

Real-world Safety of Enarodustat in Patients with Chronic Kidney Disease-associated Anemia

Interim Results of An Observational Post-marketing Surveillance Study in Japan

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ABSTRACT

Background: Enarodustat is a novel oral hypoxia-inducible factor-prolyl hydroxylase inhibitor for the treatment of anemia in patients with chronic kidney disease (CKD). It induces erythropoietin production and enhances iron utilization. Anemia is a common complication in patients with CKD, and effective management is crucial for improving their quality of life. This study aimed to evaluate the safety of enarodustat in patients with CKD and anemia under real-world clinical conditions in Japan.

Methods: This prospective, observational, post-marketing surveillance study to monitor the clinical safety of enarodustat has been ongoing since January 2022. Patients with anemia in CKD who received enarodustat for the first time were included. Safety evaluations included documented adverse drug reactions (ADRs). ADRs of special interest were thromboembolism, hypertension, cardiovascular disease, retinal hemorrhage, malignant tumor, and the progression of autosomal dominant polycystic kidney disease.

Results: Of 1636 patients in the safety analysis population, 1270 patients without dialysis, 108 with peritoneal dialysis, and 257 with hemodialysis were included. ADRs were observed in 10.76% of patients, with hypertension being the most common. Hypertension-related ADRs were also the most frequent ADRs of special interest. Enarodustat maintained hemoglobin within target ranges in patients across all CKD subgroups.

Conclusion: The safety profile of enarodustat was consistent with that shown in pre-

Key words : Enarodustat, Hypoxia-inducible factor-prolyl hydroxylase inhibitor, Chronic kidney disease, Anemia, Safety

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approval clinical trials. No new safety concerns were identified in this interim analysis; however, long-term observations are necessary, and continued vigilance is recommended for patients with pre-existing conditions or complications.

INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD), and its prevalence increases as the estimated glomerular filtration rate (eGFR) declines¹⁾. Hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors are a new class of agents for the treatment of anemia in patients with CKD. These HIF-PH inhibitors mimic physiological responses to hypoxia, leading to increased expression of HIF-target genes related to erythropoietin production and iron metabolism²⁾. Enarodustat (ENAROY®, Japan Tobacco Inc., Tokyo, Japan) is a novel oral HIF-PH inhibitor that became available for treating anemia in patients with CKD in 2020. Phase 3 clinical trials in Japan confirmed the efficacy and safety of enarodustat for treating anemia in patients with CKD who were not on dialysis (ND patients), patients receiving peritoneal dialysis (PD), and patients on hemodialysis (HD)³⁻⁵⁾.

Given the restricted eligibility of clinical trials, however, ongoing real-world monitoring is essential to assess the safety profile of enarodustat. In addition, the longest observation period of phase 3 trials was 52 weeks⁶⁾, and further evaluation of its long-term safety is warranted. To address these issues, we have been conducting a post-marketing surveillance (PMS) study of enarodustat since January 20, 2022, with the aim of assessing its safety under clinical conditions in Japan. Herein, we report the results of an interim analysis from January 2022 to September 2024.

MATERIALS AND METHODS

1 Study design

This was an interim analysis of a multicenter, open label, prospective, observational PMS study carried out in Japan to evaluate the safety of enarodustat in patients with anemia in CKD. This ongoing study is being conducted in compliance with the Good Post-Marketing Study Practice ordinance of the Ministry of Health, Labour and Welfare in Japan. The planned data collection period is from January 20, 2022 and will continue to be collected until 24 September 2027. The enrollment period was from February 7, 2022 to February 6, 2025. Data are being collected as anonymized information using an electronic data capture (EDC) system. The observation period is up to 2 years. The follow-up period for patients who discontinue enarodustat is 7 days. The data cutoff for the interim analysis was 24 September 2024. This observational PMS study did not require ethical approval by an institutional review board. The trial is registered at the Japan Registry of Clinical Trials <https://jrct.mhlw.go.jp/latest-detail/jRCT2031210549> (identifier: jRCT2031210549).

2 Patient enrollment

Patients with anemia in CKD who were receiving enarodustat for the first time and who provided consent either directly or through their legal representatives were enrolled in the study. The investigators registered patients within 14 days after the first treatment with enarodustat.

3 Enarodustat treatment

The recommended starting dose of enarodustat was 2 mg orally once daily for ND patients

or patients receiving PD and 4 mg orally once daily for patients receiving HD, in accordance with the dosage and administration approved in Japan. The dose may be adjusted according to the patient's condition, with a minimum dosage of 1 mg and maximum dosage of 8 mg once daily.

4 Safety assessment

Adverse drug reactions (ADRs) were assessed by the investigators and categorized by system organ class and preferred terminology according to the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) v27.0. ADRs of special interest included thromboembolism, hypertension, cardiovascular diseases excluding thromboembolism, retinal hemorrhage, malignant tumor, and autosomal dominant polycystic kidney disease (ADPKD) progression in patients with ADPKD, as defined in the risk management plan. Laboratory data were also measured, including hemoglobin (Hb), iron-related parameters, and values related to the assessment of ADRs. Hb increases have been associated with elevated cardiovascular risk in nephrology patients and the Japanese Society of Nephrology has issued recommendations for the appropriate use of HIF-PH inhibitors⁷⁾. ADRs were therefore also assessed in a subpopulation with rapid Hb increase, defined as increase of ≥ 2.0 g/dL within 4 weeks⁸⁾.

5 Statistical analysis

Considering potential dropouts, a target sample size of 1500 patients (at least 100 patients PD and 500 ND patients) was calculated, to ensure the detection of unknown ADRs occurring at a frequency of $\geq 0.3\%$ with a 95% probability. Continuous variables were summarized using descriptive statistics, including mean and standard deviation (SD) or median with 1st quartile and 3rd quartile. Discrete variables were summarized as frequencies and proportions. For patients who discontinued treatment, data were

treated as censored at the final observation. No imputation was made for missing data. We prepared a detailed statistical analysis plan before database finalization and locking. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

1 Patients

A total of 2261 patients from 346 sites were included. Of 1684 patients from whom survey forms were collected, 48 patients were excluded because of withdrawal of consent, no visits after the first treatment, unreliability of the data from the study site, and deviation from enrollment eligibility. Therefore, final safety analysis population comprised 1636 patients, including 1270 ND, 108 PD, and 257 HD patients, and one PD and HD patient. Dialysis status was determined at baseline. Long-term follow-up of at least 12 months was conducted in 570 patients (**Fig. 1**).

The patients' baseline characteristics, including age, primary disease in the safety analysis population, and pre-treatment medications are shown in **Table 1**. The reasons for switching from erythropoiesis stimulating agents were change of administration route (14.67%), insufficient efficacy (14.55%), and ADRs (0.12%).

