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Vadadustat for anemia in chronic kidney disease patients on peritoneal dialysis: A phase 3 open-label study in Japan

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Abstract

Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor for the treatment of anemia in patients with chronic kidney disease (CKD). This phase 3, open-label, 24-week single-arm study evaluated the efficacy and safety of vadadustat in 42 Japanese CKD patients with anemia undergoing peritoneal dialysis. Patients received oral vadadustat for 24 weeks, initiated at 300 mg/day and doses were adjusted to achieve the target hemoglobin (Hb) range of 11.0-13.0 g/dL. Least squares mean of average Hb at weeks 20 and 24 was 11.35 g/dL, which was within the target range. The most frequent adverse events were catheter site infections (23.8%), which were not related to vadadustat treatment. Vadadustat was generally well tolerated and effective in controlling Hb levels within the target range, indicating the usefulness of vadadustat for treating anemia in Japanese CKD patients undergoing peritoneal dialysis.

KEYWORDS

anemia, chronic kidney disease, hypoxia-inducible factor prolyl hydroxylase inhibitor, peritoneal dialysis, vadadustat

1 | INTRODUCTION

An estimated 13% of the Japanese adult population, approximately 13.3 million individuals, have chronic kidney disease (CKD), almost 11 million of whom have CKD stage G3-G5.[1] Anemia is one of the major complications of CKD that develops in about 10% of individuals with CKD stage G3-G5,[2,3] equating to as many as 1.1 million Japanese adults with anemia in CKD.[3] Anemia develops in individuals with CKD primarily due to reduced renal erythropoietin production,[2] can lead to compensatory changes in the structure and function of the heart,[4] and is associated with increased morbidity and mortality from cardiovascular disease.[5–7] In addition, symptoms of anemia such as fatigue, shortness of breath, and weakness can have a substantial negative impact on quality of life.[8,9]

Injectable erythropoiesis-stimulating agents (ESAs) are the current standard of care for anemia in CKD; however, concerns about possible safety risks of ESA therapy have been reported in several studies, where the higher ESA doses and higher hemoglobin (Hb) targets were associated with an increased risk of mortality and cardiovascular events.[10–13] Hemodialysis patients can receive ESA injections during their scheduled dialysis. However,

peritoneal dialysis patients who receive their dialysis at home must make regular clinic visits specifically for ESA injections. This can be especially burdensome for patients who have chosen home peritoneal dialysis in order to avoid the constraints of frequent dialysis center visits.[14,15] Although current use of peritoneal dialysis in Japan is relatively low compared with other countries,[16,17] its use is anticipated to increase in the near future because it enables home medical care and reduces the burden on hospitals.[15] In addition, the benefits of peritoneal dialysis, such as better control of blood pressure and milder dietary restrictions compared with hemodialysis, are being increasingly recognized among healthcare professionals and patients.[15,18] Therefore, an orally administered treatment option for anemia in CKD may be of value to patients undergoing peritoneal dialysis, allowing them to administer their dialysis and anemia treatments at home.

Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) for the treatment of anemia in CKD. HIF acts as a central regulator of erythropoiesis, coordinating hypoxic responses such as erythropoietin production.[13] In phase 2 clinical trials, vadadustat significantly raised and maintained Hb levels in patients with anemia in nondialysis-dependent or hemodialysis-dependent CKD,[19–21] and maintained mean Hb concentrations on switching from ESA in patients with hemodialysis-dependent CKD.[22] Recent phase 3 trials have shown noninferiority of vadadustat to darbepoetin alfa in controlling Hb in Japanese patients with anemia associated with nondialysis-dependent CKD[23] and hemodialysis-dependent CKD.[24] No studies in patients with anemia receiving peritoneal dialysis have yet been reported with vadadustat.

The objective of this study was to evaluate the efficacy and safety of vadadustat in Japanese CKD patients with anemia undergoing peritoneal dialysis.

