Safety of Daprodustat for the Treatment of Chronic Kidney Disease Anemia

An Interim Analysis of a Multicenter Postmarketing Surveillance Study in Japan

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ABSTRACT

Background: Anemia is common in patients with chronic kidney disease (CKD) and negatively impacts outcomes. The efficacy and safety of daprodustat has been demonstrated in global and Japanese clinical trials, and daprodustat has been clinically used for the treatment of CKD anemia in Japan since 2020.

Objective: This interim analysis of an ongoing multicenter, prospective postmarketing surveillance study evaluated the safety of daprodustat in routine clinical practice in Japan.

Methods: Patients in Japan who initiated daprodustat between September 2020 and July 2022 were registered by electronic data capture. The observation period was 52 weeks from the start of daprodustat treatment, or until discontinuation, to assess overall safety. Patients were followed for an additional 52 weeks after the observation period (or daprodustat withdrawal) to assess cancer-related events.

Results: Of 877 patients in the safety analysis set, mean (SD) age was 75.3 (12.3) years and 91.8% received prior treatment for CKD anemia. Adverse drug reactions (ADRs) were reported in 5.9% of patients (4.1% not undergoing dialysis; 7.4% undergo-

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ing peritoneal dialysis; 8.3% undergoing hemodialysis) and severe ADRs occurred in 15 patients (1.7%) treated with daprodustat for up to 52 weeks. Adverse drug reactions related to thromboembolism, hypertension, CV (cardiovascular) events, cancer, progression of ADPKD (autosomal dominant polycystic kidney disease), and retinal hemorrhage were each reported in less than 1% of patients overall and in the subgroups based on dialysis status.

Conclusions: In this interim analysis, no new safety signals were identified for daprodustat in the real-world setting in Japan. Additional observation and follow-up of cancer-related events is ongoing.

INTRODUCTION

An estimated 1 in 8 adults in Japan have CKD, with highest prevalence among older adults[1]. According to the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR), at the end of 2021, the number of patients in Japan on chronic dialysis was 349,700, or 2786 per million population[2]. The proportion of patients undergoing hemodialysis compared to peritoneal dialysis and renal transplant is higher in Japan than other regions of the world, including North America and Europe, with hemodialysis accounting for over 90% of renal replacement therapy in Japan[1]. Peritoneal dialysis (including in combination with hemodialysis) accounts for only 3% of dialysis modalities in Japan[1].

Anemia is a common complication in patients with chronic kidney disease (CKD), which worsens as kidney function declines[3,4]. The cause of anemia in patients with CKD is multifactorial, including erythropoiesis suppression, decreased red blood cell survival, iron metabolism disorders, residual blood in the dialysis circuit, bleeding, and malnutrition, with decreased renal production of erythropoietin (EPO), which promotes red blood cell formation, being a key contributor[5]. Anemia negatively impacts patients with CKD, and is associated with increased cardiovascular (CV) risk, increased morbidity and mortality, and a decrease in patient health-related quality of life[4,6–9]. Injectable erythropoiesis-stimulating agents (ESAs) are commonly used to treat anemia in patients with CKD[5]; however, they have been associated with CV risk and an increased risk of thromboembolism, especially when used to attain higher than recommended hemoglobin levels[7,10–14].

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) are a class of oral drugs that stimulate erythropoiesis by activating the body's response to oxygen deprivation[15–17]. Five HIF-PHIs (daprodustat, roxadustat, vadadustat, enarodustat, and molidustat) are currently approved and used in clinical practice for the treatment of CKD anemia in Japan. Based on their mechanism of action, preclinical studies, and adverse events (AEs) reported in clinical trials, the Japanese Society of Nephrology's guidelines for the use of HIF-PHI inhibitors include a list of diseases and symptoms to screen for and monitor in patients being treated with this class of drugs[18]. These include thromboembolism, hypertension, cancer, retinal hemorrhage, autosomal dominant polycystic kidney disease (ADPKD), heart failure/pulmonary hypertension, vascular calcification, hyperkalemia, hepatic function, and CV complications associated with impaired glucose and lipid metabolism.

The safety and efficacy of daprodustat for

the treatment of CKD anemia has been demonstrated in three Japanese phase 3 studies, including in patients undergoing hemodialysis (HD), peritoneal dialysis (PD), and those not on dialysis (ND)[19–22]. Improvement in hemoglobin levels were comparable in patients treated with daprodustat and patients treated with injectable ESAs, and the adverse event profile was also comparable between treatments.

The safety profile of daprodustat was further evaluated in a pooled analysis of the Japanese phase 3 program[23]. A similar incidence of thromboembolic events, retinal AEs, CV events, and cancer-related AEs were reported in patients treated with daprodustat compared with injectable ESAs. No new safety signals were identified.

Daprodustat was approved in Japan for the treatment of anemia in patients with CKD in June of 2020. At the time of approval, it was requested that postmarketing surveillance be conducted to assess the safety of daprodustat in the real-world setting. The objective of this interim analysis is to report on the postmarketing surveillance data for patients treated with daprodustat in the real-world clinical setting in Japan through June 28, 2023.

PATIENTS AND METHODS

1 Study design and patient population

Patients in Japan who initiated treatment with daprodustat between September 2020 and July 2022 were registered in this prospective, observational, postmarketing surveillance study. Patients were registered using an electronic data capture (EDC) system within 14 days of the start of daprodustat treatment. The observation period was 52 weeks from the start of daprodustat treatment, or until discontinuation of daprodustat if discontinued prior to 52 weeks, to assess overall safety. Patients were followed for an additional 52 weeks after the observation period (or after daprodustat withdrawal) to assess cancer-related events. A target enrollment of 1500 patients (including ≧100 patients receiving peritoneal dialysis) from approximately 200 sites was selected to achieve a target population of 1300 patients (assuming dropouts), which would allow for the detection of unexpected adverse events (AEs) that occur at a frequency of ≧ 0.25% with a probability of 95%. The estimated study completion date is August 2025. This study reports the results of an interim analysis of observational data (up to 52 weeks) and follow-up data for cancer-related events (additional 52 weeks) collected before June 28th, 2023.

This study protocol was reviewed by the Pharmaceuticals and Medical Devices Agency (PMDA) and approved by the Ethics Review Board of Kitamachi Clinic (central ethics committee) and was conducted in accordance with the Ministry of Health, Labour and Welfare (MHLW) Ordinance No. 171 dated December 20, 2004 (Good Postmarketing Surveillance Practice) concerning the standards for the implementation of postmarketing surveillance and studies of drugs. All patients provided written informed consent to participate in this study, and no data was collected that could be used to identify individuals.

2 Data collection and analyses

An EDC system was used for patient enrollment and data collection. The following data were collected: patient baseline characteristics and medical history, prior and concurrent medications, CKD stage and dialysis status, daprodustat dosing information, and laboratory values, including hemoglobin. Adverse events that occurred after daprodustat initiation were collected regardless of whether they were suspected of being related to daprodustat. Terminology from the Medical Dictionary for Regulatory

Activities/Japanese Edition (MedDRA/J; version 26.0) was used to summarize and report AE and adverse drug reactions (ADR) according to system organ class and preferred terms. Adverse events that were deemed to have a causal relationship with daprodustat by the research team or the investigator as well as those that were not classified as having no causal relationship to daprodustat were considered as ADRs. Thromboembolism, hypertension, CV events (excluding thromboembolism), cancer, progression of disease in patients with ADPKD, and retinal hemorrhage were defined as ADRs of special interest. For ADRs of special interest, rate per 100 patient years was calculated along with the exact 95% Poisson confidence interval using chi-square distribution.

The safety analysis population included all patients, regardless of dialysis status during the observation period. Patient follow-up occurred until discontinuation/termination of the drug or completion of the observation period (week 52). Follow-up for cancer-related events continued for an additional 52 weeks up to a maximum of 2 years. This interim analysis reports available data as of June 28th, 2023.