2 Enarodustat treatment

The initial daily doses (mean $\pm$ SD) of enarodustat were 2.07 ± 0.43 mg in ND patients, 2.37 ± 0.84 mg in PD patients, and 3.77 ± 0.86 mg in HD patients. Enarodustat administration was initiated at a higher dose than recommended by the manufacturer in 46 ND, 19 PD, and six HD patients: one ND, one PD, and four HD patients received 6 mg/day, and one ND and two HD patients received 8 mg/day. During the observation period, the daily dose (mean $\pm$ SD) was 2.59 ± 1.03 mg in ND, 3.11 ± 1.47 mg in PD, and 4.32 ± 1.43 mg in HD patients, with respective actual

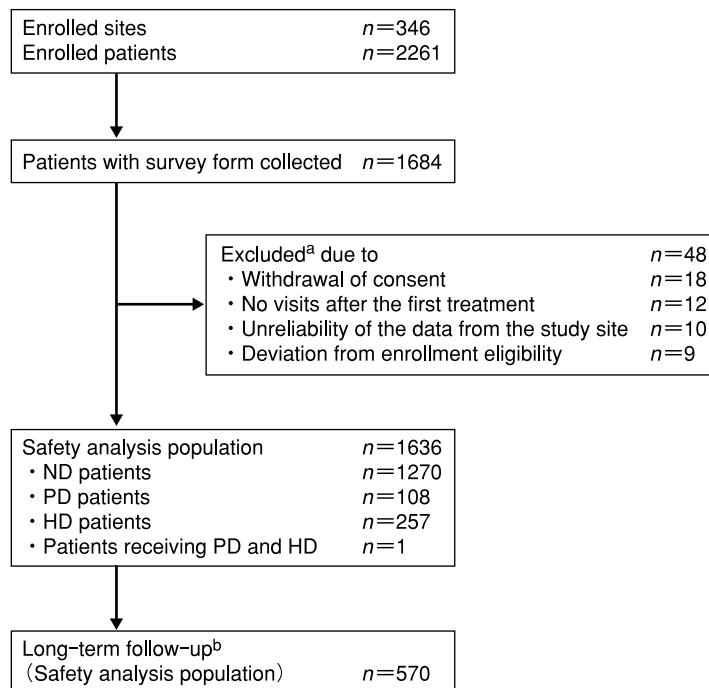


Fig. 1 Patient characteristics

ND: not on dialysis, PD: peritoneal dialysis, HD: hemodialysis

^aSome patients were excluded for multiple reasons, ^bobservation period ≥ 12 months, including periods of drug suspension

observation periods (median) of 184, 183, and 183 days. The actual observation period in the safety analysis population was 184 days. The maximum observation periods in this interim analysis were 732 days for ND, 638 days for PD, and 732 days for HD patients. Iron preparations and iron-containing phosphate binders were concomitantly administered in 19.13% and 7.09%, respectively, of ND patients, 9.26% and 33.33%, respectively, of PD patients, and 28.40% and 27.24%, respectively, of HD patients.

3 Safety summary of adverse drug reactions

Details of the ADRs that occurred in at least three patients in the overall population are presented in **Table 2**. Overall, ADRs occurred in 10.76% of patients. The most common ADRs (incidence $\geq 0.5\%$) were hypertension, iron deficiency anaemia, and haemoglobin increased.

Seven of 13 patients who experienced iron deficiency anaemia, received iron supplementation after enarodustat initiation. ADRs occurred in 10.63% of ND patients, with hypertension and iron deficiency anaemia being the most common. ADRs occurred in 7.41% of PD patients, mainly comprising hypertension, and in 12.84% of HD patients, including hypertension, iron deficiency anaemia, septic shock, nephrogenic anaemia, haemoglobin increased, and serum ferritin increased.

ADRs were observed in 10.18% of patients who received long-term enarodustat administration (≥ 12 months). The major ADRs in this population were hypertension (2.63%), protein urine present (1.05%), iron deficiency anaemia (0.88%), constipation (0.70%), blood albumin decreased (0.70%), haemoglobin increased

Table 1 Demographic characteristics (safety analysis population)

Characteristic		Overall <i>n</i> = 1636	ND <i>n</i> = 1270	PD <i>n</i> = 108	HD <i>n</i> = 257
		<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Sex	Male	928 (56.72)	700 (55.12)	67 (62.04)	160 (62.26)
	Female	708 (43.28)	570 (44.88)	41 (37.96)	97 (37.74)
Age (years)	mean ± SD	74.1 ± 13.4	75.6 ± 13.0	63.2 ± 14.0	71.3 ± 12.8
Body weight (kg)	mean ± SD	57.21 ± 13.23	57.20 ± 12.85	62.70 ± 14.86	54.96 ± 13.47
Primary disease of CKD (including duplicates) ^a	Nephrosclerosis	555 (33.92)	487 (38.35)	26 (24.07)	42 (16.34)
	Diabetic nephropathy	388 (23.72)	261 (20.55)	33 (30.56)	93 (36.19)
	Chronic glomerulonephritis (including IgA nephropathy)	275 (16.81)	182 (14.33)	32 (29.63)	61 (23.74)
	Polycystic kidney disease	32 (1.96)	23 (1.81)	3 (2.78)	6 (2.33)
	Autosomal dominant	23 (1.41)	17 (1.34)	3 (2.78)	3 (1.17)
	Autosomal recessive	1 (0.06)	0 (0.00)	0 (0.00)	1 (0.39)
	Not determined	8 (0.49)	6 (0.47)	0 (0.00)	2 (0.78)
	Others	128 (7.82)	98 (7.72)	8 (7.41)	22 (8.56)
	Unknown	302 (18.46)	256 (20.16)	11 (10.19)	35 (13.62)
Medical history (including duplicates) ^a	No	1085 (66.32)	869 (68.43)	65 (60.19)	150 (58.37)
	Yes	551 (33.68)	401 (31.57)	43 (39.81)	107 (41.63)
	Thromboembolism	118 (7.21)	82 (6.46)	12 (11.11)	24 (9.34)
	Hypertension	76 (4.65)	58 (4.57)	7 (6.48)	11 (4.28)
	Cardiovascular disease (excluding thromboembolism)	91 (5.56)	66 (5.20)	8 (7.41)	17 (6.61)
	Retinal haemorrhage	3 (0.18)	2 (0.16)	1 (0.93)	0 (0.00)
	Malignant tumor	109 (6.66)	86 (6.77)	5 (4.63)	18 (7.00)
	Diabetes	34 (2.08)	18 (1.42)	7 (6.48)	9 (3.50)
	Dyslipidemia	7 (0.43)	7 (0.55)	0 (0.00)	0 (0.00)
	Eye disorders	33 (2.02)	22 (1.73)	2 (1.85)	9 (3.50)
	Others	254 (15.53)	177 (13.94)	17 (15.74)	60 (23.35)
Complications (including duplicates) ^a	No	110 (6.72)	83 (6.54)	9 (8.33)	18 (7.00)
	Yes	1526 (93.28)	1187 (93.46)	99 (91.67)	239 (93.00)
	Hepatic disease	27 (1.65)	22 (1.73)	0 (0.00)	5 (1.95)
	Thromboembolism	156 (9.54)	98 (7.72)	4 (3.70)	54 (21.01)
	Hypertension	1280 (78.24)	989 (77.87)	92 (85.19)	198 (77.04)
	Cardiovascular disease (excluding thromboembolism)	399 (24.39)	291 (22.91)	18 (16.67)	90 (35.02)
	Retinal haemorrhage	3 (0.18)	2 (0.16)	1 (0.93)	0 (0.00)
	Malignant tumor	34 (2.08)	27 (2.13)	0 (0.00)	7 (2.72)
	Diabetes mellitus	471 (28.79)	344 (27.09)	30 (27.78)	96 (37.35)
	Dyslipidemia	584 (35.70)	469 (36.93)	48 (44.44)	67 (26.07)
	Cardiac failure	217 (13.26)	183 (14.41)	9 (8.33)	25 (9.73)
	Eye disorders	49 (3.00)	29 (2.28)	3 (2.78)	17 (6.61)
	Others	1068 (65.28)	830 (65.35)	68 (62.96)	169 (65.76)