2 | PATIENTS AND METHODS

2.1 | Study design

This was a phase 3, open-label, single-arm study in patients with anemia in CKD receiving peritoneal dialysis and was conducted at 25 sites in Japan. The study comprised a screening period of up to 6 weeks, a 24-week treatment period, and follow-up until 2 weeks after the end of the treatment period (Figure 1). The protocol was approved by each site's institutional review board, and all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and applicable laws and regulations. The study was registered at www.clinicaltrials.gov (NCT03402386).

2.2 | Study population

Major inclusion criteria were age ≥ 20 years, with CKD and receiving peritoneal dialysis for >4 weeks before screening, and not expecting to start hemodialysis during the study. Both "ESA users" and "ESA nonusers" were enrolled in this study. ESA users were to have received the same ESA for ≥8 weeks before screening and have mean Hb of 9.0-12.5 g/dL (based on the last 2 Hb measurements) during screening. ESA nonusers had not received any ESA for 8 weeks before screening, and were to have mean Hb of 8.0-11.0 g/dL during screening. All patients were to have serum ferritin ≥100 ng/mL or transferrin saturation (TSAT) ≥20%.

Key exclusion criteria were nonrenal causes of anemia; uncontrolled hypertension; active fundus disease or ocular fundus observations not available; severe heart failure; cerebrovascular disorder; acute coronary syndrome; or malignancy in the last 5 years.

2.3 | Treatment protocol

During the treatment period, study visits were conducted at day 1 (baseline), every 2 weeks up to week 12, and every 4 weeks thereafter until week 24. Patients received oral vadadustat (Akebia Therapeutics Inc., Cambridge, MA, USA) during the treatment period at an initial dose of 300 mg/day, administered once daily, and the dose was adjusted to within the range of 150 to 600 mg/day using a dose-adjustment algorithm to maintain Hb levels within

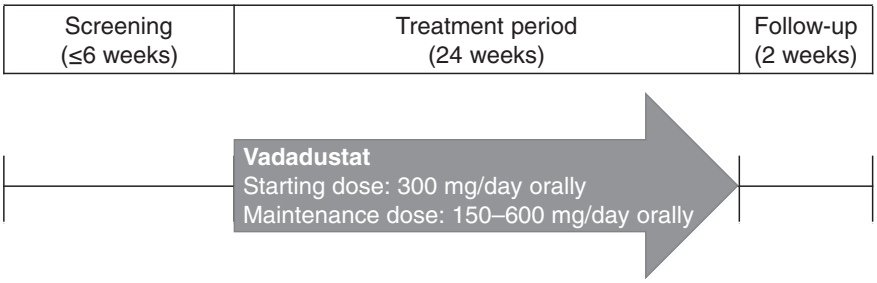


FIGURE 1 Study design

the predefined target range of 11.0 to 13.0 g/dL. In accordance with the dose-adjustment algorithm, vadadustat dose was reduced by 150 mg if a patient's Hb was >12.5 g/dL or they experienced a rapid Hb rise (defined as an Hb rise >2.0 g/dL over 4 weeks). Vadadustat dose was increased by 150 mg if a patient's Hb was <11.0 g/dL. For patients with Hb 13.0-13.5 g/dL and with rapid Hb rise, or Hb >13.5 g/dL, vadadustat was interrupted until Hb was 13.0 g/dL or lower, and was then resumed at a dose reduced by 150 mg. In principle, the interval between vadadustat dose increases was to be 4 or more weeks.

Iron supplements were administered during the screening and treatment periods to maintain serum ferritin levels ≥100 ng/mL or TSAT ≥20%. Patients receiving an iron-containing phosphate binder at screening continued its use at the same dose until the end of the treatment period.

ESAs, red blood cell transfusion, or phlebotomy were only permitted as rescue therapy at the investigator's discretion during the treatment period.

