81)	75.9 (60/79)
DA group	88.4 (76/86)	89.5 (77/86)	84.9 (73/86)	82.6 (71/86)	76.7 (66/86)	76.5 (65/85)	83.5 (71/85)	82.1 (69/84)	85.4 (70/82)

Time point (Week)	22	24	End of treatment	Follow-up
Enarodustat group	70.9 (56/79)	73.4 (58/79)	70.9 (61/86)	60.8 (48/79)
DA group	83.8 (67/80)	85.0 (68/80)	83.7 (72/86)	62.5 (50/80)

Proportion (%) (No. of subjects with Hb levels within target range/No. of subjects assessed at each time point)
Follow-up: 2 weeks after the end of treatment

In a long-term treatment study in HD patients with prior use of ESA (Study MBA4-2), the time course of the mean Hb levels up to Week 52 and the proportions of subjects with Hb levels within the target range (≥10.0 g/dL and <12.0 g/dL) at different time points are shown in Figure 6 and Table 74, respectively. The mean Hb levels were maintained within the target range (≥10.0 g/dL and <12.0 g/dL), as in the enarodustat group of Study MBA4-5.



Time point (Week)	Screening	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52	End of treatment	Follow-up
Enarodustat-treated patients (N)	136	136	136	132	127	126	124	121	121	120	120	118	118	118	118	136	118

Follow-up: 2 weeks after the end of treatment

Figure 6. Time course of mean Hb levels (Mean ± SD) (Study MBA4-2, FAS)

Table 74. Proportions of subjects with Hb levels within target range (≥10.0 g/dL and <12.0 g/dL) at different time points (%) (Study MBA4-2, FAS)

Time point (Week)	Screening	Baseline	4	8	12	16	20	24	28
Enarodustat-treated patients	83.1 (113/136)	75.0 (102/136)	64.7 (88/136)	50.8 (67/132)	61.4 (78/127)	70.6 (89/126)	75.8 (94/124)	73.6 (89/121)	70.2 (85/121)
Time point (Week)	32	36	40	44	48	52	End of treatment	Follow-up	
Enarodustat-treated patients	75.8 (91/120)	76.7 (92/120)	72.0 (85/118)	74.6 (88/118)	82.2 (97/118)	71.2 (84/118)	68.4 (93/136)	57.6 (68/118)	

Proportion (%) (No. of subjects with Hb levels within target range/No. of subjects assessed at each time point)
Follow-up: 2 weeks after the end of treatment

PMDA's view:

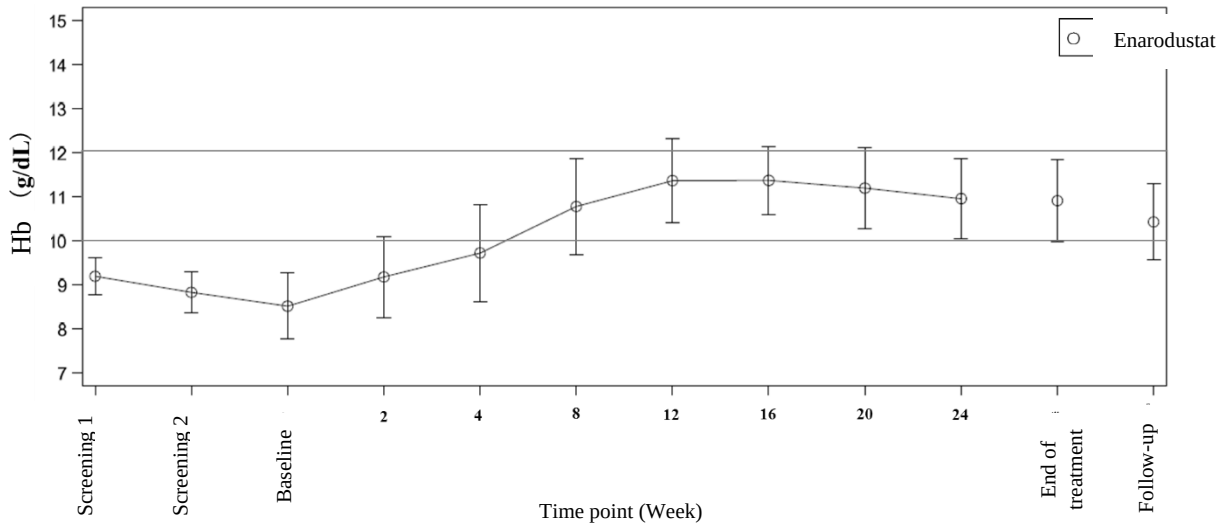
Study MBA4-5 demonstrated the non-inferiority of enarodustat to DA, and Studies MBA4-5 and MBA4-2 showed that the mean Hb levels were maintained within the target range (≥10.0 g/dL and <12.0 g/dL). Thus, the efficacy of enarodustat in HD patients with prior use of ESA was demonstrated.

7.R.1.2.2 HD patients without prior use of ESA

The applicant's explanation about the efficacy of enarodustat in HD patients without prior use of ESA:

In a phase III study in HD patients without prior use of ESA (Study MBA4-6), the primary endpoint of the rate of Hb rise during Weeks 0 to 4 [95% CI] was estimated at 0.302 [0.239, 0.365] g/dL/week.

Among the secondary endpoints, the time course of the mean Hb levels up to Week 24 and the proportions of subjects with Hb levels within the target range (≥10.0 g/dL and <12.0 g/dL) at different time points are shown in Figure 7 and Table 75, respectively. The mean Hb levels were maintained within the target range (≥10.0 g/dL and <12.0 g/dL) after Week 8.



Time point (Week)	Screening 1	Screening 2	Baseline	2	4	8	12	16	20	24	End of treatment	Follow-up
Enarodustat group (N)	34	34	34	34	34	33	33	33	33	33	34	33

Follow-up: 2 weeks after the end of treatment

Figure 7. Time course of mean Hb levels (Mean ± SD) (Study MBA4-6, FAS)

Table 75. Proportions of subjects with Hb levels within target range (≥10.0 g/dL and <12.0 g/dL) at different time points (%) (Study MBA4-6, FAS)

Time point (Week)	Screening 1	Screening 2	Baseline	2	4	8	12	16	20
Enarodustat group	0 (0/34)	0 (0/34)	2.9 (1/34)	23.5 (8/34)	41.2 (14/34)	60.6 (20/33)	66.7 (22/33)	75.8 (25/33)	75.8 (25/33)
Time point (Week)	24	End of treatment	Follow-up						
Enarodustat group	63.6 (21/33)	61.8 (21/34)	63.6 (21/33)						

Proportion (%) (No. of subjects with Hb levels within target range/No. of subjects assessed at each time point)
Follow-up: 2 weeks after the end of treatment

PMDA's view:

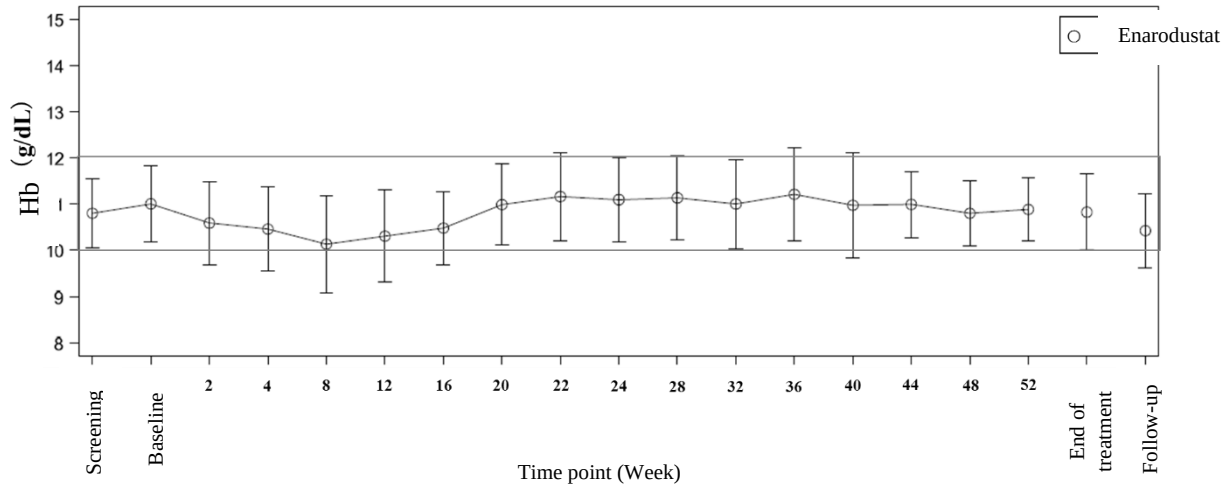
In Study MBA4-6, Hb rose after the start of treatment with enarodustat, and the mean Hb levels were maintained within the target range (≥10.0 g/dL and <12.0 g/dL) by adjusting the dose of enarodustat according to Hb levels. Thus, the efficacy of enarodustat is expected also in HD patients without prior use of ESA.

7.R.1.3 PD patients

The applicant's explanation about the efficacy of enarodustat in PD patients:

In a phase III study in PD patients (Study MBA4-3), the time course of the mean Hb levels and the proportions of subjects with Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL) at different time points are shown in Figure 8 and Table 76, respectively. The mean Hb levels were maintained within the target range (≥10.0 g/dL and ≤12.0 g/dL).

In Study MBA4-3, there was only 1 patient without prior use of ESA among 41 subjects in the FAS. In this subject, the change in Hb from baseline (10.4 g/dL) to Week 4 was 0.7 g/dL, and then the Hb levels were largely maintained within the target range (≥10.0 g/dL and ≤12.0 g/dL).