The ND, PD, and HD subgroups include patients who were in each designated category at study entry. If a patient switched therapy (eg, ND to PD or HD; PD to HD; or HD to ND due to renal transplant) during the observation or follow-up period, any ADRs reported after switching were no longer counted within the subgroup they were assigned to at baseline, but were still counted in the total safety analysis population.

RESULTS

1 Patient disposition

Overall, 1674 patients were registered. 898 completed the 52-week observation period and their case files were locked. Eleven patients were excluded (5 due to registration after the registration window, 2 had no patient visits after starting daprodustat, 2 because they received treatment or follow-up outside the contract period, and 2 for whom no AEs were reported and the principal investigator died), and 887 patients were included in the safety analyses set (**Fig. 1**). Of these, 543 patients (61.2%) were not undergoing dialysis (ND), 54 patients (6.1%) were undergoing peritoneal dialysis (PD), and 290 patients (32.7%) were undergoing hemodialysis (HD). 159 patients completed an additional 52-week follow-up for cancer-related events.

2 Patient baseline characteristics

The mean (SD) age was 75.3 (12.3) years and 82% (n=727) of patients were ≧65 years old (**Table 1**). Slightly over half (54.7%, n=485) of the patients were male. Forty-five patients changed dialysis status during the observation period (PD to HD or HD to PD). Before initiating daprodustat, 91.8% of patients had received prior treatment for CKD anemia, including 46.8% (415/887) who received injectable ESAs (36.1% in the ND group, 74.1% in the PD group, and 61.7% in the HD group). The majority of patients previously treated with an injectable ESA received darbepoetin alfa (n=222) followed by epoetin beta pegol (n=149) and epoetin (n=44) (**Table 2**). 120 patients (13.5%) were treated with iron (iron supplement or iron-containing phosphate binder) prior to the study (12.5% ND, 9.3% PD and 16.2% HD), and 252 patients (28.4%) were treated with concomitant iron (iron supplement or iron-containing phosphate binder) at baseline (23.6% ND, 35.2% PD, and 36.2% HD).

3 Daprodustat exposure

The mean (SD) initial daily dose of daprodustat was 3.0 (1.2) mg in the ND group, 3.6 (0.9) mg in the PD group, and 3.9 (0.8) mg in the HD group. The mean daily dose was 3.7 (2.3) mg, 6.1

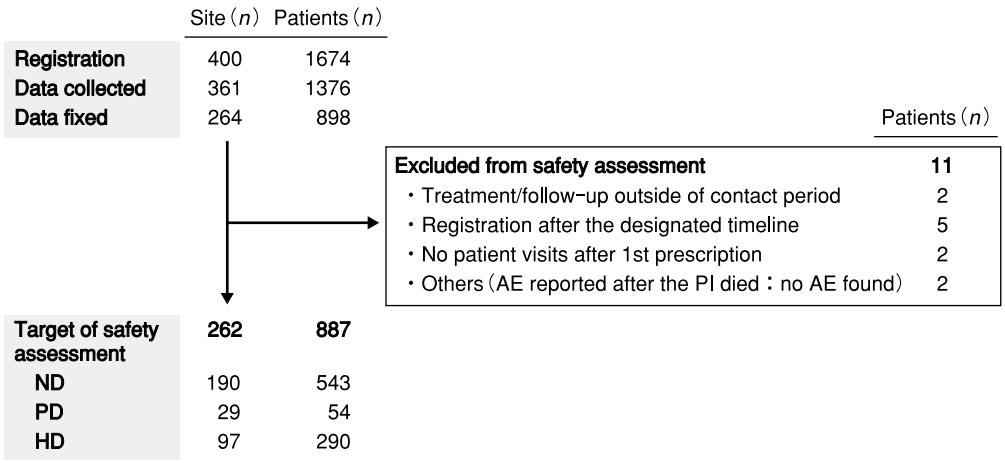

Fig. 1 Patient Disposition

AE: adverse event, HD: hemodialysis, ND: no dialysis, PI: principal investigator, PD: peritoneal dialysis

(3.7) mg, and 7.2 (5.4) mg over the observational period in the ND, PD, and HD groups, respectively. Six patients in the ND group and 6 patients in the HD group received an initial dose of daprodustat that exceeded the maximum indicated initial dose (>4 mg); however, no ADRs were reported in these patients. In addition, one patient received a daily dose of daprodustat greater than the maximum recommended daily dose of 24 mg, but no ADRs were reported in this patient.

Daprodustat dose over time by dialysis subgroup in patients with and without prior injectable ESA treatment is shown in **Supplemental Fig. 1**.

4 Adverse drug reactions

Adverse drug reactions occurred in 5.9% (n=52/887) of the total population and 4.1% (n=22/543), 7.4% (n=4/54), and 8.3% (n=24/290) of the ND, PD, and HD groups, respectively (**Table 3**). The most common ADRs were hypertension (0.8%, n=7), nausea (0.6%, n=5), and hemoglobin increase or decrease (0.3%, n=3 each). Severe ADRs occurred in 15 patients (1.7%, n=15/887) and included acute abdomen, diverticular perforation, deep vein thrombosis, condition aggravated, death, heart failure, heart failure chronic, colon cancer, lung adenocarcinoma, metastases to bone, metastases to liver, nephrogenic anemia, cerebral infarction, interstitial lung disease, deafness neurosensory, retinal hemorrhage, and occlusion of hemodialysis arteriovenous access (AVA) (n=1 in each). Of the reported deaths (n=4), 2 patients were in the ND group and 2 patients were in the HD group at the initiation of daprodustat.

5 ADRs of special interest

Adverse drug reactions related to thromboembolism were reported in 3 patients and included 1 event each of occlusion of hemodialysis AVA (HD group), stroke (HD group), and deep vein thrombosis (ND group) (**Table 4**). The stroke event was considered a reoccurrence in a patient with a history of cerebral infarction. All 3 events were considered severe, but in each case the patient recovered or was improving. The cumulative incidence of ADRs related to thromboembolism was 0 cases (0.0%) at 12 weeks, 1 case (0.1%) at 24 weeks, and 3 cases (0.4%) at 52 weeks. The incidence of ADRs