2.4 | Outcome measures

The efficacy endpoint was average Hb at weeks 20 and 24. Other efficacy endpoints included Hb at each time point; the proportion of patients with Hb within the target range (11.0-13.0 g/dL); erythropoietin; iron-related parameters (serum iron, total iron-binding capacity [TIBC], TSAT, serum ferritin, serum hepcidin); and red blood cell indices (mean corpuscular volume [MCV], mean corpuscular Hb [MCH], mean corpuscular Hb concentration [MCHC], and red blood cell distribution width [RDW]). All laboratory parameters were measured by a central laboratory (LSI Medience Corporation, Tokyo, Japan). Serum erythropoietin was measured using a chemiluminescent enzyme immunoassay. Serum hepcidin and plasma vascular endothelial growth factor (VEGF) were measured using an enzyme-linked immunosorbent assay.

Safety evaluations included adverse events (AEs) and vital signs, assessed during the treatment period. Ophthalmic fundus examination was performed during screening and during weeks 20 to 24. AEs of special interest were defined from those of mechanistic concern in the HIF-PHI class[25,26] and ESAs,[10–13] such as cardiovascular events/cardiac failure, thromboembolism, pulmonary hypertension, malignancy, retinal disorders, and hyperkalemia.

2.5 | Statistical analysis

The planned enrollment was 40 patients. Assuming a standard deviation (*SD*) of 1.78 for mean Hb based on a

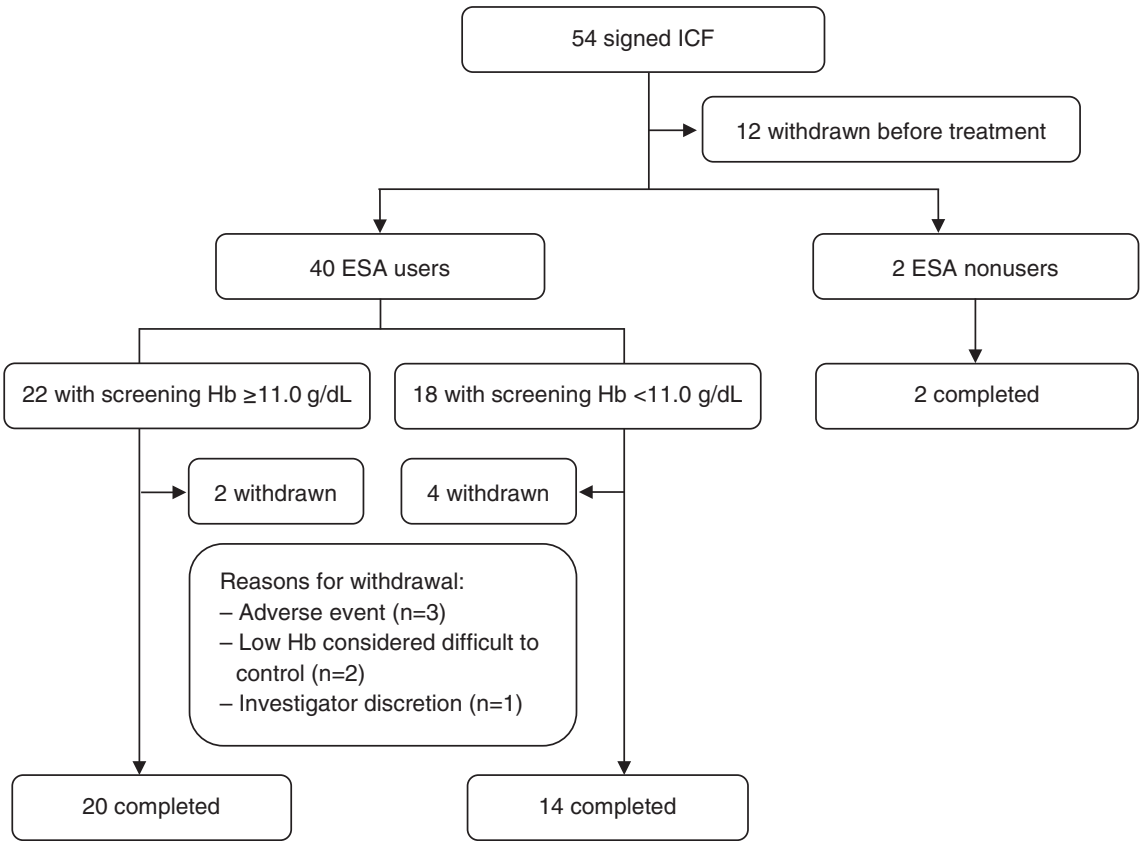


FIGURE 2 Patient flow diagram. ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ICF, informed consent form