Time point (Week)	Screening	Baseline	2	4	8	12	16	20	22	24	28	32	36	40	44	48	52	End of treatment	Follow-up
Enarodustat-treated patients (N)	41	41	41	41	40	39	38	38	38	38	38	38	36	36	33	32	32	41	32

Follow-up: 2 weeks after the end of treatment

Figure 8. Time course of mean Hb levels (Mean ± SD) (Study MBA4-3, FAS)

Table 76. Proportions of subjects with Hb levels within target range (≥10.0 and ≤12.0 g/dL) at different time points (%) (Study MBA4-3, FAS)

Time point (Week)	Screening	Baseline	2	4	8	12	16	20	22
Enarodustat-treated patients	82.9 (34/41)	82.9 (34/41)	78.0 (32/41)	78.0 (32/41)	55.0 (22/40)	61.5 (24/39)	78.9 (30/38)	76.3 (29/38)	78.9 (30/38)
Time point (Week)	24	28	32	36	40	44	48	52	End of treatment
Enarodustat-treated patients	68.4 (26/38)	81.6 (31/38)	71.1 (27/38)	72.2 (26/36)	69.4 (25/36)	90.9 (30/33)	87.5 (28/32)	84.4 (27/32)	82.9 (34/41)
Time point (Week)	Follow-up								
Enarodustat-treated patients	68.8 (22/32)								

Proportion (%) (No. of subjects with Hb levels within target range/No. of subjects assessed at each time point)
Follow-up: 2 weeks after the end of treatment

PMDA's view:

In Study MBA4-3 in PD patients, the mean Hb levels were maintained within the target range (≥10.0 g/dL and ≤12.0 g/dL) by adjusting the dose of enarodustat according to Hb levels. Thus, the efficacy of enarodustat is expected also in PD patients, regardless of prior use of ESA.

7.R.1.4 Efficacy by patient characteristics

PMDA's view:

Among patients with non-dialysis-dependent (NDD) CKD, HD patients, and PD patients, the proportions of subjects with mean Hb levels during Weeks 20 to 24 within the target range by main patient characteristics are shown in Table 77. Though it should be noted that some subgroups had a limited number of patients, there was no trend towards clearly lower efficacy of enarodustat in any specific subgroup.

Table 77. Proportions of subjects with mean Hb levels during Weeks 20-24 within target range[a)] by main patient characteristics among patients with NDD-CKD, HD patients, and PD patients (FAS)

		Patients with NDD-CKD[b)]		HD patients[c)]		PD patients[d)]	
		N	% (n)	N	% (n)	N	% (n)
Total		301	89.7 (270)	272	77.6 (211)	38	84.2 (32)
Age	<65 years	70	94.3 (66)	122	76.2 (93)	16	75.0 (12)
	≥65 years	231	88.3 (204)	150	78.7 (118)	22	90.9 (20)
Body weight	<55 kg	109	89.9 (98)	91	73.6 (67)	6	100 (6)
	≥55 kg	192	89.6 (172)	181	79.6 (144)	32	81.3 (26)
Primary disease	Diabetic nephropathy	81	95.1 (77)	93	77.4 (93)	15	86.7 (13)
	Chronic glomerulonephritis	85	90.6 (77)	92	76.1 (70)	15	86.7 (13)
	Nephrosclerosis	79	84.8 (67)	32	81.3 (26)	6	83.3 (5)
	Others	56	87.5 (49)	55	78.2 (43)	2	50.0 (1)
eGFR (mL/min/1.73 m^2)	<15	137	89.1 (122)				
	≥15 and <30	138	88.4 (122)				
	≥30 and <60	26	100 (26)				
	≥60	0	-				
Hemodialysis vintage (Study MBA4-6)	<1 year			15	73.3 (11)		
	≥1 year			18	77.8 (14)		
Hemodialysis vintage (Other HD studies[e)])	<7 years			137	74.5 (102)		
	≥7 years			102	82.4 (84)		
Peritoneal dialysis vintage	<3 years					18	77.8 (14)
	≥3 years					20	90.0 (18)
Hb at baseline (g/dL)	<10.0	98	88.8 (87)	86	80.2 (69)	3	100 (3)
	≥10.0 and <11.0	121	88.4 (107)	106	77.4 (82)	17	82.4 (14)
	≥11.0	82	92.7 (76)	80	75.0 (60)	18	83.3 (15)
TSAT at baseline (%)	<20	37	86.5 (32)	52	75.0 (39)	1	100 (1)
	≥20	264	90.2 (238)	214	78.5 (168)	37	83.8 (31)
Ferritin at baseline (ng/mL)	<100	116	92.2 (107)	101	82.2 (83)	6	83.3 (5)
	≥100	185	88.1 (163)	171	74.9 (128)	32	84.4 (27)
Prior ESA dose[f)]	Low dose	144	91.0 (131)	178	77.5 (138)	22	90.9 (20)
	High dose	28	71.4 (20)	44	75.0 (33)	15	73.3 (11)
Concomitant iron	Yes	112	85.7 (96)	135	77.0 (104)	10	80.0 (8)
	No	189	92.1 (174)	137	78.1 (107)	28	85.7 (24)
Concomitant anti-hyperphosphatemia drug	Yes	42	90.5 (38)	257	77.0 (198)	36	86.1 (31)
	No	259	89.6 (232)	15	86.7 (13)	2	50.0 (1)

a) Patients with NDD-CKD and PD patients, ≥10.0 g/dL and ≤12.0 g/dL; HD patients, ≥10.0 g/dL and <12.0 g/dL

b) Pooled data from phase II (Study MBA3-1 [excluding data from the placebo group before initiation of enarodustat treatment and data from [redacted]]) and phase III (Study MBA4-1, Study MBA4-4) studies in patients with NDD-CKD

c) Pooled data from phase II (Study MBA3-2 [excluding data from [redacted]], Study MBA3-3 [excluding data from the placebo group before initiation of enarodustat treatment and data from [redacted]]) and phase III (Study MBA4-2, Study MBA4-5, Study MBA4-6) studies in HD patients

d) Data from a phase III study in PD patients (Study MBA4-3)

e) Phase II (Study MBA3-2, Study MBA3-3) and phase III (Study MBA4-2, Study MBA4-5) studies in HD patients

f) Low dose was defined as follows: rHuEPO <12,000 IU/2 weeks, DA <120 μg/4 weeks, and CERA <150 μg/4 weeks in patients with NDD-CKD and PD patients; and rHuEPO <6,000 IU/week, DA <30 μg/week, and CERA <150 μg/4 weeks in HD patients.
High dose was defined as follows: rHuEPO ≥12,000 IU/2 weeks, DA ≥120 μg/4 weeks, and CERA ≥150 μg/4 weeks in patients with NDD-CKD and PD patients; and rHuEPO ≥6,000 IU/week, DA ≥30 μg/week, and CERA ≥150 μg/4 weeks in HD patients

7.R.2 Safety

Based on the following considerations in Sections 7.R.2.1 to 7.R.2.6, PMDA considers that enarodustat has acceptable safety in patients with renal anemia, provided that the dose of enarodustat is adjusted, monitoring Hb levels, etc. However, it is necessary to continue to collect information on the incidences of thromboembolism, cardiovascular events, hypertension, malignant tumors, and retinal events via post-marketing surveillance, etc.

7.R.2.1 Patients with non-dialysis-dependent CKD

The applicant's explanation about the safety of enarodustat in patients with non-dialysis-dependent CKD:

Table 78 shows the incidences of adverse events in the enarodustat and DA groups in a phase III study in patients with non-dialysis-dependent CKD (Study MBA4-4). No adverse events were reported at a clearly higher incidence in the enarodustat group than in the DA group. Although the incidences of adverse drug reactions and serious adverse drug reactions were higher in the enarodustat group than in the DA group, adverse drug reactions reported by ≥2 subjects in either group were hyperkalaemia (1.9% [2 of 107 subjects]) in the enarodustat group only, and there was no trend towards a higher incidence of a specific event in the enarodustat group. There was 1 death (drowning[15)]) in the DA group, and its causal relationship to study drug was denied. Table 79 shows the incidences of adverse events and adverse drug reactions by prior ESA use status in a long-term treatment study (Study MBA4-1). There were 4 deaths (subdural haematoma[17)]; chronic kidney disease[18)]; plasma cell myeloma[19)]; and death [unspecified][20)] [1 subject each]), and 1 case of death (unspecified) was classified as an adverse drug reaction. In either study, there were no major differences in the incidence of adverse events according to prior ESA use status.