Table 1　Baseline patient characteristics

Characteristic, *n*（%）	Safety population (*n*=887)	Dialysis status at baseline		
		ND (*n*=543)	PD (*n*=54)	HD (*n*=290)
Gender				
Male	485 (54.7)	265 (48.8)	33 (61.1)	187 (64.5)
Female	402 (45.3)	278 (51.2)	21 (38.9)	103 (35.5)
Age				
＜15 years	0	0	0	0
≧15 to ＜65 years	160 (18.0)	57 (10.5)	22 (40.7)	81 (27.9)
≧65 years	727 (82.0)	486 (89.5)	32 (59.3)	209 (72.1)
Cause of anemia				
DKD	320 (36.1)	187 (34.4)	14 (25.9)	119 (41.0)
Chronic glomerular Nephritis（CGN）	151 (17.0)	61 (11.2)	14 (25.9)	76 (26.2)
Nephrosclerosis	303 (34.2)	226 (41.6)	17 (31.5)	60 (20.7)
ADPKD	24 (2.7)	8 (1.5)	2 (3.7)	14 (4.8)
Other	136 (15.3)	96 (17.7)	8 (14.8)	32 (11.0)
CKD anemia duration				
≦2 years	147 (16.6)	105 (19.3)	10 (18.5)	32 (11.0)
＞2 years to ≦5 years	198 (22.3)	115 (21.2)	12 (22.2)	71 (24.5)
＞5 years to ≦10 years	148 (16.7)	80 (14.7)	10 (18.5)	58 (20.0)
＞10 years	206 (23.2)	93 (17.1)	14 (25.9)	99 (34.1)
Unknown	188 (21.2)	150 (27.6)	8 (14.8)	30 (10.3)
Body weight				
＜55 kg	394 (44.4)	242 (44.6)	18 (33.3)	134 (46.2)
≧55 kg	412 (46.4)	226 (41.6)	35 (64.8)	151 (52.1)
Unknown	81 (9.1)	75 (13.8)	1 (1.9)	5 (1.7)
BMI				
＜18.5 kg/m^2	118 (13.3)	67 (12.3)	4 (7.4)	47 (16.2)
≧18.5 to ＜25 kg/m^2	471 (53.1)	271 (49.9)	30 (55.6)	170 (58.6)
≧25 kg/m^2	182 (20.5)	109 (20.1)	18 (33.3)	55 (19.0)
Unknown	116 (13.1)	96 (17.7)	2 (3.7)	18 (6.2)
Medical history[a]				
Thromboembolism	46 (5.2)	21 (3.9)	4 (7.4)	21 (7.2)
Hypertension	9 (1.0)	6 (1.1)	2 (3.7)	1 (0.3)
Cardiovascular events	33 (3.7)	16 (2.9)	4 (7.4)	13 (4.5)
Cancer	54 (6.1)	33 (6.1)	0	21 (7.2)
Retinal hemorrhage	7 (0.8)	1 (0.2)	0	6 (2.1)
Hepatic dysfunction	8 (0.9)	4 (0.7)	2 (3.7)	2 (0.7)
Heart failure	5 (0.6)	2 (0.4)	1 (1.9)	2 (0.7)
Other	141 (15.9)	74 (13.6)	12 (22.2)	55 (19.0)

Table 1　Baseline patient characteristics（Continued）

Characteristic, *n*（%）	Safety population (*n*=887)	Dialysis status at baseline		
		ND (*n*=543)	PD (*n*=54)	HD (*n*=290)
Comorbidities[b]				
Thromboembolism	159 (17.9)	93 (17.1)	6 (11.1)	60 (20.7)
Hypertension	744 (83.9)	456 (84.0)	50 (92.6)	238 (82.1)
Cardiovascular events	218 (24.6)	142 (26.2)	17 (31.5)	59 (20.3)
Cancer	30 (3.4)	17 (3.1)	2 (3.7)	11 (3.8)
Retinal hemorrhage	21 (2.4)	12 (2.2)	2 (3.7)	7 (2.4)
Hepatic dysfunction	47 (5.3)	32 (5.9)	2 (3.7)	13 (4.5)
Heart failure	139 (15.7)	100 (18.4)	14 (25.9)	25 (8.6)
Other	882 (99.4)	541 (99.6)	54 (100)	287 (99.0)
History of renal transplant	27 (3.0)	13 (2.4)	2 (3.7)	12 (4.1)
History of nephrectomy	25 (2.8)	10 (1.8)	0	15 (5.2)
Number of kidneys				
0	5 (0.6)	0	0	5 (1.7)
1	15 (1.7)	6 (1.1)	0	9 (3.1)
2	867 (97.7)	537 (98.9)	54 (100)	276 (95.2)
Any prior treatment				
Yes	814 (91.8)	486 (89.5)	54 (100)	274 (94.5)
No	73 (8.2)	57 (10.5)	0 (0)	16 (5.5)
Prior treatments				
Iron supplements	89 (10.0)	60 (11.0)	3 (5.6)	26 (9.0)
Phosphate binders containing iron	34 (3.8)	8 (1.5)	2 (3.7)	24 (8.3)
Any iron[c]	120 (13.5)	68 (12.5)	5 (9.3)	47 (16.2)
HIF-PHI	49 (5.5)	13 (2.4)	4 (7.4)	32 (11.0)
Injectable ESA	415 (46.8)	196 (36.1)	40 (74.1)	179 (61.7)
ESA＋any iron[c]	480 (54.1)	239 (44.0)	42 (77.8)	199 (68.6)
HIF-PHI＋any iron[c]	160 (18.0)	81 (14.9)	7 (13.0)	72 (24.8)
Concomitant iron[c]	252 (28.4)	128 (23.6)	19 (35.2)	105 (36.2)
Baseline hemoglobin				
＜9 g/dL	142 (16.0)	84 (15.5)	10 (18.5)	48 (16.6)
≧9 to ＜10 g/dL	255 (28.7)	171 (31.5)	8 (14.8)	76 (26.2)
≧10 to ＜11 g/dL	275 (31.0)	183 (33.7)	11 (20.4)	81 (27.9)
≧11 to ＜12 g/dL	127 (14.3)	58 (10.7)	18 (33.3)	51 (17.6)
≧12 to ＜13 g/dL	63 (7.1)	30 (5.5)	5 (9.3)	28 (9.7)
≧13 g/dL	17 (1.9)	9 (1.7)	2 (3.7)	6 (2.1)
Unknown	8 (0.9)	8 (1.5)	0	0

Table 1　Baseline patient characteristics（Continued）

Characteristic, *n*（%）	Safety population (*n*=887)	Dialysis status at baseline		
		ND (*n*=543)	PD (*n*=54)	HD (*n*=290)
Baseline SBP				
＜130 mmHg	308（34.7）	230（42.4）	18（33.3）	60（20.7）
≧130 mmHg	564（63.6）	299（55.1）	36（66.7）	229（79.0）
Unknown	15（1.7）	14（2.6）	0	1（0.3）
Baseline DBP				
＜80 mmHg	592（66.7）	400（73.7）	26（48.1）	166（57.2）
≧80 mmHg	280（31.6）	129（23.8）	28（51.9）	123（42.4）
Unknown	15（1.7）	14（2.6）	0	1（0.3）
Baseline eGRF, mL/min/1.73 m^2				
＜15	313（35.3）	137（25.2）	N/A	N/A
≧15 to ＜30	221（24.9）	218（40.1）	N/A	N/A
≧30 to ＜60	150（16.9）	150（27.6）	N/A	N/A
≧60	8（0.9）	8（1.5）	N/A	N/A
Unknown	195（22.0）	30（5.5）	N/A	N/A

ADPKD：autosomal dominant polycystic kidney disease, BMI：body mass index, CGN：chronic glomerulonephritis, CKD：chronic kidney disease, DBP：diastolic blood pressure, DKD：diabetic kidney disease, eGRF：estimated glomerular filtration rate, ESA：erythropoiesis-stimulating agent, HD：hemodialysis, HIF-PHI：hypoxia-inducible factor prolyl hydroxylase inhibitor, N/A：not applicable, ND：no dialysis, PD：peritoneal dialysis, SBP：systolic blood pressure

[a] Resolved prior to initiation of daprodustat

[b] Ongoing when initiating daprodustat

[c] Iron supplements or phosphate binders containing iron

related to thromboembolism per 100 patient years was 0.4/100 patient years（95% CI：0.1-1.3）and the rate of ADRs was 0.3%（95% CI：0.1-1.0）.

Adverse drug reactions related to hypertension were reported in 8 patients（7 patients with hypertension and 1 patient with increased blood pressure）. Five of these occurred in in the ND group and 2 in the HD group. None of the hypertension-related adverse events were considered severe and all patients improved or recovered. All 8 patients reported hypertension at baseline. The cumulative incidence of ADRs related to hypertension was 6 cases（0.7%）at 12 weeks, 7 cases（0.8%）at 24 weeks, and 8 cases at 52 weeks（1.0%）. The incidence of ADRs related to hypertension per 100 patient years was 1.2/100 patient years（95% CI：0.5-2.3）, and the rate of ADRs was 0.9%（95% CI：0.4-1.8）.