previous clinical study of vadadustat,[20] a sample size of 40 patients allows for mean Hb estimation with 95% confidence interval (CI) of ±0.57 g/dL. As Hb values vary in a range of about 1 g/dL in normal clinical contexts,[27] a level of precision of mean Hb ±0.57 g/dL (95% CI) should allow for clinically meaningful analysis. The full analysis set (FAS) and safety populations included all patients with efficacy and safety data after receiving vadadustat, respectively. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

The average Hb at weeks 20 and 24 was modeled using mixed-model repeated measures (MMRM) and calculated as least squares (LS) mean with two-sided 95% CIs. This MMRM model included visits as a fixed effect, baseline values as covariate effects, and patient as a random effect (covariance matrix: unstructured). Missing data were not imputed for this efficacy endpoint.

For the analysis of other efficacy and safety endpoints, including iron-related parameters, red blood cell indices, and blood pressure, descriptive statistics were calculated for week 24 using last observation carried forward (LOCF). To be consistent with other efficacy endpoints, post hoc analyses were conducted to calculate 95% CIs for MCHC and RDW. Changes from baseline were analyzed using paired *t*-tests at the two-sided alpha level of 0.05. Mean doses of vadadustat and oral iron supplementation were calculated for the period between each time point. The McNemar test was used to compare the percentage of patients with Hb within the target range to baseline.

As well as the FAS, efficacy data and vadadustat dose were analyzed for the ESA user group, and for the subgroups of ESA users with mean Hb <11.0 g/dL and Hb ≥11.0 g/dL. Statistical analyses for the subgroup of ESA nonusers, which included only 2 patients, were not performed.

3 | RESULTS

3.1 | Demographic and baseline clinical characteristics

A total of 54 patients provided informed consent and 42 patients were enrolled in the study. All 42 enrolled patients were included in the FAS and safety population. Overall, 36 patients (85.7%) completed the study (Figure 2); six patients (14.3%) were withdrawn from the study owing to AEs (three patients), low Hb that the investigator considered difficult to control (two patients), or inability to attend study visits (one patient).

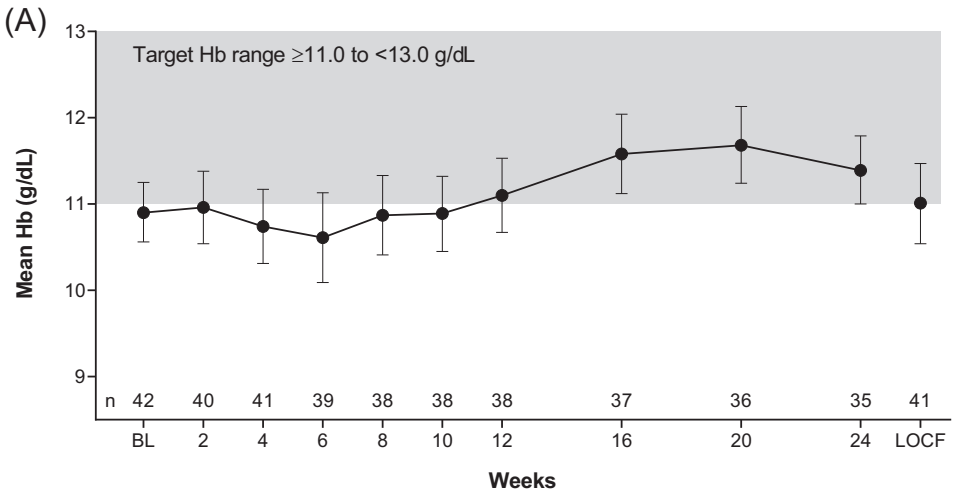
Patient characteristics at baseline are shown in Table 1 for the FAS. Mean age was 63.0 years and mean Hb was 10.9 g/dL. Mean duration of anemia in CKD was 4.16 years, and mean duration of peritoneal dialysis therapy was 3.04 years. All 42 patients had at least one complication such as hypertension (95.2%), dyslipidemia (61.9%), or diabetes (19.0%) (Table 1).