Table 78. Incidences of adverse events and adverse drug reactions in Study MBA4-4 (24 weeks of treatment) (Safety population)

	With prior use of ESA		Without prior use of ESA		Total	
	Enarodustat (N = 57)	DA (N = 57)	Enarodustat (N = 50)	DA (N = 52)	Enarodustat (N = 107)	DA (N = 109)
Adverse events	59.6 (34)	78.9 (45)	72.0 (36)	86.5 (45)	65.4 (70)	82.6 (90)
Adverse drug reactions	7.0 (4)	1.8 (1)	14.0 (7)	5.8 (3)	10.3 (11)	3.7 (4)
Deaths	0 (0)	1.8 (1)	0 (0)	0 (0)	0 (0)	0.9 (1)
Serious adverse events[a)]	8.8 (5)	8.8 (5)	16.0 (8)	11.5 (6)	12.1 (13)	10.1 (11)
Serious adverse drug reactions[a)]	3.5 (2)	0 (0)	4.0 (2)	0 (0)	3.7 (4)	0 (0)
Adverse events leading to treatment discontinuation[b)]	0 (0)	1.8 (1)	4.0 (2)	1.9 (1)	1.9 (2)	1.8 (2)
Adverse drug reactions leading to treatment discontinuation[b)]	0 (0)	0 (0)	2.0 (1)	0 (0)	0.9 (1)	0 (0)

Incidence % (n)
a) Excluding adverse events leading to death
b) Excluding adverse events leading to death and serious adverse events

Table 79. Incidences of adverse events and adverse drug reactions in Study MBA4-1 (52 weeks of treatment) (Safety population)

	Enarodustat-treated patients		
	With prior use of ESA (N = 90)	Without prior use of ESA (N = 42)	Total (N = 132)
Adverse events	87.8 (79)	85.7 (36)	87.1 (115)
Adverse drug reactions	13.3 (12)	14.3 (6)	13.6 (18)
Deaths	2.2 (2)	4.8 (2)	3.0 (4)
Serious adverse events[a)]	28.9 (26)	23.8 (10)	27.3 (36)
Serious adverse drug reactions[a)]	0 (0)	4.8 (2)	1.5 (2)
Adverse events leading to treatment discontinuation[b)]	5.6 (5)	7.1 (3)	6.1 (8)
Adverse drug reactions leading to treatment discontinuation[b)]	1.1 (1)	0 (0)	0.8 (1)

Incidence % (n)
a) Excluding adverse events leading to death
b) Excluding adverse events leading to death and serious adverse events

PMDA's view:

There was no clinically relevant trend in the incidence of adverse events in the enarodustat group compared with the DA group in Study MBA4-4, and there were no major differences in the incidence of adverse events according to prior ESA use status in Studies MBA4-4 and MBA4-1.

7.R.2.2 HD patients

The applicant's explanation about the safety of enarodustat in HD patients:

Table 80 shows the incidences of adverse events in phase III studies in HD patients (Study MBA4-5, Study MBA4-6, Study MBA4-2). In Study MBA4-5, i.e. a comparative study of enarodustat vs. DA, there were no major differences in the incidences of adverse events, adverse drug reactions, serious adverse events, etc. between the enarodustat and DA groups. The incidences of the following adverse events tended to be higher in the enarodustat group than in the DA group: vomiting (10.3% [9 of 86 subjects] in the enarodustat group, 2.3% [2 of 86 subjects] in the DA group) and gastroenteritis (5.7% [5 of 86 subjects] in the enarodustat group, 0% [0 of 86 subjects] in the DA group). Adverse drug reactions reported by ≥2 subjects in either group were fibrin D dimer increased (2.3% [2 of 86 subjects]) in the enarodustat group and retinal haemorrhage (2.3% [2 of 86 subjects]) in the DA group. In Study MBA4-6 compared with Study MBA4-5, the incidence of serious adverse events was higher, but serious adverse events reported by ≥2 subjects were shunt stenosis (2 subjects), and there was no trend towards a higher incidence of a specific event in patients without prior use of ESA compared with patients with prior use of ESA. In Study MBA4-2 in patients with prior use of ESA, serious adverse drug reactions reported were peripheral arterial occlusive disease; and brain stem infarction (1 subject each), both of which had an outcome of "resolved." No deaths were reported in the clinical studies in HD patients.

Table 80. Incidences of adverse events and adverse drug reactions in Studies MBA4-5, MBA4-6, and MBA4-2 (Safety population)

	MBA4-5 (With prior use of ESA)		MBA4-6 (Without prior use of ESA)	MBA4-2 (With prior use of ESA)
Duration of treatment	24 weeks		24 weeks	52 weeks
N	Enarodustat group (N = 87)	DA group (N = 86)	Enarodustat-treated patients (N = 34)	Enarodustat-treated patients (N = 136)
Adverse events	87.4 (76)	83.7 (72)	85.3 (29)	97.8 (133)
Adverse drug reactions	4.6 (4)	3.5 (3)	5.9 (2)	8.8 (12)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events	14.9 (13)	14.0 (12)	23.5 (8)	22.8 (31)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)	2 (1.5)
Adverse events leading to treatment discontinuation[a)]	2.3 (2)	1.2 (1)	0 (0)	5.9 (8)
Adverse drug reactions leading to treatment discontinuation[a)]	0 (0)	0 (0)	0 (0)	1.5 (2)

Incidence % (n)

a) Excluding serious adverse events

PMDA's view:

There was no clinically relevant trend in the incidence of adverse events in the enarodustat group compared with the DA group in Study MBA4-5 in patients with prior use of ESA. There were no major problems with the incidence of adverse events in Studies MBA4-6 and MBA4-2. The incidence of thromboembolism will be assessed in Section 7.R.2.5.1.

7.R.2.3 PD patients

The applicant's explanation about the safety of enarodustat in PD patients:

Table 81 shows the incidences of adverse events and adverse drug reactions in a phase III study in PD patients (Study MBA4-3). In PD patients, as peritoneal dialysis-related events, catheter site infection occurred in 26.2%

(11 of 42) of subjects, peritonitis occurred in 16.7% (7 of 42) of subjects, and device related infection occurred in 14.3% (6 of 42) of subjects. There were 3 deaths (pulmonary embolism[26]; influenzal pneumonia[27]; and thalamus haemorrhage[28] [1 subject each]), and pulmonary embolism was classified as an adverse drug reaction.

Table 81. Incidences of adverse events and adverse drug reactions in Study MBA4-3 (52 weeks of treatment) (Safety population)

	Enarodustat-treated patients (N = 42)
Adverse events	100 (42)
Adverse drug reactions	16.7 (7)
Deaths	7.1 (3)
Serious adverse events[a]	42.9 (18)
Serious adverse drug reactions[a]	0 (0)
Adverse events leading to treatment discontinuation[b]	2.4 (1)
Adverse drug reactions leading to treatment discontinuation[b]	2.4 (1)

Incidence % (n)
a) Excluding adverse events leading to death
b) Excluding adverse events leading to death and serious adverse events

PMDA's view:

In Study MBA4-3, 3 of 42 subjects died. A causal relationship to study drug was denied for 2 cases, and the case of pulmonary embolism was classified as an adverse drug reaction. Since thromboembolism requires attention during treatment with HIF-PH inhibitors including enarodustat, as assessed in Section 7.R.2.5.1, the package insert, etc. should include a relevant precautionary statement. Enarodustat has acceptable safety also in PD patients as well as in patients with non-dialysis-dependent CKD and HD patients, provided that appropriate measures such as monitoring for and management of adverse events, are taken.

7.R.2.4 Long-term safety

PMDA's view:

Table 82 shows the incidences of adverse events by time from onset of therapy in patients with non-dialysis-dependent CKD, HD patients, and PD patients. There was no trend towards increasing incidence of adverse events with prolonged treatment with enarodustat.

Table 82. Incidences of adverse events by time from onset of therapy

		Weeks 0-4	Weeks 4-12	Weeks 12-24	Weeks 24-36	Weeks 36-48	Week 48 onward	Entire period
Pooled enarodustat-treated NDD-CKD[a]	N	436	435	402	373	136	99	436
	Adverse events	20.0 (87)	38.2 (166)	43.8 (176)	32.2 (120)	38.2 (52)	21.2 (21)	76.6 (334)
	Deaths	0 (0)	0.5 (2)	0 (0)	0.3 (1)	0 (0)	1.0 (1)	0.9 (4)
	Serious adverse events[d]	1.8 (8)	3.7 (16)	6.0 (24)	2.9 (11)	5.9 (8)	3.0 (3)	15.1 (66)
Pooled enarodustat-treated HD[b]	N	407	403	370	344	128	118	407
	Adverse events	35.9 (146)	57.3 (231)	62.7 (232)	48.3 (166)	58.6 (75)	44.9 (53)	88.0 (358)
	Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Serious adverse events	1.7 (7)	6.5 (26)	8.6 (32)	3.2 (11)	4.7 (6)	0.8 (1)	16.5 (67)
Enarodustat-treated PD[c]	N	42	41	41	39	38	34	42
	Adverse events	33.3 (14)	56.1 (23)	61.0 (25)	64.1 (25)	60.5 (23)	55.9 (19)	100 (42)
	Deaths	2.4 (1)	0 (0)	0 (0)	2.6 (1)	2.6 (1)	0 (0)	7.1 (3)
	Serious adverse events[d]	4.8 (2)	14.6 (6)	4.9 (2)	10.3 (4)	21.1 (8)	11.8 (4)	42.9 (18)

Incidence % (n)
a) Pooled data from phase II (Study MBA3-1) and phase III (Study MBA4-1, Study MBA4-4) studies in patients with NDD-CKD
b) Pooled data from phase II (Study MBA3-2, Study MBA3-3) and phase III (Study MBA4-2, Study MBA4-5, Study MBA4-6) studies in HD patients
c) Data from a phase III study in PD patients (Study MBA4-3)
d) Excluding adverse events leading to death

7.R.2.5 Adverse events of special interest associated with enarodustat

Based on the mechanism of action of enarodustat, non-clinical and clinical data, etc., PMDA assessed the incidences of thromboembolism, cardiovascular events, retinal events, hypertension, and malignant tumors as adverse events of special interest, as described in Sections 7.R.2.5.1 to 7.R.2.5.5.

7.R.2.5.1 Thromboembolism

The applicant's explanation about thromboembolism:

In Studies MBA4-4 and MBA4-5, which were comparative studies of enarodustat vs. DA, there were no major differences in the incidence of adverse events related to thromboembolism and infarction between the enarodustat and DA groups (Table 83). In either study, there were no adverse drug reactions related to thromboembolism and infarction in the enarodustat or DA group.