Other CV events, excluding thromboembolism, included one case each of new onset heart failure and exacerbation of chronic heart failure, both of which were severe. The new onset heart failure event resulted in death and the patient did not have a history heart failure when they initiated daprodustat treatment. The patient with

Table 2　Prior treatment with injectable ESAs

Characteristic, *n*（%）	Safety Population (*n*＝887)	Dialysis status at baseline		
		ND (*n*＝543)	PD (*n*＝54)	HD (*n*＝290)
Patients with prior ESA	415	196	40	179
Prior ESA				
Epoetin	44 (10.6)	0	0 (0)	44 (24.6)
Epoetin beta pegol	149 (35.9)	104 (53.1)	26 (65.0)	19 (10.6)
Darbepoetin alfa	222 (53.5)	92 (46.9)	14 (35.0)	116 (64.8)
ESA dose（IU/week）				
＜4500	169 (40.7)	120 (61.2)	12 (30.0)	37 (20.7)
≧4500 to ＜6000	48 (11.6)	19 (9.7)	5 (12.5)	24 (13.4)
≧6000	198 (47.7)	57 (29.1)	23 (57.5)	118 (65.9)
ERI（IU/week/kg/g/dL）				
＜5.7	99 (23.9)	60 (30.6)	7 (17.5)	32 (17.9)
≧5.7 to ＜9.7	88 (21.2)	47 (24.0)	10 (25.0)	31 (17.3)
≧9.7 to ＜15.5	71 (17.1)	30 (15.3)	9 (22.5)	32 (17.9)
≧15.5	131 (31.6)	34 (17.3)	13 (32.5)	84 (46.9)
Unknown	26 (6.3)	25 (12.8)	1 (2.5)	0
Insufficient effectiveness of prior ESA treatment	177 (42.7)	89 (45.4)	12 (30.0)	76 (42.5)
Baseline HgB in patients without prior ESA treatment（g/dL）				
＜9 g/dL	78 (18.8)	55 (28.1)	2 (5.0)	21 (11.7)
≧9 to ＜10 g/dL	151 (36.4)	122 (62.2)	1 (2.5)	28 (15.6)
≧10 to ＜11 g/dL	156 (37.6)	125 (63.8)	3 (7.5)	28 (15.6)
≧11 to ＜12 g/dL	49 (11.8)	23 (11.7)	5 (12.5)	21 (11.7)
≧12 to ＜13 g/dL	25 (6.0)	11 (5.6)	2 (5.0)	12 (6.7)
≧13 g/dL	6 (1.4)	4 (2.0)	1 (2.5)	1 (0.6)
Unknown	7 (1.7)	7 (3.6)	0	0
Baseline HgB in patients with prior ESA treatment（g/dL）				
＜9 g/dL	64 (15.4)	29 (14.8)	8 (20.0)	27 (15.1)
≧9 to ＜10 g/dL	104 (25.1)	49 (25.0)	7 (17.5)	48 (26.8)
≧10 to ＜11 g/dL	119 (28.7)	58 (29.6)	8 (20.0)	53 (29.6)
≧11 to ＜12 g/dL	78 (18.8)	35 (17.9)	13 (32.5)	30 (16.8)
≧12 to ＜13 g/dL	38 (9.2)	19 (9.7)	3 (7.5)	16 (8.9)
≧13 g/dL	11 (2.7)	5 (2.6)	1 (2.5)	5 (2.8)
Unknown	1 (0.2)	1 (0.5)	0	0

ERI：ESA resistance index, ESA：erythropoietin-stimulating agent, HD：hemodialysis, Hgb：hemoglobin, ND：no dialysis, PD：peritoneal dialysis

Table 3 ADRs after initiation of daprodustat treatment[a]

ADR, *n* (%)	Safety population (*n*=887)		ND (*n*=543)		PD (*n*=54)		HD (*n*=290)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
Any ADR	52 (5.9)	15 (1.7)	22 (4.1)	6 (1.1)	4 (7.4)	0	24 (8.3)	8 (2.8)
GI disorders	8 (0.9)	2 (0.2)	1 (0.2)	0	1 (1.9)	0	6 (2.1)	2 (0.7)
Nausea	5 (0.6)	0	1 (0.2)	0	1 (1.9)	0	3 (1.0)	0
Diarrhea	2 (0.2)	0	0	0	0	0	2 (0.7)	0
Abdominal pain	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Acute abdomen	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Diverticular perforation	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Investigations	8 (0.9)	0	3 (0.6)	0	1 (1.9)	0	4 (1.4)	0
Hgb decreased	3 (0.3)	0	1 (0.2)	0	0	0	2 (0.7)	0
Hgb increased	3 (0.3)	0	0	0	1 (1.9)	0	2 (0.7)	0
Blood iron decreased	1 (0.1)	0	1 (0.2)	0	0	0	0	0
BP increased	1 (0.1)	0	1 (0.2)	0	0	0	0	0
Platelets decreased	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Transferrin saturation decreased	1 (0.1)	0	1 (0.2)	0	0	0	0	0
Vascular disorders	8 (0.9)	1 (0.1)	5 (0.9)	1 (0.2)	0	0	2 (0.7)	0
Hypertension	7 (0.8)	0	4 (0.7)	0 (0.0)	0	0	2 (0.7)	0
DVT	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	0	0	0
General disorders and administration site conditions	6 (0.7)	2 (0.2)	2 (0.4)	1 (0.2)	1 (1.9)	0	3 (1.0)	1 (0.3)
Condition aggravated	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Death	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	0	0	0
Feeling abnormal	1 (0.1)	0	0	0	1 (1.9)	0	0	0
Malaise	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Pain	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Thirst	1 (0.1)	0	1 (0.2)	0	0	0	0	0
Skin and subcutaneous tissue disorders	5 (0.6)	0	4 (0.7)	0	1 (1.9)	0	0	0
Drug eruption	2 (0.2)	0	1 (0.2)	0	1 (1.9)	0	0	0
Pruritus	2 (0.2)	0	2 (0.4)	0	0	0	0	0
Rash	1 (0.1)	0	1 (0.2)	0	0	0	0	0
Cardiac disorders	4 (0.5)	2 (0.2)	2 (0.4)	1 (0.2)	0	0	2 (0.7)	1 (0.3)
Palpitations	2 (0.2)	0	1 (0.2)	0	0	0	1 (0.3)	0
Heart failure	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Heart failure chronic	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	0	0	0

Table 3 ADRs after initiation of daprodustat treatment[a] (Continued)

ADR, *n* (%)	Safety population (*n*=887)		ND (*n*=543)		PD (*n*=54)		HD (*n*=290)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
Neoplasms[b]	4 (0.5)	3 (0.3)	2 (0.4)	2 (0.4)	0	0	2 (0.7)	1 (0.3)
Colon cancer	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Lung adenocarcinoma	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	0	0	0
Marrow hyperplasia	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Metastases to bone	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Metastases to liver	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	0	0	0
Blood and lymph system disorders	3 (0.3)	1 (0.1)	0	0	0	0	3 (1.0)	1 (0.3)
Anemia	2 (0.2)	0	0	0	0	0	2 (0.7)	0
Nephrogenic anemia	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Nervous system disorders	3 (0.3)	1 (0.1)	1 (0.2)	0	0	0	2 (0.7)	1 (0.3)
Cerebral infarction	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Dizziness	1 (0.1)	0	1 (0.2)	0	0	0	0	0
Balance disorder	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	2 (0.2)	1 (0.1)	0	0	0	0	1 (0.3)	0
Dyspnea exertional	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Interstitial lung disease	1 (0.1)	1 (0.1)	0	0	0	0	0	0
Wheezing	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Ear and labyrinth disorders	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	0	0	0
Deafness neurosensory	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	0	0	0
Tinnitus	1 (0.1)	0	1 (0.2)	0	0	0	0	0
Eye disorders	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Retinal hemorrhage	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Hepatobiliary disorders	1 (0.3)	0	1 (0.2)	0	0	0	0	0
Hepatic function abnormal	1 (0.3)	0	1 (0.2)	0	0	0	0	0
Injury, poisoning, and procedural complications	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)
Occlusion of hemodialysis AVA	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.3)	1 (0.3)