Forty patients were included in the ESA user group. Of these 40 patients, 18 patients (45.0%) had Hb <11.0 g/dL and 22 patients (55.0%) had Hb ≥11.0 g/dL at screening (Figure 2). In the ESA user group, prior ESA

TABLE 1 Baseline characteristics (FAS)

Characteristic	Vadadustat (N = 42)
Sex (male), n (%)	30 (71.4)
Age (y)	63.0 (12.6)
Height (cm)	162.0 (9.2)
Body weight (kg)	64.7 (12.9)
BMI (kg/m^2)	24.5 (3.9)
Duration of anemia from CKD (y)	4.16 (3.43)
Duration of peritoneal dialysis (y)	3.04 (3.19)
Etiology of CKD, n (%)	
Autoimmune/glomerulonephritis/vasculitis	15 (35.7)
Hypertension	11 (26.2)
Diabetes	8 (19.0)
Cystic/hereditary/congenital disease	3 (7.1)
Other	4 (9.5)
Unknown	3 (7.1)
Complications, n (%)	
Hypertension	40 (95.2)
Diabetes	8 (19.0)
Dyslipidemia	26 (61.9)
Hb (g/dL)	10.90 (1.10)
Serum ferritin (ng/mL)	193.9 (182.7)
TSAT (%)	33.8 (11.1)
Patients receiving oral iron, n (%)	8 (19.0)
Patients receiving iron-containing phosphate binder, n (%)	11 (26.2)
Prior ESA treatment, n (%)	n = 40
Darbepoetin alfa	21 (52.5)
Epoetin beta pegol	19 (47.5)
Prior ESA dose (μg/week)	
Darbepoetin alfa (n = 21)	21.9 (14.2)
Epoetin beta pegol (n = 19)	27.1 (20.4)

Note: Data are mean (*SD*) unless otherwise stated.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agents; FAS, full analysis set; Hb, hemoglobin; TSAT, transferrin saturation; y, year(s).



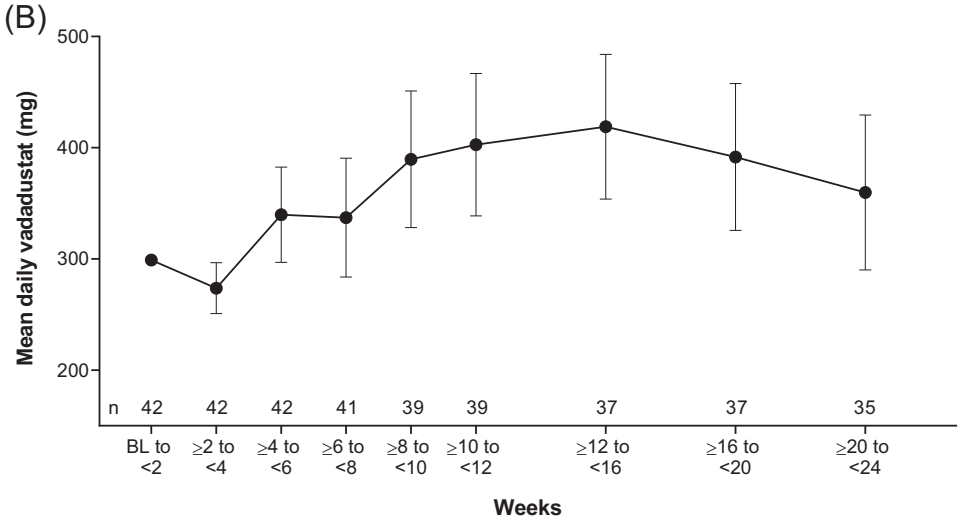


FIGURE 3 Mean (A) hemoglobin and (B) vadadustat dose over 24 weeks (FAS). Symbols represent mean values and bars indicate 95% confidence intervals (CIs). BL, baseline; FAS, full analysis set; Hb, hemoglobin; LOCF, last observation carried forward; n, number of patients

treatments were darbepoetin alfa (52.5%) at a mean dose of 21.9 μg/week, or epoetin beta pegol (47.5%) at a mean dose of 27.1 μg/week (Table 1). Two patients were included in the ESA nonuser group (Figure 2).