According to the pooled data from a total of 9 studies (phase II and III studies that served as the main efficacy and safety evaluation data) (the pooled data from 9 studies),[34)] the incidence of adverse events related to thromboembolism and infarction in enarodustat-treated subjects is shown in Table 84. The incidence of adverse drug reactions was 0.8% (7 of 885 subjects) (deep vein thrombosis [2 subjects]; and shunt occlusion; brain stem infarction; coronary artery stenosis; peripheral arterial occlusive disease; and pulmonary embolism [1 subject each]). One PD patient treated with enarodustat died (pulmonary embolism), and this case was assessed as causally related to study drug [see Section 7.R.2.3]. Non-fatal serious adverse drug reactions occurred in 4 subjects (brain stem infarction; coronary artery stenosis; peripheral arterial occlusive disease; and deep vein thrombosis [1 subject each]).

Table 83. Incidences of adverse events related to thromboembolism and infarction in Studies MBA4-4 and MBA4-5 (Safety population)

	MBA4-4 (NDD-CKD)				MBA4-5 (HD)			
	Enarodustat (N = 107)		DA (N = 109)		Enarodustat (N = 87)		DA (N = 86)	
	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events
Any event	0 (0)	0 (0)	0.9 (1)	0.9 (1)	11.5 (10)	6.9 (6)	16.3 (14)	5.8 (5)
Shunt stenosis	0 (0)	0 (0)	0 (0)	0 (0)	5.7 (5)	2.3 (2)	10.5 (9)	2.3 (2)
Shunt occlusion	0 (0)	0 (0)	0 (0)	0 (0)	4.6 (4)	3.4 (3)	4.7 (4)	2.3 (2)
Acute myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	1.1 (1)	0 (0)	0 (0)
Pulmonary embolism	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	1.1 (1)	0 (0)	0 (0)
Lacunar infarction	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Brachiocephalic vein stenosis	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Myocardial ischaemia	0 (0)	0 (0)	0.9 (1)	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Angina pectoris	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.2 (1)	1.2 (1)

MedDRA/J ver 22.0; Incidence % (n)

[34)] Pooled data from phase II studies (Study MBA3-1, Study MBA3-2, Study MBA3-3) and phase III studies (Study MBA4-1, Study MBA4-2, Study MBA4-3, Study MBA4-4, Study MBA4-5, Study MBA4-6)

Table 84. Incidence of adverse events related to thromboembolism and infarction according to the pooled data from 9 studies (Safety population)

	Pooled enarodustat-treated NDD-CKD [a] (N = 436)		Pooled enarodustat-treated HD [b] (N = 407)		Enarodustat-treated PD [c] (N = 42)		Enarodustat-treated subjects pooled from 9 studies [d] (N = 885)	
	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events
Any event	1.6 (7)	0.7 (3)	16.0 (65)	5.7 (23)	9.5 (4)	9.5 (4)	8.6 (76)	3.4 (30)
Shunt stenosis	0.2 (1)	0 (0)	8.6 (35)	1.0 (4)	0 (0)	0 (0)	4.1 (36)	0.5 (4)
Shunt occlusion	0 (0)	0 (0)	5.2 (21)	2.4 (10)	0 (0)	0 (0)	2.4 (21)	1.1 (10)
Coronary artery stenosis	0 (0)	0 (0)	0.7 (3)	0.7 (3)	4.8 (2)	4.8 (2)	0.6 (5)	0.6 (5)
Peripheral arterial occlusive disease	0.2 (1)	0.2 (1)	0.7 (3)	0.5 (2)	2.4 (1)	2.4 (1)	0.6 (5)	0.5 (4)
Cerebral infarction	0 (0)	0 (0)	1.0 (4)	0.5 (2)	2.4 (1)	2.4 (1)	0.6 (5)	0.3 (3)
Myocardial ischaemia	0.2 (1)	0.2 (1)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0.2 (2)	0.2 (2)
Acute myocardial infarction	0 (0)	0 (0)	0.5 (2)	0.5 (2)	0 (0)	0 (0)	0.2 (2)	0.2 (2)
Pulmonary embolism	0 (0)	0 (0)	0.2 (1)	0.2 (1)	2.4 (1)	2.4 (1)	0.2 (2)	0.2 (2)
Deep vein thrombosis	0.5 (2)	0.2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (2)	0.1 (1)
Lacunar infarction	0.2 (1)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.2 (2)	0 (0)
Angina pectoris	0 (0)	0 (0)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0.1 (1)	0.1 (1)
Basal ganglia infarction	0 (0)	0 (0)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0.1 (1)	0.1 (1)
Brain stem infarction	0 (0)	0 (0)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0.1 (1)	0.1 (1)
Retinal artery occlusion	0 (0)	0 (0)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0.1 (1)	0.1 (1)
Disseminated intravascular coagulation	0.2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Brachiocephalic vein stenosis	0 (0)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Carotid artery stenosis	0 (0)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Retinal vein occlusion	0 (0)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Transient ischaemic attack	0 (0)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Venous occlusion	0 (0)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Arteriosclerosis	0 (0)	0 (0)	0 (0)	0 (0)	2.4 (1)	0 (0)	0.1 (1)	0 (0)

MedDRA/J ver 22.0; Incidence % (n)

a) Pooled data from phase II (Study MBA3-1) and phase III (Study MBA4-1, Study MBA4-4) studies in patients with NDD-CKD

b) Pooled data from phase II (Study MBA3-2, Study MBA3-3) and phase III (Study MBA4-2, Study MBA4-5, Study MBA4-6) studies in HD patients

c) Data from a phase III study in PD patients (Study MBA4-3)

d) Pooled data from phase II (Study MBA3-1, Study MBA3-2, Study MBA3-3) and phase III (Study MBA4-1, Study MBA4-2, Study MBA4-3, Study MBA4-4, Study MBA4-5, Study MBA4-6) studies

Based on the above, the occurrence of events related to thromboembolism and infarction is unlikely to become a clinically relevant problem following administration of enarodustat compared with DA.

PMDA's view:

In Studies MBA4-4 and MBA4-5, there were no major differences in the incidence of adverse events related to thromboembolism and infarction between the enarodustat and DA groups. However, serious adverse drug reactions were reported among enarodustat-treated subjects pooled from 9 studies, and 1 case of pulmonary embolism reported in Study MBA4-3 led to death. The package insert for a previously approved HIF-PH inhibitor contains information about thromboembolism in the warnings section (it reads that thromboembolism may be fatal). Given these points, the package insert for enarodustat should also contain

similar warning information. It is also necessary to continue to collect information on the incidence of thromboembolism via post-marketing surveillance, etc.

7.R.2.5.2 Cardiovascular events

The applicant's explanation about cardiovascular events:

In Studies MBA4-4 and MBA4-5, which were comparative studies of enarodustat vs. DA, there were no major differences in the incidence of adverse events related to cardiac disease and cerebrovascular disorder between the enarodustat and DA groups (Table 85). In either study, there were no adverse drug reactions related to cardiac disease and cerebrovascular disorder in the enarodustat or DA group.

According to the pooled data from 9 studies, the incidence of adverse events related to cardiac disease and cerebrovascular disorder in enarodustat-treated subjects is shown in Table 86. The incidence of adverse drug reactions was 0.7% (6 of 885 subjects) (cardiomegaly [2 subjects]; and congestive cardiac failure; coronary artery stenosis; brain stem infarction; and cardiac hypertrophy [1 subject each]), among which 2 cases (coronary artery stenosis; and brain stem infarction [1 subject each]) were classified as serious adverse drug reactions.

Table 85. Incidences of adverse events related to cardiac disease and cerebrovascular disorder in Studies MBA4-4 and MBA4-5 (Safety population)

	MBA4-4 (NDD-CKD)				MBA4-5 (HD)			
	Enarodustat (N = 107)		DA (N = 109)		Enarodustat (N = 87)		DA (N = 86)	
	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events
Any event	1.9 (2)	0.9 (1)	2.8 (3)	0.9 (1)	6.9 (6)	4.6 (4)	3.5 (3)	3.5 (3)
Cerebral haemorrhage	0 (0)	0 (0)	0.9 (1)	0 (0)	2.3 (2)	2.3 (2)	0 (0)	0 (0)
Cardiac failure	0.9 (1)	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Supraventricular tachycardia	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Acute myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	1.1 (1)	0 (0)	0 (0)
Mitral valve incompetence	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	1.1 (1)	0 (0)	0 (0)
Electrocardiogram T wave inversion	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Lacunar infarction	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Myocardial ischaemia	0 (0)	0 (0)	0.9 (1)	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiomegaly	0 (0)	0 (0)	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Congestive cardiac failure	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.2 (1)	1.2 (1)
Arrhythmia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.2 (1)	1.2 (1)
Angina pectoris	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.2 (1)	1.2 (1)

MedDRA/J ver 22.0; Incidence % (n)

Table 86. Incidence of adverse events related to cardiac disease and cerebrovascular disorder (those reported by ≥2 subjects) according to the pooled data from 9 studies (Safety population)