Table 3 ADRs after initiation of daprodustat treatment[a] (Continued)

ADR, *n* (%)	Safety population (*n*=887)		ND (*n*=543)		PD (*n*=54)		HD (*n*=290)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
Metabolism and nutritional disorders	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Fluid retention	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Musculoskeletal and connective tissue disorders	1 (0.1)	0	0	0	0	0	1 (0.3)	0
Pain in extremity	1 (0.1)	0	0	0	0	0	1 (0.3)	0

ADR: adverse drug reaction, AVA: arteriovenous access, BP: blood pressure, DVT: deep vein thrombosis, GI: gastrointestinal, HD: hemodialysis, HgB: hemoglobin, ND: no dialysis, PD: peritoneal dialysis

[a] The safety analysis population includes ADRs reported for all patients included in the study until the end of the observation period (or follow-up period for cancer-related events). The ND, PD, and HD groups included ADRs reported for patients within each subgroup until they switched therapy or until the end of the observation period (or follow-up period for cancer-related events) if they did not switch therapy

[b] Benign, malignant, and unspecified (including cysts and polyps)

Table 4 ADRs of special interest

ADR, *n* (%)	Safety population (*n*=887)		ND (*n*=543)		PD (*n*=54)		HD (*n*=290)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
Thromboembolism	3 (0.3)	3 (0.3)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.7)
Hypertension	8 (0.9)	0 (0.0)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
CV events[a]	2 (0.2)	2 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Cancer	3 (0.3)	3 (0.3)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Progression in patients with ADPKD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal hemorrhage	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
GI erosion	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)

ADPKD: autosomal dominant polycystic kidney disease, ADR: adverse drug reaction, CV: cardiovascular, GI: gastrointestinal, HD: hemodialysis, ND: no dialysis, PD: peritoneal dialysis

[a] Except thromboembolism

chronic heart failure had a history of chronic heart failure at baseline and recovered. The ADR of new onset heart failure occurred in a patient in the HD group and exacerbation of heart failure in a patient in the ND group (**Supplemental Table 1**). The cumulative incidence of ADRs related to CV events (excluding thromboembolism) was 2 cases (0.2%) at any of the 12-, 24-, and 52-week time points. The incidence of ADRs related to CV events (excluding thromboembolism) was 0.3/100 patient years (95% CI: 0.0-1.0), and the incidence of ADRs was 0.2% (95% CI: 0.0-0.8).

Adverse drug reactions related to cancer

Table 5 Hemoglobin increase and ADRs

	＜0.1 g/dL/week	≧0.1～＜0.2 g/dL/week	≧0.2～＜0.3 g/dL/week	≧0.3～＜0.4 g/dL/week	≧0.4～＜0.5 g/dL/week	≧0.5～＜1 g/dL/week	≧1 g/dL/week	Total
Safety population (*n*)	279	95	55	37	19	32	3	520
All ADRs, *n* (%)	19 (6.8)	5 (5.3)	5 (9.1)	3 (8.1)	1 (5.3)	2 (6.3)	0 (0.0)	35 (6.7)
Severe ADRs, *n* (%)	8 (2.9)	1 (1.1)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (1.9)
ND group (*n*)	118	56	38	21	12	17	2	264
All ADRs, *n* (%)	7 (5.9)	4 (7.1)	3 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (5.3)
Severe ADRs, *n* (%)	3 (2.5)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.5)
PD group (*n*)	17	4	1	3	3	5	1	34
All ADRs, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (2.9)
Severe ADRs, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HD group (*n*)	144	35	16	12	4	10	0	221
All ADRs, *n* (%)	11 (7.6)	1 (2.9)	2 (12.5)	2 (16.7)	0 (0.0)	2 (20.0)	0 (0.0)	18 (8.1)
Severe ADRs, *n* (%)	4 (2.8)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.3)

ADR: adverse drug reaction, HD: hemodialysis, ND: no dialysis, PD: peritoneal dialysis

were reported in 3 patients in this interim analysis. All cases were considered severe. One patient in the HD group without prior history developed colon cancer, which metastasized to the bone and the patient died. Metastasis to the liver was reported in a patient undergoing ND that had a history of colon and gastric cancer and that patient also died. The third patient, also in the ND group, had lung adenocarcinoma, with no prior history, and the patient went into remission. The cumulative incidence rate of cancer was 1 case (0.1%) at 12 weeks, 2 cases (0.2%) at 24 weeks, and 3 cases (0.4%) at 52 and 103 weeks. The incidence of ADRs per 100 patient years for cancer was 0.4/100 patient years (95% CI: 0.1–1.0), and the rate of ADRs was 0.3% (95% CI: 0.1–1.0). In the 159 patients where a 52-week follow-up was conducted at the data lock point of this analysis, no new cancer-related adverse events were observed.

Other ADRs of special interest included one event of retinal hemorrhage that was considered severe, but improved, and one ADR related to GI erosion (not a prespecified safety consideration) of severe diverticular perforation that improved, both in the HD group. No ADRs related to ADPKD were reported.

No ADRs related to central hypothyroidism were reported during the 52-week observation period.

No correlation was seen between the rate of hemoglobin rise (g/dL per week) 4 weeks after daprodustat administration and ADRs (**Table 5**). Overall, the rate of ADRs ranged from 9.1% (5/55) in patients with a hemoglobin rise of ≧0.2 to ＜0.3 g/dL/week to 5.3% in both patients with a hemoglobin rise of ≧0.4 to ＜0.5 g/dL/week (1/19) and ≧0.1 to ＜0.2 g/dL/week (5/95). No

patients with a hemoglobin rise ≧1 g/dL/week (n=3) reported an ADR and no severe ADRs were reported in patients with a hemoglobin rise ≧0.3 g/dL/week (n=91). Changes in hemoglobin levels over time during the observation period are shown in **Fig. 2**.

There were no consistent trends between daprodustat dose and ADRs. However, the effect of average daily daprodustat dose and maximum daily dose on ADRs could not be effectively evaluated because the patient characteristics between dose groups were not consistent and there were not sufficient patients in each group, especially high-dose groups, to draw meaningful conclusions (**Supplemental Table 2**).

DISCUSSION

In this interim analysis of a postmarketing surveillance study to assess the safety of daprodustat in routine clinical practice in Japan, the incidence rate of ADRs was 5.9% overall. A higher proportion of patients on dialysis (PD 7.4%, HD 8.3%) reported an ADR compared to the ND group (4.1%). All ADRs of special interest (thromboembolism, hypertension, CV events, cancer, progression of ADPKD, and retinal hemorrhage) were reported in less than 1% of patients overall and in the subgroups based on dialysis status. No correlation was seen between the rate of hemoglobin rise (g/dL per week) and ADRs, and no new safety signals were identified.

The safety of daprodustat has been previously assessed both in Japanese and global clinical trials[19-21,24,25]. In a pooled analysis of 3 Japanese clinical trials that included patients undergoing HD, PD, or ND, with a median drug exposure of 365 days[23], drug-related adverse events were reported in 7% of patients, and the incidence of ADRs of special interest was similar in patients treated with daprodustat compared with injectable ESAs. For cancer-related events, the incidence rate was 1.53 per patient years in patients treated with ESAs and 1.28 per 100 patient years in patients treated with daprodustat, which is higher than what was observed in the current study (0.4/100 patient years). However, follow-up for cancer-related events is still ongoing. In addition, differences in daprodustat use in the real world compared to clinical trial setting, such as differences in patient selection or more conservative dosing, could be a factor. Moreover, cancers may be more likely to remain undetected in the real-world setting compared with prospective interventional studies in which screening may be more frequent.