3.2 | Hb levels

Mean Hb levels are shown in Figure 3A for the overall population. The LS mean of average Hb at weeks 20 and 24 was 11.35 g/dL (95% CI, 10.99-11.70).

For ESA users with screening Hb <11.0 g/dL, mean Hb levels reached the target range at week 16 (Figure 4A); the percentage of patients with Hb within the target range increased from 22.2% at baseline (n = 18, within range: 4; below range: 14) to 61.5% at week 24 (n = 13, within range: 8; below range: 5). One patient experienced a rapid Hb rise from baseline to week 4. For ESA users with screening Hb ≥11.0 g/dL, mean Hb levels were maintained within the target range throughout the 24-week treatment period (Figure 4B), and no patients experienced a rapid Hb rise. The percentage of patients with Hb within the target range was 90.9% at baseline (n = 22, above range: 1; within range: 20; below range: 1) and 70.0% at week 24 (n = 20, above range: 2; within range: 14; below range: 4).

Both of the two ESA nonusers showed increases in Hb levels during the treatment period, from 8.6 g/dL at baseline to 9.7 g/dL at week 24 in one patient, and from 9.2 to 11.1 g/dL in the other patient. A rapid Hb rise was not observed.

Mean (*SD*) serum erythropoietin was 18.5 (19.5) mIU/mL at baseline and 14.9 (14.0) mIU/mL at week 24 in the overall population. There was no clear change from baseline in serum erythropoietin levels. The maximum value of serum erythropoietin observed during the treatment period from all patients was 187.0 mIU/mL. The erythropoietin data are limited by the fact that the timing of blood sampling for erythropoietin analysis was not consistent across patients; however, the maximum concentrations of