Table 1 Demographic characteristics (safety analysis population) (continued)

Characteristic		Overall <i>n</i> = 1636	ND <i>n</i> = 1270	PD <i>n</i> = 108	HD <i>n</i> = 257
		<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Previous anemia medication ^b (including duplicates) ^a	No	960 (58.68)	882 (69.45)	30 (27.78)	48 (18.68)
	Yes	676 (41.32)	388 (30.55)	78 (72.22)	209 (81.32)
	ESA	479 (29.28)	255 (20.08)	49 (45.37)	174 (67.70)
	HIF-PH inhibitor	196 (11.98)	132 (10.39)	29 (26.85)	34 (13.23)
	Other	3 (0.18)	2 (0.16)	0 (0.00)	1 (0.39)
Hb level (g/dL)	< 9.0	225 (13.75)	163 (12.83)	14 (12.96)	47 (18.29)
	9.0 to < 10.0	483 (29.52)	396 (31.18)	25 (23.15)	62 (24.12)
	10.0 to < 11.0	528 (32.27)	423 (33.31)	34 (31.48)	71 (27.63)
	11.0 to < 12.0	255 (15.59)	168 (13.23)	23 (21.30)	64 (24.90)
	12.0 to < 13.0	91 (5.56)	79 (6.22)	7 (6.48)	5 (1.95)
	≥ 13.0	38 (2.32)	32 (2.52)	4 (3.70)	2 (0.78)
	Unknown	16 (0.98)	9 (0.71)	1 (0.93)	6 (2.33)
Serum ferritin level (ng/mL)	< 50.0	170 (10.39)	142 (11.18)	4 (3.70)	24 (9.34)
	50.0 to < 100.0	219 (13.39)	164 (12.91)	9 (8.33)	46 (17.90)
	100.0 to < 300.0	526 (32.15)	406 (31.97)	40 (37.04)	80 (31.13)
	≥ 300.0	197 (12.04)	141 (11.10)	29 (26.85)	26 (10.12)
	Unknown	524 (32.03)	417 (32.83)	26 (24.07)	81 (31.52)
TSAT (%)	< 20.0	185 (11.31)	132 (10.39)	6 (5.56)	47 (18.29)
	≥ 20.0	825 (50.43)	633 (49.84)	74 (68.52)	117 (45.53)
	Unknown	626 (38.26)	505 (39.76)	28 (25.93)	93 (36.19)
CRP level (mg/dL)	< 0.3	696 (42.54)	552 (43.46)	53 (49.07)	91 (35.41)
	≥ 0.3	327 (19.99)	214 (16.85)	28 (25.93)	84 (32.68)
	Unknown	613 (37.47)	504 (39.69)	27 (25.00)	82 (31.91)
eGFR ^c (mL/min/1.73 m ²)	< 15.0	729 (44.56)	378 (29.76)	105 (97.22)	245 (95.33)
	15.0 to < 30.0	496 (30.32)	491 (38.66)	2 (1.85)	3 (1.17)
	30.0 to < 45.0	242 (14.79)	242 (19.06)	0 (0.00)	0 (0.00)
	45.0 to < 60.0	104 (6.36)	104 (8.19)	0 (0.00)	0 (0.00)
	60.0 to < 90.0	37 (2.26)	37 (2.91)	0 (0.00)	0 (0.00)
	≥ 90.0	2 (0.12)	2 (0.16)	0 (0.00)	0 (0.00)
	Unknown	26 (1.59)	16 (1.26)	1 (0.93)	9 (3.50)

^aSome patients had multiple choices.

^bMedications administered within 4 weeks of enarodustat initiation.

^cMale: $\text{eGFR} = 194 \times \text{serum creatinine level (mg/dL)}^{-1.094} \times \text{age (years)}^{-0.287}$; female: $\text{eGFR} = 194 \times \text{serum creatinine level (mg/dL)}^{-1.094} \times \text{age (years)}^{-0.287} \times 0.739$

CKD: chronic kidney disease, CRP: c-reactive protein, eGFR: estimated glomerular filtration rate, ESA: erythropoiesis stimulating agent, Hb: hemoglobin, HD: hemodialysis, HIF-PH: hypoxia-inducible factor-prolyl hydroxylase, IgA: immunoglobulin A, ND: not on dialysis, PD: peritoneal dialysis, SD: standard deviation, TSAT: transferrin saturation

(0.70%), and cerebral infarction (0.53%), oedema peripheral (0.53%), blood pressure increased (0.53%), and serum ferritin increased (0.53%). ADRs were reported in two patients at

52–76 weeks and in three patients at ≥ 76 weeks. Observed ADRs were myoclonus, pulmonary infarction, diabetes mellitus, cardiac failure congestive, constipation, and protein urine present.