In the global ASCEND program, there was no notable increase in adverse events in patients treated with daprodustat compared with injectable ESAs[24,25]. The frequency of adverse events of special interest for daprodustat were similar to injectable ESAs in both the dialysis (HD and PD) and ND groups, except for increased cancer and gastric erosion in the daprodustat group in patients undergoing ND. In a post-hoc analysis of the ASCEND-D an ASCEND-ND trials, daprodustat was not associated with an increased risk of cancer compared to ESA for both ND and HD patients[26]. A first MACE event (defined as a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke) occurred at a similar frequency in the daprodustat and injectable ESA groups in patients undergoing dialysis (25.2% vs 26.7%) and in patients not undergoing dialysis (19.5% vs 19.2%) during a median follow-up of 2.5 years and 1.9 years, respectively. In a post hoc analysis of the ASCEND trial, hospitalization for heart failure (first or recurrent) was increased in ND patients (rate ratio 1.46 [1.11-1.92], p=0.007) treated with daprodustat, but not HD patients (rate ratio 1.01 [0.74-1.39], p=0.93)[27]. In the current study, only 2 events of heart failure or

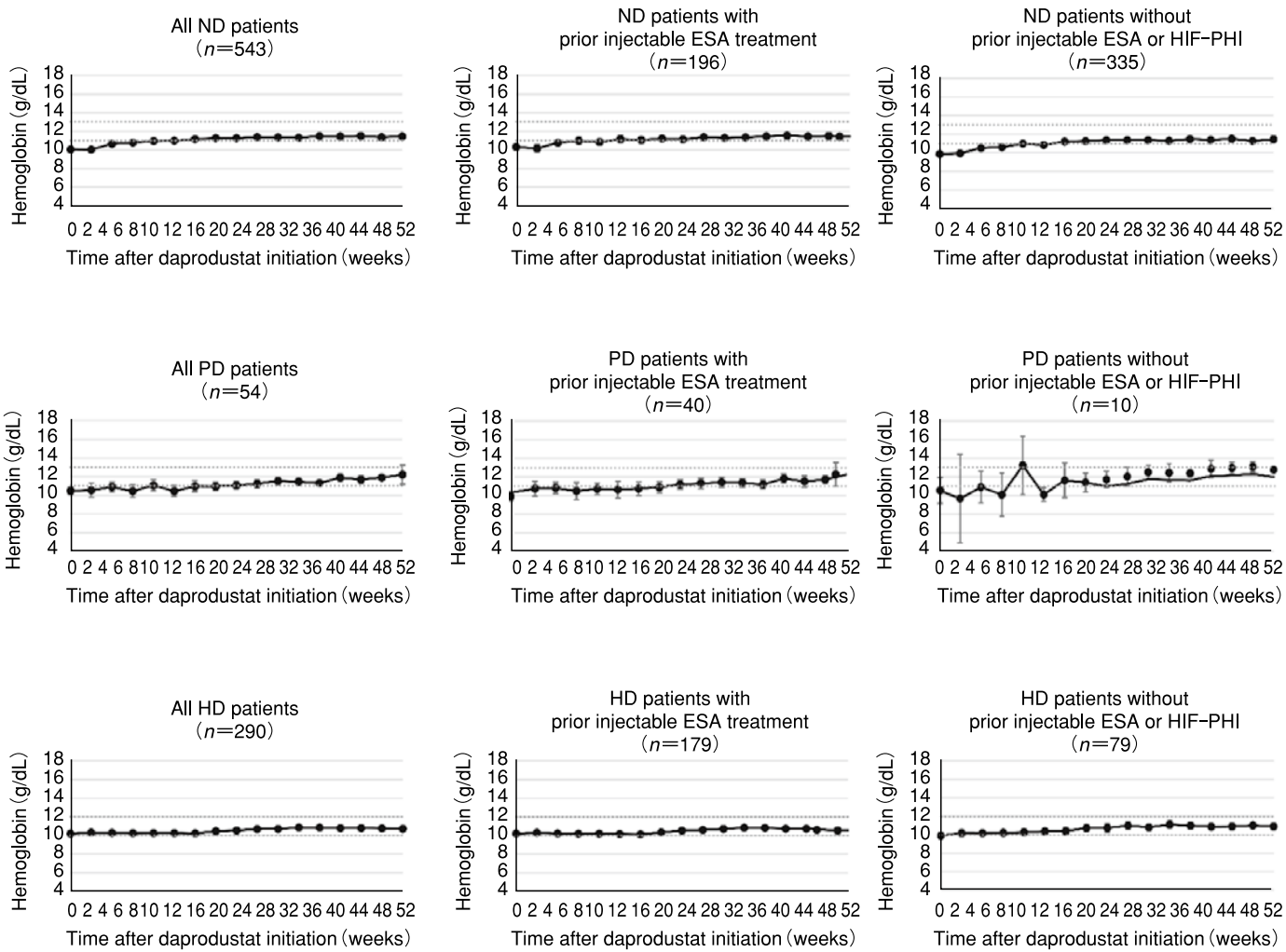

Fig. 2 Hemoglobin over time

exacerbation of heart failure were reported (1 exacerbation of heart failure in the ND group and 1 first heart failure event in the HD group).

While direct comparison between the current study and the Japanese phase 3 and ASCEND studies is not possible due to differences in patient population, study methods, and the terms/definitions used to classify adverse events, the current interim findings show no new safety signals for daprodustat in the real-world clinical setting in Japan compared with what has been observed during the daprodustat clinical development program.

Limitations of this study include that this interim analysis only included 887 patients ; however, additional analysis is ongoing. In addition, the observational period for ADRs in this study was up to 52 weeks for most patients, with only 159 patients having completed the 52-week follow-up for cancer-related events. Therefore, future studies are required to assess potential long-term ADRs, including cancer-related events and CV events. Additionally, some patients were treated with daprodustat at doses lower than the recommended starting dose, which may have impacted the incident rate of ADRs, and the study did not include a control group, so conclusions about safety in relation to other treatments could not be made.

CONCLUSIONS

In this interim analysis of an observational daprodustat safety study conducted in Japan, no new safety signals were identified in real-world clinical settings. The ongoing 52-week observation and cancer follow-up will provide additional safety data for daprodustat in the real-world setting in Japan.

CONFLICT OF INTEREST DISCLOSURE

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AUTHOR CONTRIBUTIONS

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

Kyomi Kanaya, Kenji Oda, Masanori Onoki, Sakiyo Tsukamoto, Naohiro Takahashi, and Yoshiaki Kawano contributed to the conception or design of the study. Shigeomi Iimura, Kyomi Kanaya, Kenji Oda, and Masanori Onoki contributed to the acquisition of the data. Tadao Akizawa, Shigeomi Iimura, Kyomi Kanaya, Sakiyo Tsukamoto, Kazuko Suzuki, Ryuji Nagao, Naohiro Takahashi, Yoshiaki Kawano, and Ai Hayashi contributed to the data analysis or interpretation. All authors provided critical review and final approval of the publication.

DATA SHARING STATEMENT

The anonymized individual participant data from this study are not available to the public, as the contract with the study site does not permit data sharing with third parties, excluding health authorities. The related documents for this study can be found at www.gsk-studyregister.com/en.