	Pooled enarodustat-treated NDD-CKD [a] (N = 436)		Pooled enarodustat-treated HD [b] (N = 407)		Enarodustat-treated PD [c] (N = 42)		Enarodustat-treated subjects pooled from 9 studies [d] (N = 885)	
	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events
Any event	5.5 (24)	2.5 (11)	6.9 (28)	3.9 (16)	19.0 (8)	19.0 (8)	6.8 (60)	4.0 (35)
Congestive cardiac failure	1.4 (6)	0.7 (3)	0 (0)	0 (0)	4.8 (2)	4.8 (2)	0.9 (8)	0.6 (5)
Coronary artery stenosis	0 (0)	0 (0)	0.7 (3)	0.7 (3)	4.8 (2)	4.8 (2)	0.6 (5)	0.6 (5)
Cardiac failure	0.7 (3)	0.2 (1)	0.2 (1)	0.2 (1)	2.4 (1)	2.4 (1)	0.6 (5)	0.3 (3)
Cerebral infarction	0 (0)	0 (0)	1.0 (4)	0.5 (2)	2.4 (1)	2.4 (1)	0.6 (5)	0.3 (3)
Atrial fibrillation	0.7 (3)	0.5 (2)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.5 (4)	0.2 (2)
Cardiomegaly	0.9 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4)	0 (0)
Subdural haematoma	0.2 (1)	0.2 (1)	0.5 (2)	0.2 (1)	0 (0)	0 (0)	0.3 (3)	0.2 (2)
Tachycardia	0.2 (1)	0 (0)	0.5 (2)	0 (0)	0 (0)	0 (0)	0.3 (3)	0 (0)
Atrioventricular block complete	0.2 (1)	0.2 (1)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0.2 (2)	0.2 (2)
Chronic cardiac failure	0.2 (1)	0.2 (1)	0 (0)	0 (0)	2.4 (1)	2.4 (1)	0.2 (2)	0.2 (2)
Myocardial ischaemia	0.2 (1)	0.2 (1)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0.2 (2)	0.2 (2)
Pericarditis	0.2 (1)	0.2 (1)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0.2 (2)	0.2 (2)
Acute myocardial infarction	0 (0)	0 (0)	0.5 (2)	0.5 (2)	0 (0)	0 (0)	0.2 (2)	0.2 (2)
Cerebral haemorrhage	0 (0)	0 (0)	0.5 (2)	0.5 (2)	0 (0)	0 (0)	0.2 (2)	0.2 (2)
Aortic valve stenosis	0 (0)	0 (0)	0.2 (1)	0 (0)	2.4 (1)	2.4 (1)	0.2 (2)	0.1 (1)
Arrhythmia	0.2 (1)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.2 (2)	0 (0)
Lacunar infarction	0.2 (1)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.2 (2)	0 (0)
Supraventricular tachycardia	0.2 (1)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.2 (2)	0 (0)
Electrocardiogram T wave inversion	0 (0)	0 (0)	0.5 (2)	0 (0)	0 (0)	0 (0)	0.2 (2)	0 (0)

MedDRA/J ver 22.0; Incidence % (n)

a) Pooled data from phase II (Study MBA3-1) and phase III (Study MBA4-1, Study MBA4-4) studies in patients with NDD-CKD

b) Pooled data from phase II (Study MBA3-2, Study MBA3-3) and phase III (Study MBA4-2, Study MBA4-5, Study MBA4-6) studies in HD patients

c) Data from a phase III study in PD patients (Study MBA4-3)

d) Pooled data from phase II (Study MBA3-1, Study MBA3-2, Study MBA3-3) and phase III (Study MBA4-1, Study MBA4-2, Study MBA4-3, Study MBA4-4, Study MBA4-5, Study MBA4-6) studies

Based on the above, the occurrence of events related to cardiac disease and cerebrovascular disorder is unlikely to become a clinically relevant problem following administration of enarodustat compared with DA.

PMDA's view:

In Studies MBA4-4 and MBA4-5, there were no major differences in the incidence of adverse events related to cardiac disease and cerebrovascular disorder between the enarodustat and DA groups. However, since serious adverse drug reactions were reported among enarodustat-treated subjects pooled from 9 studies, taking account of the risk of thromboembolism, it is also necessary to continue to collect information on the incidence of cardiovascular events via post-marketing surveillance, etc.

7.R.2.5.3 Retinal events

The applicant's explanation about retinal events:

In Studies MBA4-4 and MBA4-5, which were comparative studies of enarodustat vs. DA, there were no major differences in the incidence of retinal and choroidal adverse events between the enarodustat and DA groups (Table 87). The incidences of retinal and choroidal adverse drug reactions were 0.9% (1 of 107 subjects) in the enarodustat group (retinal haemorrhage [1 subject]) in Study MBA4-4 and 1.1% (1 of 87 subjects) in the enarodustat group (retinal haemorrhage [1 subject]) and 2.3% (2 of 86 subjects) in the DA group (retinal haemorrhage [2 subjects]) in Study MBA4-5.

According to the pooled data from 9 studies, the incidence of retinal and choroidal adverse events in enarodustat-treated subjects is shown in Table 88. The incidence of adverse drug reactions was 1.1% (10 of 885 subjects) (retinal haemorrhage [5 subjects]; macular oedema [2 subjects]; and diabetic retinopathy; vitreous haemorrhage; chorioretinopathy; neovascular age-related macular degeneration; and retinal aneurysm [1 subject each] [some subjects had more than 1 event]).

Table 87. Incidences of retinal and choroidal adverse events in Studies MBA4-4 and MBA4-5 (Safety population)

	MBA4-4 (NDD-CKD)				MBA4-5 (HD)			
	Enarodustat (N = 107)		DA (N = 109)		Enarodustat (N = 87)		DA (N = 86)	
	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events
Any event	3.7 (4)	0 (0)	0.9 (1)	0 (0)	6.9 (6)	1.1 (1)	3.5 (3)	0 (0)
Retinal haemorrhage	1.9 (2)	0 (0)	0 (0)	0 (0)	3.4 (3)	0 (0)	3.5 (3)	0 (0)
Macular oedema	0.9 (1)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Retinal tear	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serous retinal detachment	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vitreous haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	1.1 (1)	0 (0)	0 (0)
Diabetic retinopathy	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Chorioretinopathy	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Diabetic retinal oedema	0 (0)	0 (0)	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

MedDRA/J ver 22.0; Incidence % (n)

Table 88. Incidence of retinal and choroidal adverse events according to the pooled data from 9 studies (Safety population)

	Pooled enarodustat-treated NDD-CKD [a] (N = 436)		Pooled enarodustat-treated HD [b] (N = 407)		Enarodustat-treated PD [c] (N = 42)		Enarodustat-treated subjects pooled from 9 studies [d] (N = 885)	
	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events	Adverse events	Serious adverse events
Any event	**5.3 (23)**	**0.5 (2)**	**6.6 (27)**	**1.0 (4)**	**9.5 (4)**	**2.4 (1)**	**6.1 (54)**	**0.8 (7)**
Retinal haemorrhage	**1.8 (8)**	**0 (0)**	**2.5 (10)**	**0 (0)**	**4.8 (2)**	**0 (0)**	**2.3 (20)**	**0 (0)**
Macular oedema	**0.9 (4)**	**0 (0)**	**0.7 (3)**	**0 (0)**	**2.4 (1)**	**0 (0)**	**0.9 (8)**	**0 (0)**
Diabetic retinopathy	**0.5 (2)**	**0 (0)**	**1.0 (4)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.7 (6)**	**0 (0)**
Retinal tear	**1.1 (5)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.6 (5)**	**0 (0)**
Vitreous haemorrhage	**0.5 (2)**	**0 (0)**	**0.5 (2)**	**0.2 (1)**	**0 (0)**	**0 (0)**	**0.5 (4)**	**0.1 (1)**
Retinal exudates	**0.5 (2)**	**0 (0)**	**0.5 (2)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.5 (4)**	**0 (0)**
Retinal detachment	**0.5 (2)**	**0.5 (2)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.2 (2)**	**0.2 (2)**
Macular hole	**0 (0)**	**0 (0)**	**0.2 (1)**	**0.2 (1)**	**2.4 (1)**	**2.4 (1)**	**0.2 (2)**	**0.2 (2)**
Chorioretinopathy	**0.2 (1)**	**0 (0)**	**0.2 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.2 (2)**	**0 (0)**
Serous retinal detachment	**0.2 (1)**	**0 (0)**	**0.2 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.2 (2)**	**0 (0)**
Vitreous floaters	**0.2 (1)**	**0 (0)**	**0.2 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.2 (2)**	**0 (0)**
Diabetic retinal oedema	**0 (0)**	**0 (0)**	**0.2 (1)**	**0 (0)**	**2.4 (1)**	**0 (0)**	**0.2 (2)**	**0 (0)**
Retinal artery occlusion	**0 (0)**	**0 (0)**	**0.2 (1)**	**0.2 (1)**	**0 (0)**	**0 (0)**	**0.1 (1)**	**0.1 (1)**
Vitreous opacities	**0 (0)**	**0 (0)**	**0.2 (1)**	**0.2 (1)**	**0 (0)**	**0 (0)**	**0.1 (1)**	**0.1 (1)**
Age-related macular degeneration	**0.2 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.1 (1)**	**0 (0)**
Neovascular age-related macular degeneration	**0.2 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.1 (1)**	**0 (0)**
Macular fibrosis	**0 (0)**	**0 (0)**	**0.2 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.1 (1)**	**0 (0)**
Retinal vein occlusion	**0 (0)**	**0 (0)**	**0.2 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0.1 (1)**	**0 (0)**
Retinal aneurysm	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**2.4 (1)**	**0 (0)**	**0.1 (1)**	**0 (0)**

MedDRA/J ver 22.0; Incidence % (n)

a) Pooled data from phase II (Study MBA3-1) and phase III (Study MBA4-1, Study MBA4-4) studies in patients with NDD-CKD

b) Pooled data from phase II (Study MBA3-2, Study MBA3-3) and phase III (Study MBA4-2, Study MBA4-5, Study MBA4-6) studies in HD patients

c) Data from a phase III study in PD patients (Study MBA4-3)

d) Pooled data from phase II (Study MBA3-1, Study MBA3-2, Study MBA3-3) and phase III (Study MBA4-1, Study MBA4-2, Study MBA4-3, Study MBA4-4, Study MBA4-5, Study MBA4-6) studies

Based on the results of ophthalmic examinations, the proportions of subjects who shifted from a "normal" to "abnormal" fundus examination were 0% (0 of 99 subjects) for the right eye and 2.0% (2 of 99 subjects) for the left eye in the enarodustat group and 0% (0 of 97 subjects) for the right eye and 1.0% (1 of 97 subjects) for the left eye in the DA group in Study MBA4-4 and 1.3% (1 of 77 subjects) for the right eye and 2.5% (2 of 79 subjects) for the left eye in the enarodustat group and 1.3% (1 of 79 subjects) for the right eye and 0% (1 of 80 subjects) for the left eye in the DA group in Study MBA4-5. There were no major differences in the proportion of subjects who shifted from a "normal" to "abnormal" fundus examination between the enarodustat and DA groups.