Table 2 Safety summary of adverse drug reactions (safety analysis population)

	Overall <i>n</i> = 1636 <i>n</i> (%)	ND <i>n</i> = 1270 <i>n</i> (%)	PD <i>n</i> = 108 <i>n</i> (%)	HD <i>n</i> = 257 <i>n</i> (%)
Number of patients with ADRs	176 (10.76)	135 (10.63)	8 (7.41)	33 (12.84)
Blood and lymphatic system disorders				
Iron deficiency anaemia	13 (0.79)	10 (0.79)	0 (0.00)	3 (1.17)
Nephrogenic anaemia	5 (0.31)	3 (0.24)	0 (0.00)	2 (0.78)
Metabolism and nutrition disorders				
Hyperuricaemia	5 (0.31)	5 (0.39)	0 (0.00)	0 (0.00)
Decreased appetite	3 (0.18)	3 (0.24)	0 (0.00)	0 (0.00)
Nervous system disorders				
Cerebral infarction	4 (0.24)	3 (0.24)	0 (0.00)	1 (0.39)
Dizziness	4 (0.24)	4 (0.31)	0 (0.00)	0 (0.00)
Cardiac disorders				
Cardiac failure chronic	3 (0.18)	3 (0.24)	0 (0.00)	0 (0.00)
Cardiac failure congestive	3 (0.18)	3 (0.24)	0 (0.00)	0 (0.00)
Vascular disorders				
Hypertension	42 (2.57)	33 (2.60)	2 (1.85)	7 (2.72)
Gastrointestinal disorders				
Constipation	7 (0.43)	6 (0.47)	1 (0.93)	0 (0.00)
Nausea	5 (0.31)	3 (0.24)	1 (0.93)	1 (0.39)
Diarrhea	4 (0.24)	3 (0.24)	0 (0.00)	1 (0.39)
Hepatobiliary disorders				
Hepatic function abnormal	3 (0.18)	3 (0.24)	0 (0.00)	0 (0.00)
Renal and urinary disorders				
Renal impairment	5 (0.31)	5 (0.39)	0 (0.00)	0 (0.00)
Chronic kidney disease	4 (0.24)	4 (0.31)	0 (0.00)	0 (0.00)
General disorders and administration site conditions				
Oedema peripheral	4 (0.24)	4 (0.31)	0 (0.00)	0 (0.00)
Malaise	3 (0.18)	3 (0.24)	0 (0.00)	0 (0.00)
Investigations				
Haemoglobin increased	9 (0.55)	6 (0.47)	1 (0.93)	2 (0.78)
Protein urine present	6 (0.37)	6 (0.47)	0 (0.00)	0 (0.00)
Blood albumin decreased	5 (0.31)	5 (0.39)	0 (0.00)	0 (0.00)
Blood pressure increased	4 (0.24)	3 (0.24)	1 (0.93)	0 (0.00)
C-reactive protein increased	4 (0.24)	3 (0.24)	0 (0.00)	1 (0.39)
Serum ferritin increased	4 (0.24)	2 (0.16)	0 (0.00)	2 (0.78)
Low density lipoprotein decreased	3 (0.18)	3 (0.24)	0 (0.00)	0 (0.00)
Transferrin saturation increased	3 (0.18)	2 (0.16)	0 (0.00)	1 (0.39)

MedDRA ver. 27.0

ADR: adverse drug reaction, CRP: C-reactive protein, HD: hemodialysis, ND: not on dialysis, PD: peritoneal dialysis, MedDRA: Medical Dictionary for Regulatory Activities

Thirty of 1636 patients (1.83%) showed increased Hb levels >2.0 g/dL within 4 weeks of initiating enarodustat, of whom 16.67% devel-

oped ADRs, including increased Hb, cardiac failure chronic, chronic obstructive pulmonary disease, nephrogenic anaemia, shunt malfunction,

Table 3 Adverse drug reactions of special interest (safety analysis population)

Type of ADRs	Overall <i>n</i> = 1636 <i>n</i> (%)		ND <i>n</i> = 1270 <i>n</i> (%)		PD <i>n</i> = 108 <i>n</i> (%)		HD <i>n</i> = 257 <i>n</i> (%)	
	Total	Serious	Total	Serious	Total	Serious	Total	Serious
Thromboembolism								
Cerebral infarction	4 (0.24)	4 (0.24)	3 (0.24)	3 (0.24)	0	0	1 (0.39)	1 (0.39)
Venous thrombosis limb	2 (0.12)	1 (0.06)	2 (0.16)	1 (0.08)	0	0	0	0
Carotid arterial embolus	1 (0.06)	1 (0.06)	0	0	0	0	1 (0.39)	1 (0.39)
Amaurosis	1 (0.06)	0	1 (0.08)	0	0	0	0	0
Atrial thrombosis	1 (0.06)	1 (0.06)	0	0	0	0	1 (0.39)	1 (0.39)
Cardiac ventricular thrombosis	1 (0.06)	1 (0.06)	0	0	0	0	1 (0.39)	1 (0.39)
Thrombosis	1 (0.06)	0	1 (0.08)	0	0	0	0	0
Arterial occlusive disease	1 (0.06)	1 (0.06)	0	0	0	0	1 (0.39)	1 (0.39)
Iliac artery occlusion	1 (0.06) ^a	1 (0.06) ^a	0	0	0	0	1 (0.39)	1 (0.39)
Pulmonary infarction	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Renal infarct	1 (0.06) ^a	1 (0.06) ^a	0	0	0	0	1 (0.39)	1 (0.39)
Shunt occlusion	1 (0.06)	0	1 (0.08)	0	0	0	0	0
Shunt thrombosis	1 (0.06)	1 (0.06)	0	0	0	0	1 (0.39)	1 (0.39)
Hypertension								
Hypertension	44 (2.69) ^{b,c}	3 (0.18)	34 (2.68)	3 (0.24)	3 (2.78)	0	7 (2.72)	0
Blood pressure increased	4 (0.24) ^c	0	3 (0.24)	0	1 (0.93)	0	0	0
Essential hypertension	2 (0.12)	0	2 (0.16)	0	0	0	0	0
Dialysis-induced hypertension	1 (0.06)	0	0	0	0	0	1 (0.39)	0
Cardiovascular disease (excluding thromboembolism)								
Cardiac failure congestive	3 (0.18) ^d	3 (0.18) ^d	3 (0.24)	3 (0.24)	0	0	0	0
Cardiac failure chronic	3 (0.18)	1 (0.06)	3 (0.24)	1 (0.08)	0	0	0	0
Cerebral hemorrhage	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Angina pectoris	1 (0.06)	0	0	0	0	0	1 (0.39)	0
Aortic valve stenosis	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Cardiomegaly	1 (0.06)	0	1 (0.08)	0	0	0	0	0
Myocardial ischemia	1 (0.06) ^d	1 (0.06) ^d	1 (0.08)	1 (0.08)	0	0	0	0
Coronary artery disease	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Retinal haemorrhage								
Retinal haemorrhage	1 (0.06)	0	1 (0.08)	0	0	0	0	0

pseudomonal bacteraemia, pyrexia, gastric cancer, metastases to lymph nodes, metastases to liver, body tinea, eczema asteatotic, decreased appetite, and cancer pain. Enarodustat treatment was discontinued in 6.36% of patients because of the onset of ADRs.