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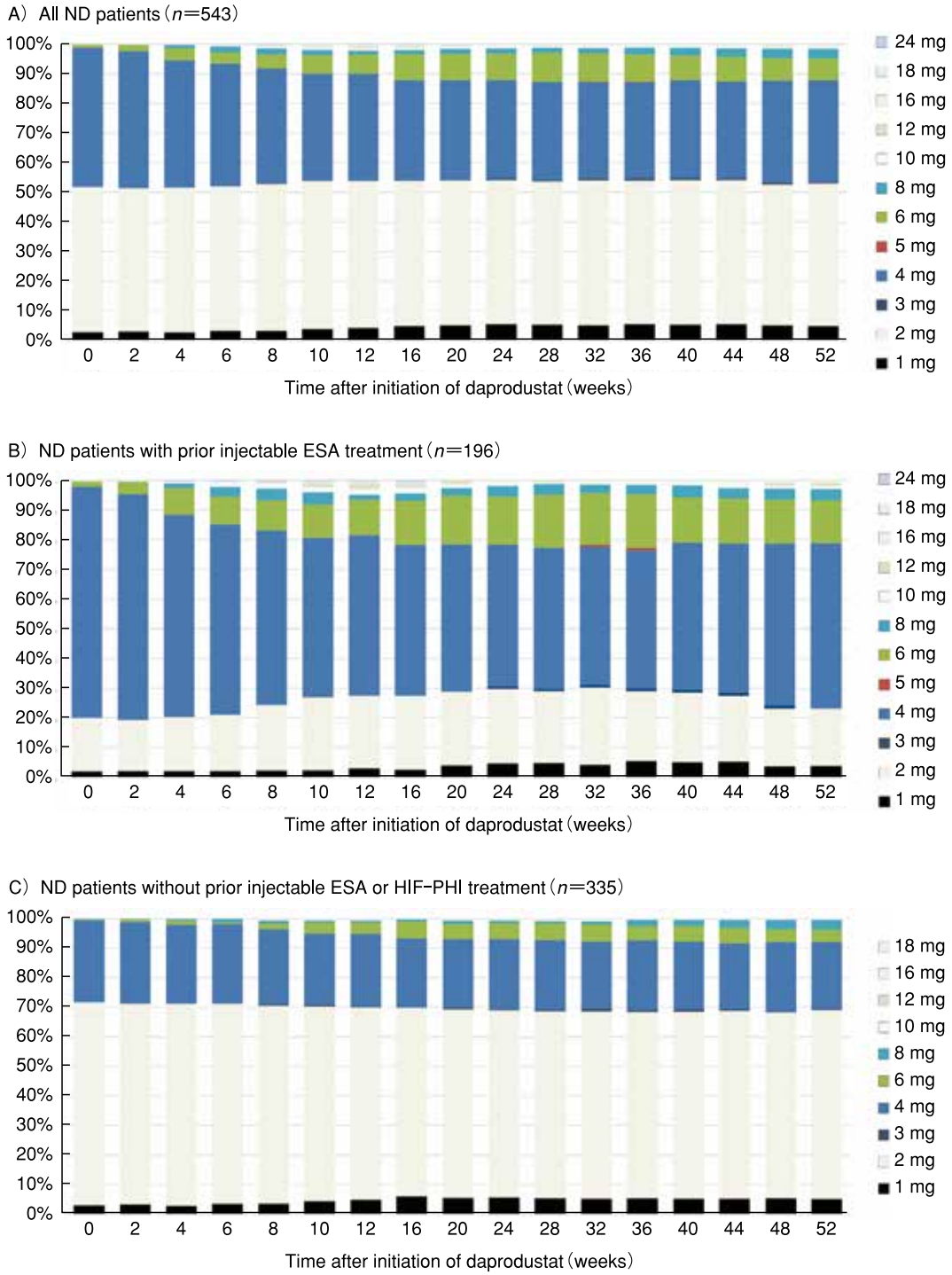
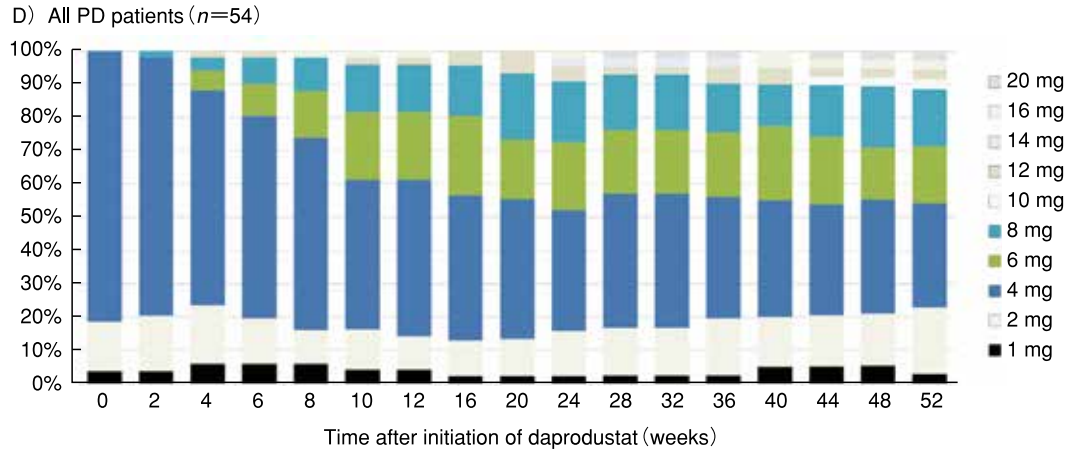
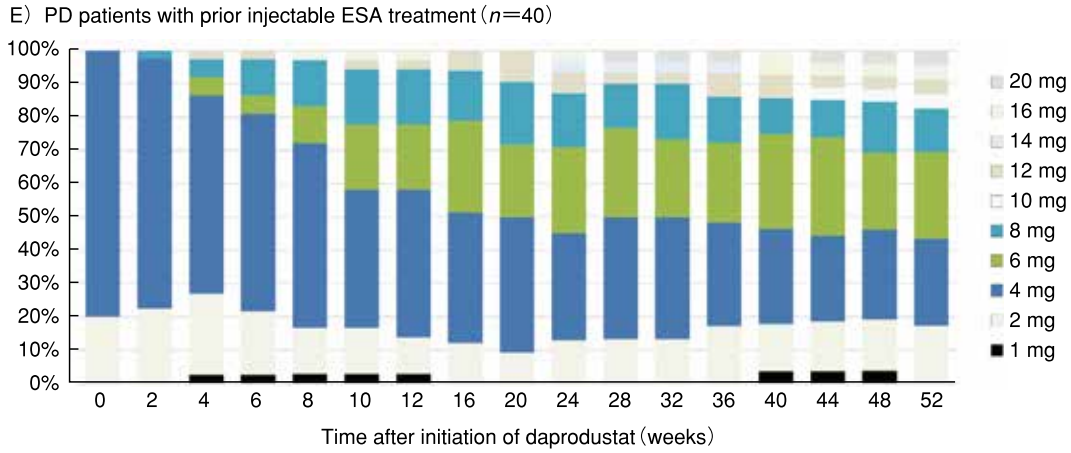
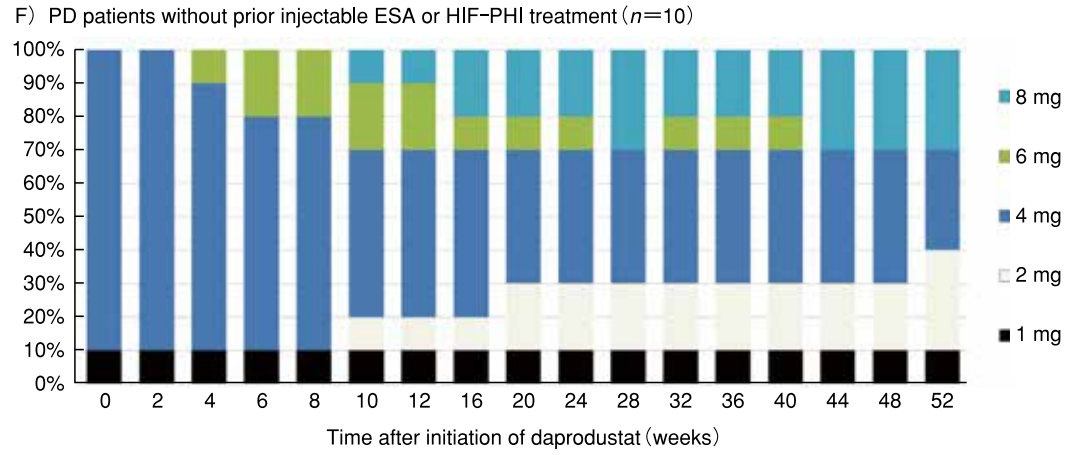