Based on the above, the occurrence of retinal events is unlikely to become a clinically relevant problem following administration of enarodustat compared with DA.

PMDA's view:

At present, there has been no trend towards clearly higher risk of retinal events with enarodustat compared with DA. However, since patients at high risk of retinal events (patients scheduled to undergo an ophthalmological procedure for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration) were excluded from clinical studies, and enarodustat may promote angiogenesis via activation of the HIF pathway, the package insert should advise that enarodustat should be used with particular caution in patients at high risk, and it is necessary to continue to collect information on the incidence of retinal events via post-marketing surveillance, etc.

7.R.2.5.4 Hypertension

The applicant's explanation about hypertension:

In Study MBA4-4, the incidences of adverse events of hypertension and blood pressure increased were 0.9% (1 of 107 subjects) and 3.7% (4 of 107 subjects), respectively, in the enarodustat group and 2.8% (3 of 109 subjects) and 1.8% (2 of 109 subjects), respectively, in the DA group. The events of blood pressure increased reported by 1 subject each in the enarodustat and DA groups (0.9% [1 of 107 subjects] and 0.9% [1 of 109 subjects], respectively) were classified as adverse drug reactions. In Study MBA4-5, the incidences of hypertension and blood pressure increased were 3.4% (3 of 87 subjects) and 1.1% (1 of 87 subjects), respectively, in the enarodustat group and 2.3% (2 of 86 subjects) and 0% (0 of 86 subjects), respectively, in the DA group. None of those events were classified as adverse drug reactions.

Among enarodustat-treated subjects pooled from 9 studies, the incidences of hypertension and blood pressure increased were 5.2% (46 of 885 subjects) and 1.5% (13 of 885 subjects), respectively, and the incidences of those classified as adverse drug reactions were 1.6% (14 of 885 subjects) and 0.6% (5 of 885 subjects), respectively.

Moreover, in Study MBA3-1 in patients with non-dialysis-dependent CKD and Part 1 (6 weeks) of Study MBA3-3 in HD patients, there were no clinically relevant changes in the mean blood pressure at any dose level in the enarodustat group (2, 4, and 6 mg), as in the placebo group. According to the pooled data from 9 studies (up to 52 weeks of treatment), there were no clinically relevant changes in the mean blood pressure.

No serious adverse events of hypertension or blood pressure increased were reported in enarodustat-treated subjects or DA-treated subjects.

Based on the above, the occurrence of hypertension-related events is unlikely to become a clinically relevant problem following administration of enarodustat compared with DA.

PMDA's view:

Since there were no major differences in the incidences of adverse events of hypertension and blood pressure increased between the enarodustat and DA groups in Studies MBA4-4 and MBA4-5, the occurrence of hypertension-related events is unlikely to become a clinically relevant problem following administration of

enarodustat compared with DA. Meanwhile, as the package insert for ESA includes a precaution about blood pressure increased, etc., the package insert for enarodustat should also include a relevant precaution, and it is necessary to continue to collect information on the incidence of hypertension-related events via post-marketing surveillance, etc.

7.R.2.5.5 Malignant tumors

The applicant's explanation about malignant tumors:
According to the pooled data from 9 studies, malignancy-related adverse events occurred in 1.4% (12 of 885) of enarodustat-treated subjects, which include colon cancer (3 subjects); gastric cancer; and renal cancer (2 subjects each); and bone cancer; glottis carcinoma; plasma cell myeloma; rectosigmoid cancer; renal cell carcinoma; and renal neoplasm (1 subject each). The event of bone cancer was classified as an adverse drug reaction by the investigator. However, since enarodustat was considered to have little genotoxic potential and no carcinogenic potential [see Sections 5.3 and 5.4], and it should generally take several years from the development of bone cancer to vertebral bone destruction, this event was assessed by the sponsor as causally unrelated to study drug. A causal relationship to study drug was denied for other events.

When compared with DA, in Study MBA4-4, no malignancy-related events occurred in the enarodustat group, while gastric cancer occurred in 0.9% (1 of 109) of subjects and malignant neoplasm of renal pelvis occurred in 0.9% (1 of 109) of subjects in the DA group. In Study MBA4-5, renal cancer occurred in 1.1% (1 of 87) of subjects in the enarodustat group and malignant neoplasm of renal pelvis occurred in 1.2% (1 of 86) of subjects in the DA group. A causal relationship to study drug was denied for all those events.

Based on the above, malignant tumors are unlikely to become a problem in the clinical use of enarodustat.

PMDA's view:
At present, there have been no particular problems with the incidence of malignant tumors associated with enarodustat. However, since patients with malignant tumors were excluded from clinical studies, and the possibility that enarodustat enhances tumor progression by promoting angiogenesis via activation of the HIF pathway cannot be ruled out, the package insert should include a relevant precaution, and it is necessary to continue to collect information on the incidence of malignant tumors via post-marketing surveillance, etc.

7.R.3 Indication and clinical positioning

The applicant's explanation about the indication for and clinical positioning of enarodustat:
Phase III studies demonstrated the efficacy of enarodustat in HD patients, patients with non-dialysis-dependent CKD, and PD patients [see Section 7.R.1] and its acceptable safety [see Section 7.R.2]. Thus, the indication of "renal anemia" was proposed.

With regard to the clinical positioning of enarodustat, ESAs (intravenous or subcutaneous administration) are mainly used for the treatment of renal anemia at present, whereas ESAs have problems such as the development of anti-EPO antibody-positive pure red cell aplasia, injection site pain, and the risk of

infections. Enarodustat will offer a new treatment option for patients with renal anemia because it has a different route of administration (oral administration) and a different mechanism of action from ESAs. Enarodustat is not assumed to be used in combination with ESAs or other HIF-PH inhibitors.

PMDA's view:
Since phase III studies in patients with renal anemia on HD, anemic non-dialysis-dependent CKD patients, and patients with renal anemia on PD demonstrated the efficacy [see Section 7.R.1] and acceptable safety of enarodustat [see Section 7.R.2], the proposed indication of "renal anemia" is acceptable. As with ESAs, enarodustat will offer a treatment option for patients with renal anemia.

7.R.4 Dosage and administration

7.R.4.1 Starting dose

7.R.4.1.1 Patients with non-dialysis-dependent CKD

The applicant's explanation about the starting dose of enarodustat in patients with non-dialysis-dependent CKD:
In a phase II study in patients with non-dialysis-dependent CKD (Study MBA3-1), the rate of Hb rise per week in Part 1 (the first 6 weeks of treatment) showed a dose response relationship of enarodustat, and Hb rose at ≥2 mg/day in the correction group (Table 33). In the conversion group, the proportion of subjects with a mean of the Hb levels at the end of treatment and the previous time point within ± 1.0 g/dL of baseline in Part 1 (the first 6 weeks of treatment) was 80.8% (21 of 26 subjects) in the 2 mg group (Table 36). Based on the above results, a starting dose of 2 mg/day was chosen for phase III studies in patients with non-dialysis-dependent CKD (Studies MBA4-4 and MBA4-1).

In Study MBA4-4, among patients without prior use of ESA, the changes in Hb from baseline to Week 4 (Mean ± SD) in the enarodustat and DA groups were 0.32 ± 0.65 and 0.92 ± 0.64 g/dL, respectively, and Hb rose in both groups. In the enarodustat group, the proportion of subjects with Hb levels within the target range (≥10.0 g/dL and ≤12.0 g/dL) increased gradually to 81.3% (39 of 48 subjects) at Week 8 (Table 70). Among patients with prior use of ESA, the changes in Hb from baseline to Week 4 in the enarodustat and DA groups were −0.26 ± 0.69 and −0.08 ± 0.44 g/dL, respectively, and the proportions of subjects with Hb levels at Week 4 within ±1.0 g/dL of baseline in the enarodustat and DA groups were 87.7% (50 of 57 subjects) and 100% (55 of 55 subjects), respectively. Hb levels were stable early after switching from ESAs in both groups.

In Study MBA4-1, among patients without prior use of ESA, the change in Hb from baseline to Week 4 (Mean ± SD) was 0.42 ± 0.62 g/dL. Among patients with prior use of ESA, the change in Hb from baseline to Week 4 was −0.32 ± 0.72 g/dL, and the proportion of subjects with Hb levels at Week 4 within ±1.0 g/dL of baseline was 83.0% (73 of 88 subjects).

In Studies MBA4-4 and MBA4-1, none of enarodustat-treated subjects had a change in Hb from baseline to Week 4 >2.0 g/dL. There were no safety concerns in the initial phase of treatment (4 weeks) in Studies MBA4-4 and MBA4-1.