4 Adverse drug reactions of special interest

The ADRs of special interest in this study are summarized in **Table 3**. Thromboembolism-related ADRs were observed in 16/1636 patients (0.98%). Serious ADRs, including cerebral infar-

tion, venous thrombosis limb, carotid arterial embolus, atrial thrombosis, cardiac ventricular thrombosis, arterial occlusive disease, iliac artery occlusion, pulmonary infarction, renal infarct, and shunt thrombosis were observed in 12/1636 patients (0.73%). Two patients died of pulmonary infarction and two died of arterial occlusive disease. Seven patients had prior or current thromboembolism. In 16 patients, the Hb level did not increase by >2.0 g/dL within 4 weeks. Seven patients received concomitant iron

Table 3 Adverse drug reactions of special interest (safety analysis population) (continued)

Type of ADRs	Overall <i>n</i> = 1636 <i>n</i> (%)		ND <i>n</i> = 1270 <i>n</i> (%)		PD <i>n</i> = 108 <i>n</i> (%)		HD <i>n</i> = 257 <i>n</i> (%)	
	Total	Serious	Total	Serious	Total	Serious	Total	Serious
Malignant tumor								
Gastric cancer	2 (0.12)	2 (0.12)	2 (0.16)	2 (0.16)	0	0	0	0
Bladder cancer recurrent	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Lung adenocarcinoma stage IV	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Metastases to liver	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Lymph node metastases	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Rectal cancer	1 (0.06)	1 (0.06)	1 (0.08)	1 (0.08)	0	0	0	0
Disease progression in patients with ADPKD ^a								
Renal cyst ruptured	1 (4.35)	1 (4.35)	1 (5.88)	1 (5.88)	0	0	0	0

MedDRA ver. 27.0

^aOne patient had iliac occlusion and renal infarction.

^bTwo patients showed multiple occurrences.

^cOne patient had hypertension and increased blood pressure.

^dOne patient had congestive heart failure and myocardial ischemia.

^eOf 1636 patients included in the safety analysis population, 23 patients with ADPKD as the primary chronic kidney disease were used as the denominator (ND : 17, PD : 3, HD : 3).

ADPKD: autosomal dominant polycystic kidney disease, ADR: adverse drug reaction, HD: hemodialysis, ND: not on dialysis, PD: peritoneal dialysis, MedDRA: Medical Dictionary for Regulatory Activities

preparations/iron-containing phosphate binders initiated prior to start of enarodustat or at least 1 month before the day of thromboembolism onset. Nine patients had no concomitant use of these drugs during the observation period. Among the 10 of the 16 patients with the most recent iron parameters, four had serum ferritin levels < 100 ng/mL with transferrin saturation (TSAT) ≤ 20%, and all other patients exhibited serum ferritin ≥ 100 ng/mL or TSAT ≥ 20%.

Hypertension-related ADRs were observed in 48/1636 patients (2.93%), including serious ADRs in 3/1636 patients (0.18%), all of whom were ND patients. Of the 48 patients, 46 patients had prior or current hypertension.

ADRs related to cardiovascular disease (excluding thromboembolism) were observed in 11/1636 patients (0.67%), including seven patients (0.43%) with serious ADRs. Five of the 11 patients had prior or current cardiovascular

disease (excluding thromboembolism). Four of the six patients with cardiac failure experienced worsening of their cardiac failure, and one patient died from cardiac failure chronic.

One ND patient (0.06%) with no relevant medical history or complications experienced an ADR related to retinal haemorrhage.

Malignant tumor-related ADRs were observed in five patients (0.31%), including two patients (0.12%) with gastric cancer, and one patient (0.06%) each with bladder cancer recurrent, lung adenocarcinoma stage IV, liver metastases, lymph node metastases, and rectal cancer. One patient died of gastric cancer, with liver and metastases lymph nodes. Four patients had prior or current malignant tumors.

Among 23 patients with ADPKD, one ND patient with a history of treatment with erythropoiesis-stimulating agents (4.35%) experienced a renal cyst ruptured that was considered a seri-

ous ADR related to disease progression. The cyst ruptured 238 days after the initiation of enarodustat, and other suspected contributing factors included polycystic kidney enlargement.

5 Laboratory test values

Laboratory test values, including Hb level, serum ferritin level, and TSAT, were assessed at baseline and at week 52 following enarodustat initiation, stratified by dialysis status (ND, PD, and HD) (**Fig. 2**). The mean Hb level increased from 10.20 to 11.30 g/dL in ND patients, from 10.42 to 11.31 g/dL in PD patients, and from 10.13 to 11.05 g/dL in HD patients. The median serum ferritin level decreased from 137.00 to 103.70 ng/mL in ND patients, from 243.00 to 146.25 ng/mL in PD patients, and from 131.95 to 99.40 ng/mL in HD patients. The mean TSAT shifted from 30.54 to 31.54% in ND patients, from 37.12 to 30.11% in PD patients, and from 28.72 to 34.33% in HD patients. The Hb level, serum ferritin level, and TSAT showed similar time-course changes after administration in ND patients despite the concomitant use or lack of iron preparations or iron-containing phosphate binders (**Figs. 3 and 4**). Regardless of eGFR classification at enarodustat initiation, the Hb level ranged approximately 10 to 12 g/dL after administration in ND patients (**Fig. 5**).

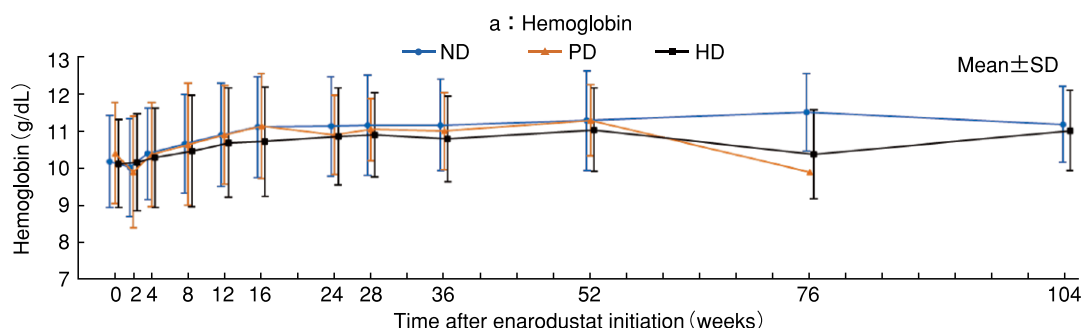
DISCUSSION

In this study, enarodustat was administered to patients with CKD and anemia, and its safety was assessed under real-world clinical conditions in Japan. ADRs were observed in 10.76% of all patients, including 10.63% of ND patients, 7.41% of PD patients, and 12.84% of HD patients. The mean daily dose of enarodustat during the observation period was similar to that used in previous clinical trials^{3-6,9}. The incidences of ADRs were similar across renal dialysis category groups, and there was no obvious

difference in the incidence of ADRs in patients treated for longer than or less than 12 months, which was consistent with previous clinical trials⁶.