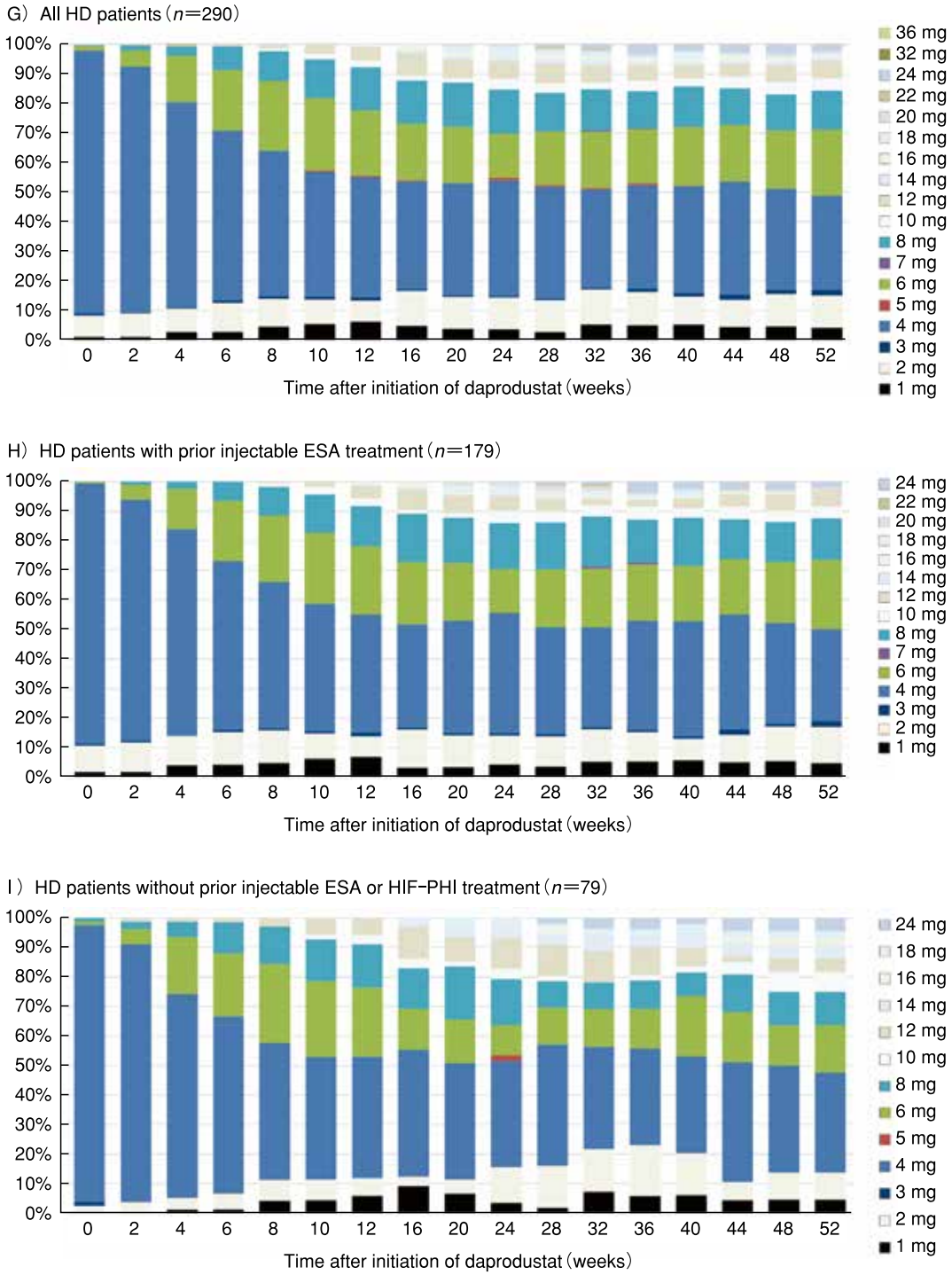
Supplemental Fig. 1 Daprodustat dosing







Supplemental Fig. 1 Daprodustat dosing (Continued)



Supplemental Fig. 1 Daprodustat dosing (Continued)

Supplemental Table 1　Heart failure–related ADRs

Dialysis status at baseline	Preexisting HF	No prior HF
ND	*n*＝100	*n*＝443
ADR of HF or exacerbation of HF, *n*（%）	1（1）	0
PD	*n*＝14	*n*＝40
ADR of HF or exacerbation of HF, *n*（%）	0	0
HD	*n*＝25	*n*＝265
ADR of HF or exacerbation of HF, *n*（%）	0	1（0.4）

ADR：adverse drug reaction, HD：hemodialysis, HF：heart failure, ND：no dialysis, PD：peritoneal dialysis

Supplemental Table 2　ADRs based on daprodustat dose

	Safety population (*n*＝887)		ND (*n*＝543)		PD (*n*＝54)		HD (*n*＝290)	
	Patients, *n*	ADR, *n*（%）	Patients, *n*	ADR, *n*（%）	Patients, *n*	ADR, *n*（%）	Patients, *n*	ADR, *n*（%）
Total initial dose, mg								
＜2	20	1（5.0）	15	0	2	0	3	0
2	295	10（3.4）	266	7（2.6）	8	0	21	3（14.3）
＞2 to ＜4	2	0	0	0	0	0	2	0
4	558	41（7.3）	256	15（5.9）	44	4（9.1）	258	21（8.1）
＞4	12	0	6	0	0	0	6	0
Average daily dose, mg/day								
＜2	42	2（4.8）	29	0	4	0	9	1（11.1）
≧2 to ＜4	372	15（4.0）	300	8（2.7）	10	1（10.0）	60	5（8.3）
≧4 to ＜6	355	27（7.6）	190	11（5.8）	28	3（10.7）	141	13（9.2）
≧6 to ＜8	66	6（9.1）	14	3（21.4）	8	0	42	3（7.1）
≧8 to ＜12	35	0	7	0	2	0	26	0
≧12 to ＜18	15	2（13.3）	2	0	2	0	11	2（18.2）
≧18 to≦24	2	0	1	0	0	0	1	0
＞24	0	0	0	0	0	0	0	0
Maximum daily dose, mg								
＜2	10	0	9	0	2	0	0	0
≧2 to ＜4	231	7（3.0）	216	5（2.3）	4	0	10	1（10.0）
≧4 to ＜6	359	24（6.7）	231	10（4.3）	21	4（19.0）	110	10（9.1）
≧6 to ＜8	130	8（6.2）	53	3（5.7）	9	0	68	4（5.9）
≧8 to ＜12	97	8（8.2）	25	2（8.0）	13	0	56	6（10.7）
≧12 to ＜18	41	2（4.9）	7	2（28.6）	4	0	31	0
≧18 to ≦24	18	3（16.7）	2	0	1	0	14	3（21.4）
＞24	1	0	0	0	0	0	1	0

ADR：adverse drug reaction, HD：hemodialysis, ND：no dialysis, PD：peritoneal dialysis