Hb changes after switching to enarodustat in patients with prior use of ESA were analyzed by prior ESA dose, using the pooled data from Studies MBA3-1 (excluding data from the placebo and 6 mg groups), MBA4-4, and MBA4-1. Hb levels at Week 4 tended to decrease with higher dose of prior DA or epoetin beta pegol (genetical recombination) (CERA) (Table 89). However, the mean Hb levels at Week 4 were maintained within the target range (≥10.0 g/dL and ≤12.0 g/dL), regardless of prior ESA dose, and such differences were not considered clinically meaningful.

Table 89. Changes in Hb from baseline to Week 4 by prior ESA dose in patients with prior use of ESA (Studies MBA3-1, MBA4-4, and MBA4-1, FAS)

Prior ESA		N	Hb at baseline (g/dL)	Hb at Week 4 (g/dL)	Change in Hb (g/dL)
rHuEPO (IU/2 weeks)	<6,000	4	10.96 ± 0.90	11.18 ± 0.63	0.22 ± 0.38
	≥6,000 and <12,000	3	11.11 ± 0.93	11.07 ± 1.25	-0.04 ± 0.78
	≥12,000	0	—	—	—
DA (μg/4 weeks)	<60	35	10.81 ± 0.62	10.75 ± 0.72	-0.06 ± 0.66
	≥75 and <120	35	10.84 ± 0.94	10.74 ± 1.07	-0.10 ± 0.84
	≥120	22	10.83 ± 0.94	10.24 ± 0.99	-0.59 ± 0.76
CERA (μg/4 weeks)	<75	56	10.77 ± 0.79	10.66 ± 1.00	-0.11 ± 0.58
	≥75 and <150	34	10.93 ± 0.81	10.51 ± 1.09	-0.42 ± 0.92
	≥150	9	10.94 ± 1.18	10.62 ± 1.33	-0.32 ± 0.77

Mean ± SD

Based on the above, a starting dose of 2 mg/day for patients with non-dialysis-dependent CKD was considered appropriate, regardless of prior ESA use status.

PMDA's view:
Based on the results of Studies MBA4-4 and MBA4-1 in patients with non-dialysis-dependent CKD, a starting dose of 2 mg for patients with non-dialysis-dependent CKD is acceptable, regardless of prior ESA use status. However, as Hb tended to decrease after switching from ESAs, the package insert etc. should advise that attention should be paid to Hb changes after switching to enarodustat.

7.R.4.1.2 HD patients

The applicant's explanation about the starting dose of enarodustat in HD patients:
In a phase II study in HD patients off ESAs for a certain period of time (Study MBA3-2), the rate of Hb rise per week in Part 1 (the first 6 weeks of treatment) showed a dose response relationship of enarodustat, and Hb rose at ≥4 mg/day (Table 39). Thus, a starting dose of 4 mg/day was chosen for a phase III study in HD patients without prior use of ESA (Study MBA4-6).

In Study MBA4-6, the rate of Hb rise during Weeks 0 to 4 [95% CI] was estimated at 0.302 [0.239, 0.365] g/dL/week, and the change in Hb from baseline to Week 4 (Mean ± SD) was 1.21 ± 0.98 g/dL. Thus, enarodustat was shown to correct anemia. The proportion of subjects with a change in Hb from baseline to Week 4 >2.0 g/dL was 26.5% (9 of 34 subjects). Although there were no safety concerns in the initial phase of treatment (4 weeks) in these subjects, dose reduction or interruption of enarodustat was considered necessary in the event of excessive hematopoiesis in the initial phase of treatment with enarodustat.

In Part 1 (the first 6 weeks of treatment) of a phase II study in HD patients with prior use of ESA (Study MBA3-3), the mean of the Hb levels at the end of treatment and the previous time point decreased from baseline in the 2 mg group and increased from baseline in the 6 mg group, but the mean Hb was similar to baseline value in the 4 mg group (Table 43). Taking account of these findings, etc., a starting dose of 4 mg/day was chosen for phase III studies in HD patients with prior use of ESA (Studies MBA4-5 and MBA4-2).

In Study MBA4-5, the changes in Hb from baseline to Week 4 (Mean ± SD) in the enarodustat and DA groups were 0.21 ± 0.81 and 0.21 ± 0.56 g/dL, respectively, and the proportions of subjects with Hb levels at Week 4 within ±1.0 g/dL of baseline were 80.2% (69 of 86 subjects) and 89.5% (77 of 86 subjects), respectively. Hb levels were stable early after switching from ESAs in both the enarodustat and DA groups.

Also in Study MBA4-2, the change in Hb from baseline to Week 4 was 0.34 ± 0.94 g/dL, and the proportion of subjects with Hb levels at Week 4 within ±1.0 g/dL of baseline was 70.6% (96 of 136 subjects). Hb levels were stable early after switching from ESAs.

Regarding safety, there were no safety concerns in the initial phase of treatment (4 weeks) in Studies MBA4-6, MBA4-5, and MBA4-2.

Based on the above, a starting dose of 4 mg/day for HD patients was considered appropriate, regardless of prior ESA use status.

PMDA's view:
Based on the results of phase III studies in HD patients (Studies MBA4-6, MBA4-5, and MBA4-2), a starting dose of 4 mg for HD patients is acceptable, regardless of prior ESA use status. Since Hb rose rapidly in the initial phase of treatment in some subjects in Study MBA4-6 in patients without prior use of ESA, the package insert etc. should advise that Hb should be closely monitored in the initial phase of treatment with enarodustat, and the dose of enarodustat should be adjusted as appropriate.

7.R.4.1.3 PD patients

The applicant's explanation about the starting dose of enarodustat in PD patients:
Since the disease conditions of PD patients are similar to those of patients with non-dialysis-dependent CKD, a starting dose of 2 mg/day was chosen for a phase III study in PD patients (Study MBA4-3), based on the results of a phase II study in patients with non-dialysis-dependent CKD (Study MBA3-1).

In Study MBA4-3, among patients switching from ESAs, the change in Hb from baseline to Week 4 (Mean ± SD) was −0.58 ± 0.66 g/dL, and the proportion of subjects with Hb levels at Week 4 within ±1.0 g/dL of baseline was 77.5% (31 of 40 subjects). Hb levels were stable early after switching from ESAs. There was only 1 patient without prior use of ESA, and the change in Hb from baseline to Week 4 was 0.7 g/dL, showing an Hb increase. There were no safety concerns in the initial phase of treatment (4 weeks) in PD patients.

Based on the above, a starting dose of 2 mg/day for PD patients was considered appropriate, regardless of prior ESA use status.

PMDA's view:
Based on the results of Study MBA4-3 in PD patients, a starting dose of 2 mg for PD patients is acceptable, regardless of prior ESA use status. However, as Hb levels after switching tended to decrease (Figure 8), the package insert etc. should advise that attention should be paid to Hb changes after switching.

7.R.4.2 Maintenance dose and dose titration algorithm

The applicant's explanation about the maintenance dose and dose titration algorithm of enarodustat:
In phase III studies (Studies MBA4-1, MBA4-2, MBA4-3, MBA4-4, MBA4-5, and MBA4-6), the dose of enarodustat was adjusted within the range of 1 to 8 mg, according to Hb levels, to maintain Hb levels within the target range. The target Hb range was set at 10.0 g/dL to 12.0 g/dL for patients with non-dialysis-dependent CKD and PD patients, and at ≥10.0 g/dL and <12.0 g/dL for HD patients, referring to "Guideline for Renal Anemia in Chronic Kidney Disease" 2008 and 2015, developed by the Japanese Society for Dialysis Therapy, and "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" developed by the Japanese Society of Nephrology in 2012.

In all studies, Hb levels were largely maintained within the target range by adjusting the dose of enarodustat within the range of 1 to 8 mg/day according to Hb levels [see Section 7.R.1].

The mean dose and the number of dose adjustments during the enarodustat treatment period in the phase III studies are shown in Table 90. In all studies, the doses were widely distributed over the range of 1 to 8 mg/day, irrespective of timing of dose.

Table 90. Mean dose and number of dose adjustments during enarodustat treatment period in phase III studies (FAS)

Study population	Study	Duration of treatment	N	Mean dose (mg/day)	Number of dose adjustments
Non-dialysis-dependent CKD	MBA4-4	24 weeks	105	2.68 ± 1.25	1.6 ± 1.2
	MBA4-1	52 weeks	130	2.64 ± 1.23	2.4 ± 2.0
HD	MBA4-5	24 weeks	86	3.95 ± 1.68	2.0 ± 1.1
	MBA4-6	24 weeks	34	3.86 ± 1.51	1.9 ± 1.5
	MBA4-2	52 weeks	136	3.68 ± 1.76	3.1 ± 2.0
PD	MBA4-3	52 weeks	41	3.23 ± 1.53	3.2 ± 1.9

Mean ± SD

PMDA's view:
Adjusting the dose of enarodustat within the range of 1 to 8 mg/day, according to Hb levels, is acceptable. The package insert etc. should contain information about the dose titration algorithm used in phase III studies (the dose should be adjusted by 1 level, dose adjustment decisions should be made every 4 weeks, etc.).

7.R.4.3 Method of administration

The applicant's explanation about the method of administration of enarodustat:

Given that food decreased enarodustat exposure in a food effect study (Study MBX1-1) [see Section 6.1.1], the method of administration chosen for phase II and later clinical studies was "enarodustat administered orally once daily before a meal or at bedtime."