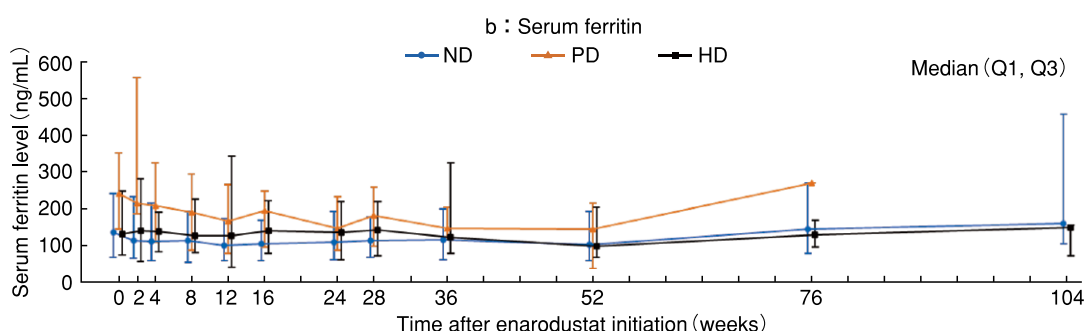
Thromboembolism is an important identified risk of enarodustat. Seven of the 16 patients (43.75%) with thromboembolism-related ADRs had prior or current thromboembolism. Continued vigilance is thus required for these patients, as outlined in the recommendations for HIF-PH inhibitors^{7,10}. Administration of HIF-PH inhibitors in patients with iron deficiency is associated with an increased risk of thromboembolism, and prompt iron supplementation is therefore recommended for patients with a serum ferritin concentration <100 ng/mL or a TSAT <20%^{7,10}. Although variations in iron parameters were observed among patients, the relationship between iron status and the development of thromboembolism could not be fully evaluated due to the limited sample size. The present study findings show that iron supplementation might be inadequate in some patients, and that iron deficiency might be overlooked even if the Hb level was managed, given that laboratory data were available in only 7 of the 11 cases. This suggests the need for continuous assessment of iron parameters and appropriate iron management.

The incidence of hypertension-related adverse events (AEs) tended to be higher than that of other AEs in the present study and previous clinical trials^{3,4,6}. Among the 48 patients exhibiting hypertension-related AEs, 46 patients had a history of hypertension or related complications. While this suggests a higher inclusion of such patients in the present study compared with previous clinical trials, no statistical tests were performed. The prevalence of hypertension was reportedly high in patients with CKD¹¹. Anemia improvement may lead to hypertension via various mechanisms¹², and enarodustat, as an HIF-



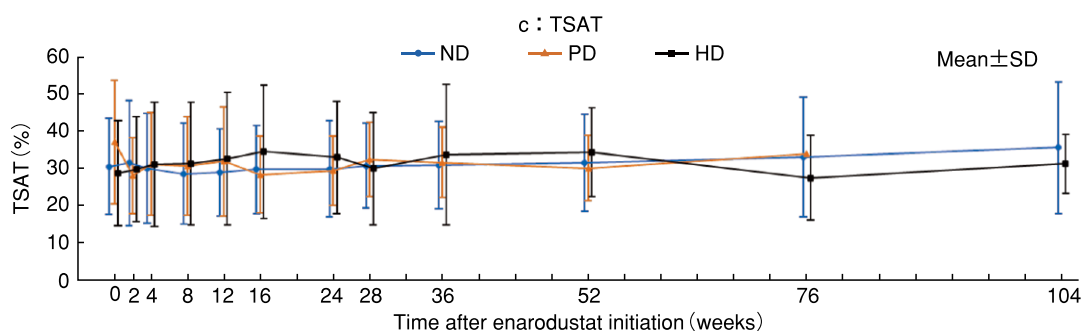
Number of patients

ND	1261	210	570	724	747	544	569	362	400	278	43	29
PD	107	32	73	87	86	53	42	21	26	20	1	0
HD	251	180	214	218	200	156	123	77	73	61	10	8



Number of patients

ND	853	89	351	447	473	366	393	267	267	195	27	19
PD	82	14	47	59	63	46	34	18	23	18	1	0
HD	176	55	92	115	96	88	89	53	48	32	8	6



Number of patients

ND	765	76	320	413	451	355	360	244	251	178	29	19
PD	80	13	45	58	63	43	34	17	23	18	1	0
HD	164	55	94	105	97	80	76	43	40	33	8	6

Fig. 2 Time courses of Hb levels (a), serum ferritin levels (b), and TSAT (c) over time (safety analysis population)

Data are presented as the mean $\pm$ SD for Hb levels and TSAT, and median (Q1, Q3) for serum ferritin levels.

Hb: hemoglobin, TSAT: transferrin saturation, ND: not on dialysis, PD: peritoneal dialysis, HD: hemodialysis, SD: standard deviation, Q: quartile