Phase III studies (Studies MBA4-1, MBA4-2, MBA4-3, MBA4-4, MBA4-5, and MBA4-6) demonstrated the efficacy of enarodustat administered orally once daily before a meal or at bedtime, and its acceptable safety. Thus, the proposed method of administration based on the phase III studies, i.e. "enarodustat administered orally once daily before a meal or at bedtime," is appropriate. Since there was little clearance of enarodustat by the dialysis membranes [see Section 6.1.2.6], and hemodialysis did not appear to affect the pharmacokinetics of enarodustat [see Section 6.2.4.2], enarodustat can be administered without regard to dialysis treatment.

PMDA accepted the applicant's explanation.

7.R.5 Post-marketing investigations

The applicant is planning a post-marketing specified use-results survey as shown in Table 91.

Table 91. Outline of specified use-results survey (draft)

Objective	**To assess the safety of enarodustat in clinical practice (including long-term treatment).**
Survey method	**Central registry system**
Population	**Patients with renal anemia**
Planned sample size	**1,300 patients (including ≥100 PD patients and ≥300 patients with NDD-CKD)**
Observation period	**2 years**
Main survey items	**Patient characteristics (the primary disease causing chronic kidney disease, dialysis status, medical history, complications, etc.), the use of enarodustat, prior treatment/concomitant medications, clinical laboratory tests, the incidence of adverse events**

PMDA's view:

Based on the considerations in Section 7.R.2, it is necessary to collect the following information after marketing. The details of post-marketing surveillance plan, etc. will be finalized, taking account of comments from the Expert Discussion.

● The incidences of thromboembolism, cardiovascular events, retinal events, hypertension, and malignant tumors

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

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

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

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

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

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

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

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

Review Report (2)

August 4, 2020

Product Submitted for Approval

Brand Name	Enaroy Tablets 2 mg, Enaroy Tablets 4 mg
Non-proprietary Name	Enarodustat
Applicant	Japan Tobacco Inc.
Date of Application	November 29, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

At the Expert Discussion, the expert advisors supported PMDA’s conclusion presented in Section "7.R.1 Efficacy" in the Review Report (1).

1.2 Safety

At the Expert Discussion, the expert advisors made the following comment and supported PMDA's conclusion presented in Section "7.R.2 Safety" in the Review Report (1).

- In accordance with PMDA's conclusion, the package insert for enarodustat should contain an alert for thromboembolism, cardiovascular events, retinal events, hypertension, and malignant tumors, as with the package insert for a previously approved HIF-PH inhibitor. Since no clinical studies followed up enarodustat-treated patients for several years or more, and there are no foreign data, it is important to continue to collect information via post-marketing surveillance, etc.

1.3 Indication and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Sections "7.R.3 Indication and clinical positioning" and "7.R.4 Dosage and administration" in the Review Report (1). The expert advisors made the following comment on dosage and administration.

- Hb levels tended to decrease after switching from a prior ESA to enarodustat in patients with non-dialysis-dependent CKD and PD patients. Attention should therefore be paid to changes in Hb in patients who have switched to enarodustat.

PMDA's conclusion:

The proposed indication of "renal anemia" is appropriate, and the Hb levels that should trigger treatment with enarodustat should be specified in the PRECAUTIONS CONCERNING INDICATION section of the package insert. The dosage and administration should be as follows (modified from the proposed wording). Precautionary statements regarding dose adjustment should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section. Taking account of the comment from the expert advisors, the IMPORTANT PRECAUTIONS section of the package insert should include a statement to the following effect:

Hb levels tended to decrease after switching from an ESA to enarodustat in patients with non-dialysis-dependent CKD and PD patients. Attention should therefore be paid to a possible decrease in Hb in patients who have switched to enarodustat.

Indication

Renal anemia

Precautions Concerning Indication

For patients naïve to erythropoiesis-stimulating agents:

Initiate treatment with enarodustat if the hemoglobin level is <11 g/dL in patients with chronic kidney disease not on dialysis and patients on peritoneal dialysis and <10 g/dL in patients on hemodialysis.

Dosage and Administration

1. Patients with chronic kidney disease not on dialysis and patients on peritoneal dialysis

   The usual adult starting dose of enarodustat is 2 mg administered orally once daily before a meal or at bedtime. Thereafter, the dose should be adjusted as appropriate according to the patient's condition. The maximum dose is 8 mg.

2. Patients on hemodialysis

   The usual adult starting dose of enarodustat is 4 mg administered orally once daily before a meal or at bedtime. Thereafter, the dose should be adjusted as appropriate according to the patient's condition. The maximum dose is 8 mg.

Precautions Concerning Dosage and Administration

- If dose adjustment is required, increase or decrease the dose by 1 level, using the following table as a guideline:

Dose level	1	2	3	4	5
Enarodustat dose	1 mg	2 mg	4 mg	6 mg	8 mg

● Do not increase the dose more frequently than once every 4 weeks.
● If the dose is interrupted, resume enarodustat at ≥1 dose level(s) lower.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.5 Post-marketing investigations" in the Review Report (1). The expert advisors made the following comments:

- (a) The new onset of malignant tumors, (b) the effect of enarodustat in patients after treatment of malignant tumors, and (c) the effect of enarodustat in patients with malignant tumors, should be investigated.
- HIF may affect the condition of patients with autosomal dominant polycystic kidney disease. The applicant should collect information on disease progression in patients with autosomal dominant polycystic kidney disease via post-marketing surveillance.

Based on the considerations in Section "7.R.5 Post-marketing investigations" in the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for enarodustat should include the safety and efficacy specifications presented in Table 92, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 93 and Table 94.

Table 92. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
· Thromboembolism · Hypertension	· Cardiovascular events (excluding thromboembolism) · Retinal haemorrhage · Malignant tumors · Disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD)	· None
Efficacy specification		
· None		

Table 93. 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 · Develop information materials to be distributed to healthcare professionals. · Develop information materials to be distributed to patients.

Table 94. Outline of specified use-results survey (draft)

Objective	To assess the safety of enarodustat in clinical practice (including long-term treatment).
Survey method	Central registry system
Population	Patients with renal anemia
Observation period	2 years
Planned sample size	1,500 patients (including ≥100 patients on peritoneal dialysis and ≥500 patients with chronic kidney disease not on dialysis)
Main survey items	Patient characteristics (primary disease causing chronic kidney disease, dialysis status, medical history, complications, etc.), use of enarodustat, prior treatment/concomitant medications, clinical laboratory tests, the incidence of adverse events

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

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

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

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

The new drug application data (CTD 5.3.5.1-2, CTD 5.3.5.1-4, CTD 5.3.5.2-4, CTD 5.3.5.2-5, CTD 5.3.5.2-6, CTD 5.3.5.2-7) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

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

Indication

Renal anemia

Dosage and Administration

1. Patients with chronic kidney disease not on dialysis and patients on peritoneal dialysis

   The usual adult starting dose of enarodustat is 2 mg administered orally once daily before a meal or at bedtime. Thereafter, the dose should be adjusted as appropriate according to the patient's condition. The maximum dose is 8 mg.

2. Patients on hemodialysis

   The usual adult starting dose of enarodustat is 4 mg administered orally once daily before a meal or at bedtime. Thereafter, the dose should be adjusted as appropriate according to the patient's condition. The maximum dose is 8 mg.

Approval Condition

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

Appendix

List of Abbreviations

ADPKD	Autosomal Dominant Polycystic Kidney Disease
Adverse drug reaction	Adverse event for which a causal relationship to study drug cannot be ruled out
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
BCRP	Breast cancer resistance protein
Caco-2 cells	Human colonic adenocarcinoma cells
CERA	Epoetin beta pegol (genetical recombination)
CHL	Chinese hamster lung
CKD	Chronic kidney disease
C_{max}	Maximum concentration
CQA	Critical quality attribute
CRP	C-reactive protein
CTD	Common technical document
CYP	Cytochrome P450
DA	Darbepoetin alfa (genetical recombination)
DMSO	Dimethyl sulfoxide
EC_{50}	Half maximal effective concentration
eGFR	Estimated glomerular filtration rate
enarodustat	Enarodustat
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
FAS	Full analysis set
Hb	Hemoglobin
HD	Hemodialysis
HEK293 cells	Human embryonic kidney cell line 293
hERG	Human ether-a-go-go related gene
HIF	Hypoxia inducible factor
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICH Q1E guideline	Guideline on Evaluation of Stability Data (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IR	Infrared absorption spectroscopy
Kim-1	Kidney injury molecule 1
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
MATE	Multidrug and toxin extrusion
M/E ratio	Myelocytic cell count/Erythroblastic cell count
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MS	Mass spectrometry
NADPH	Nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand White
OATP	Organic anion transporting polypeptide
PAI-1	Plasminogen activator inhibitor 1
PD	Peritoneal dialysis

P-gp	P-glycoprotein
PIC	α2 plasmin inhibitor-plasmin complex
PH	Prolyl hydroxylase
PMDA	Pharmaceuticals and Medical Devices Agency
Pooled data from 9 studies	Pooled data from a total of 9 studies (phase II and III studies) that served as the main efficacy and safety evaluation data
PPS	Per protocol set
PT	Prothrombin time
PTP	Press through packaging
QbD	Quality by Design
QTc	Corrected QT interval
QTcI	Individual-corrected QT interval
rHuEPO	Recombinant human erythropoietin
S2 cells	Mouse second portion of proximal tubule cells
SD	Sprague-Dawley
$t_{1/2}$	Elimination half life
The product	Enaroy tablets 2 mg, Enaroy tablets 4 mg
TIBC	Total iron binding capacity
t_{max}	Time to reach maximum concentration
TSAT	Transferrin saturation
UIBC	Unsaturated iron binding capacity
UVA	Ultraviolet A
UV-VIS	Ultraviolet-visible spectroscopy
VEGF	Vascular endothelial growth factor