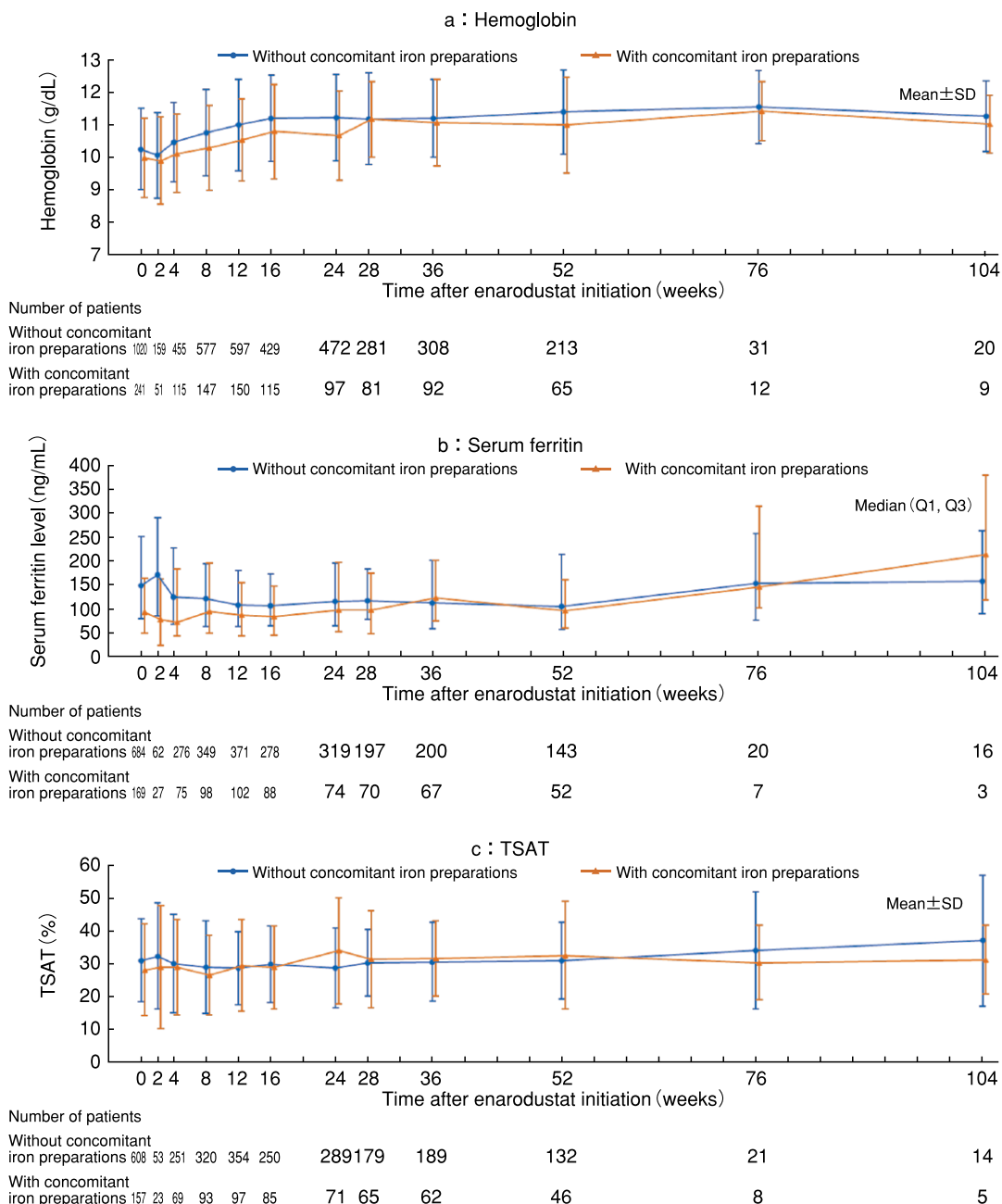


Fig. 3 Time courses of Hb levels (a), serum ferritin levels (b), and TSAT (c) over time in patients with chronic kidney disease not on dialysis with and without concomitant iron preparations (safety analysis population)

Data are presented as the mean $\pm$ SD for Hb levels and TSAT, and median (Q1, Q3) for serum ferritin levels.

Hb: hemoglobin, TSAT: transferrin saturation, SD: standard deviation, Q: quartile

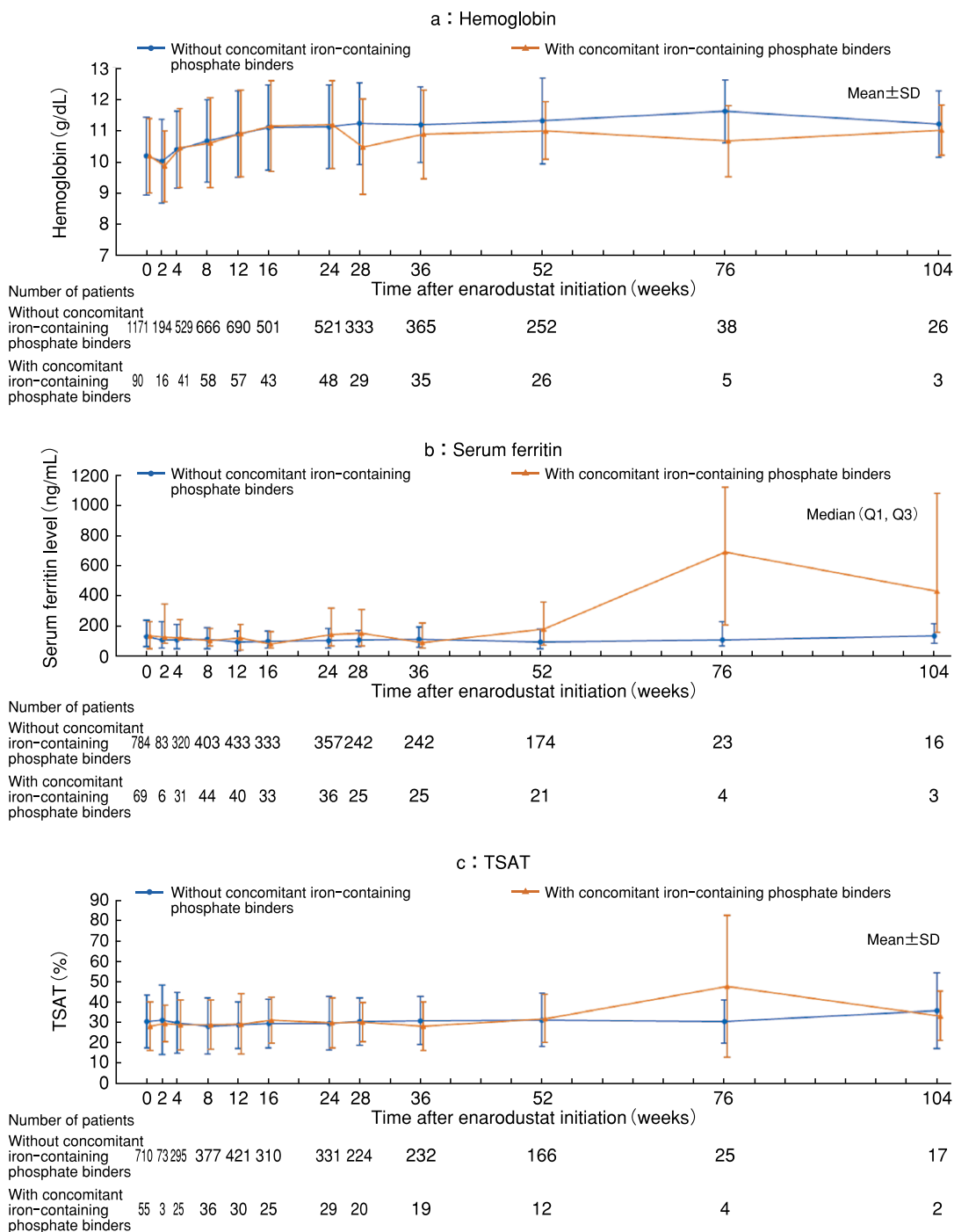
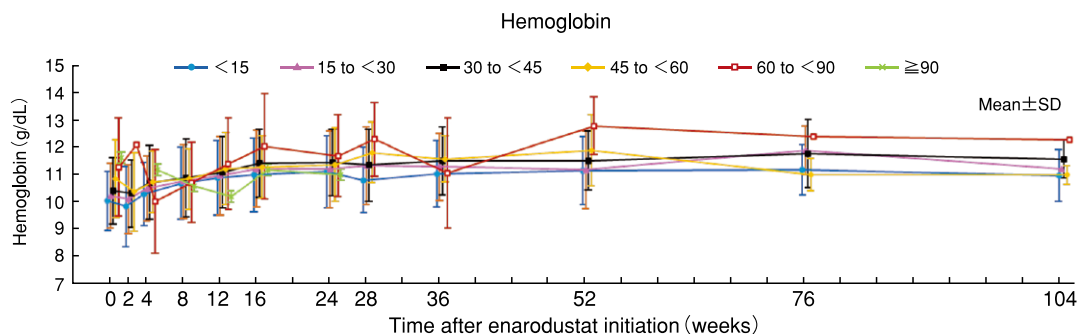


Fig. 4 Time courses of Hb levels (a), serum ferritin levels (b), and TSAT (c) over time in patients with chronic kidney disease not on dialysis and with and without concomitant iron-containing phosphate binders (safety analysis population)

Data are presented as the mean $\pm$ SD for Hb levels and TSAT, and median (Q1, Q3) for serum ferritin level.

Hb: hemoglobin, TSAT: transferrin saturation, SD: standard deviation, Q: quartile



Number of patients

eGFR

<15	378	56	183	228	229	177	180	106	121	70	7	6
15 to <30	491	76	214	289	288	204	230	133	163	113	11	8
30 to <45	242	55	107	139	128	110	104	69	77	54	18	10
45 to <60	104	18	51	49	69	36	38	35	29	24	6	4
60 to <90	37	1	10	11	24	11	11	16	8	15	1	1
≥90	2	0	1	1	1	1	1	0	0	0	0	0

Fig. 5 Time course of Hb levels over time by subgroup of eGFR at enarodustat treatment initiation in patients with chronic kidney disease not on dialysis (safety analysis population)

Data are presented as mean ± SD.

Hb: hemoglobin, eGFR: estimated glomerular filtration rate, SD: standard deviation

PH inhibitor, can increase hematocrit, which may contribute to elevated blood pressure¹²⁾. The safe use of enarodustat thus requires regular blood pressure monitoring and careful management.

Five of the 11 patients who developed cardiovascular ADRs (excluding thromboembolism) had a history of cardiovascular disease or its associated complications. The high baseline cardiovascular disease risk in patients with CKD^{13,14)} indicates the need for close monitoring in these patients.

The angiogenic effects of vascular endothelial growth factor (VEGF) are a potential risk for HIF-PH inhibitors, because HIF stabilization upregulates numerous genes associated with angiogenesis, including VEGF¹⁵⁾. Among the patients exhibiting ADRs related to retinal haemorrhage, the incidence of retinal haemorrhage was lower than that in previous clinical trials^{3,4,6)}; however, the small sample size in this study indicates the need for continuous monitoring.

HIF is involved in tumor growth, mediated by VEGF^{15,16)}. Most patients with malignant tumor-related ADRs had a history of malignancy or related complications. The short median observation period of 184 days means that the potential risk of malignancy progression or metastasis cannot be excluded.

Nonclinical studies have suggested a relationship between HIF stabilization and ADPKD progression. As renal cysts grow, they compress the nephrons and blood vessels in the kidney, causing local hypoxia, leading to an increase in HIF-1 α in cyst-forming cells¹⁷⁾. Additionally, the administration of HIF-PH inhibitors exacerbated cysts in Pkd1-knockout mice, as a disease model of ADPKD¹⁸⁾. Therefore, we evaluated ADRs related to disease progression in patients with ADPKD in this study; however, the assessment was inadequate because of the small sample size, and continued long-term observation will be necessary.

Clinical laboratory values, such as Hb and

serum ferritin levels and TSAT, tended to be maintained within the guideline-recommended ranges during the observation period in all CKD subgroups. Hb levels were maintained within the recommended range, without excessive increases, regardless of the concomitant use/non-use of iron preparations or iron-containing phosphate binders, suggesting that enarodustat is safe in this respect. Hb levels also tended to remain within recommended values in ND patients, regardless of the CKD stage at enarodustat initiation. However, the statistical interpretation of this result was limited because of the very small number of patients in the $\text{eGFR} \geq 90$ group and the heterogeneity of observation periods across in individual cases.

The safety profile of enarodustat under real-world conditions did not greatly differ from that reported in previous clinical trials^{3,4,6}, and no new safety concerns were identified from the interim results of this study.

The present study had several limitations. First, because this was an observational PMS study, the reporting of ADRs may be biased compared with controlled clinical trials. Second, like most PMS studies, this study lacked a control group, making it difficult to estimate relative risks and to compare the incidence of ADRs with similar or conventional drugs, thus hindering the accurate evaluation of specific ADR risks. Third, this study was conducted in a wide range of facilities across Japan under routine clinical practice, suggesting that its results are likely to reflect real-world clinical settings. However, because the study was conducted in Japan, caution is needed when generalizing the results to CKD populations in healthcare systems of other countries. Finally, the limited follow-up duration indicates the need for continued long-term observation.

CONCLUSION

This interim analysis of a PMS study demonstrated that enarodustat has a good safety profile in patients with CKD and anemia under clinical conditions. Although no new safety concerns were identified in this interim analysis, we plan to complete this surveillance for a 2-year observation period to evaluate the safety of long-term enarodustat treatment.

CONFLICT OF INTEREST

Suzuki S, Hashimoto T, Okuda Y, Goto Y and Yamada R are employees of Japan Tobacco Inc. Maruyama A, Ito S, Shigeta M, Horikawa E and Nishino N are employees of Torii Pharmaceutical Co., Ltd.

FUNDING

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DATA AVAILABILITY

Sharing of the anonymized data of individual participants from this study with third parties, excluding health authorities, is prohibited in the contract between study sites and Japan Tobacco Inc./Torii Pharmaceutical Co., Ltd.

COMPLIANCE WITH ETHICAL STANDARDS INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study. Patient data were collected anonymously.

ETHICAL APPROVAL

This was an observational post-marketing surveillance study and was conducted in accordance with the Good Post-Marketing Study Practice (GPSP) of the Ministry of Health, Labour and Welfare in Japan. Ethical approval by an institutional review board was not mandatory for PMS.

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