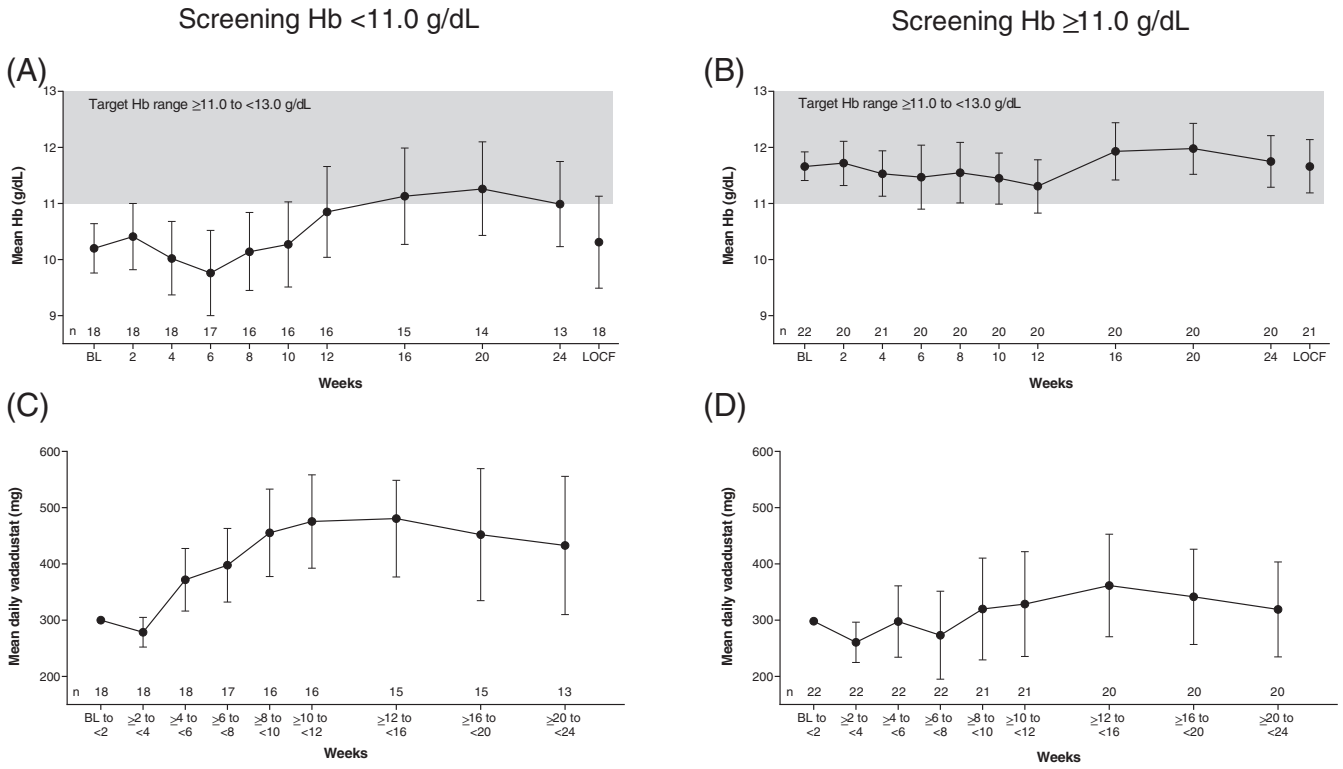


FIGURE 4 Mean hemoglobin and vadadustat dose over 24 weeks in ESA users with screening Hb <11.0 g/dL (A, C) and ESA users with screening Hb ≥11.0 g/dL (B, D). Symbols represent mean values and bars indicate 95% confidence intervals. BL, baseline; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; n, number of patients

plasma erythropoietin observed in our study were within the range of physiological fluctuations.[28]

3.3 | Vadadustat dose

Vadadustat was initiated at a dose of 300 mg/day and mean dose from weeks 20 to 24 was 360 mg/day (Figure 3B). Mean vadadustat dose from weeks 20 to 24 was 433 mg/day in ESA users with screening Hb <11.0 g/dL (Figure 4C) and 319 mg/day in ESA users with screening Hb ≥11.0 g/dL (Figure 4D).

Nearly all patients in the overall population (41 patients, 97.6%) had vadadustat dose adjustments during the treatment period. Over half (24 patients, 57.1%) had dose adjustments twice; other patients had no adjustments (1 patient, 2.4%) or 1 (8 patients, 19.0%), 3 (3 patients, 7.1%), 4 (5 patients, 11.9%), or 5 (1 patient, 2.4%) adjustments. Eleven interruptions in vadadustat dosing occurred in 10 patients (23.8%); 7 were based on the vadadustat dose-adjustment algorithm, 2 were owing to AEs, one was owing to Hb >13.0 g/dL at the lowest permitted vadadustat dose, and one was owing to a rapid drop in Hb based on the investigator's judgment. Of the 10 patients, 6 patients completed the study.

3.4 | Iron-related measures and iron supplementation

For the overall population, decreases from baseline were seen in mean serum ferritin (Figure 5A), TSAT (Figure 5B), hepcidin (Figure 5D), and RDW (Figure 5H), whereas there were increases from baseline in TIBC (Figure 5C), MCV (Figure 5E), and MCH (Figure 5F) at week 24 LOCF in this study. Mean serum iron levels and MCHC showed no changes from baseline (Figure 5I and G).

Oral iron supplements were used by eight patients (19.0%; n = 42) during the screening period and eight patients (22.2%; n = 36) during the last 4 weeks (weeks 20 to 24) of the treatment period. Mean iron dose was 1236 mg/month during screening and 1453 mg/month during weeks 20 to 24 (Figure 5J). No patients received intravenous iron.

3.5 | Rescue therapy

During the treatment period, two patients (4.8%) received red blood cell transfusions as rescue therapy, and one patient (2.4%) also received rescue ESA. The

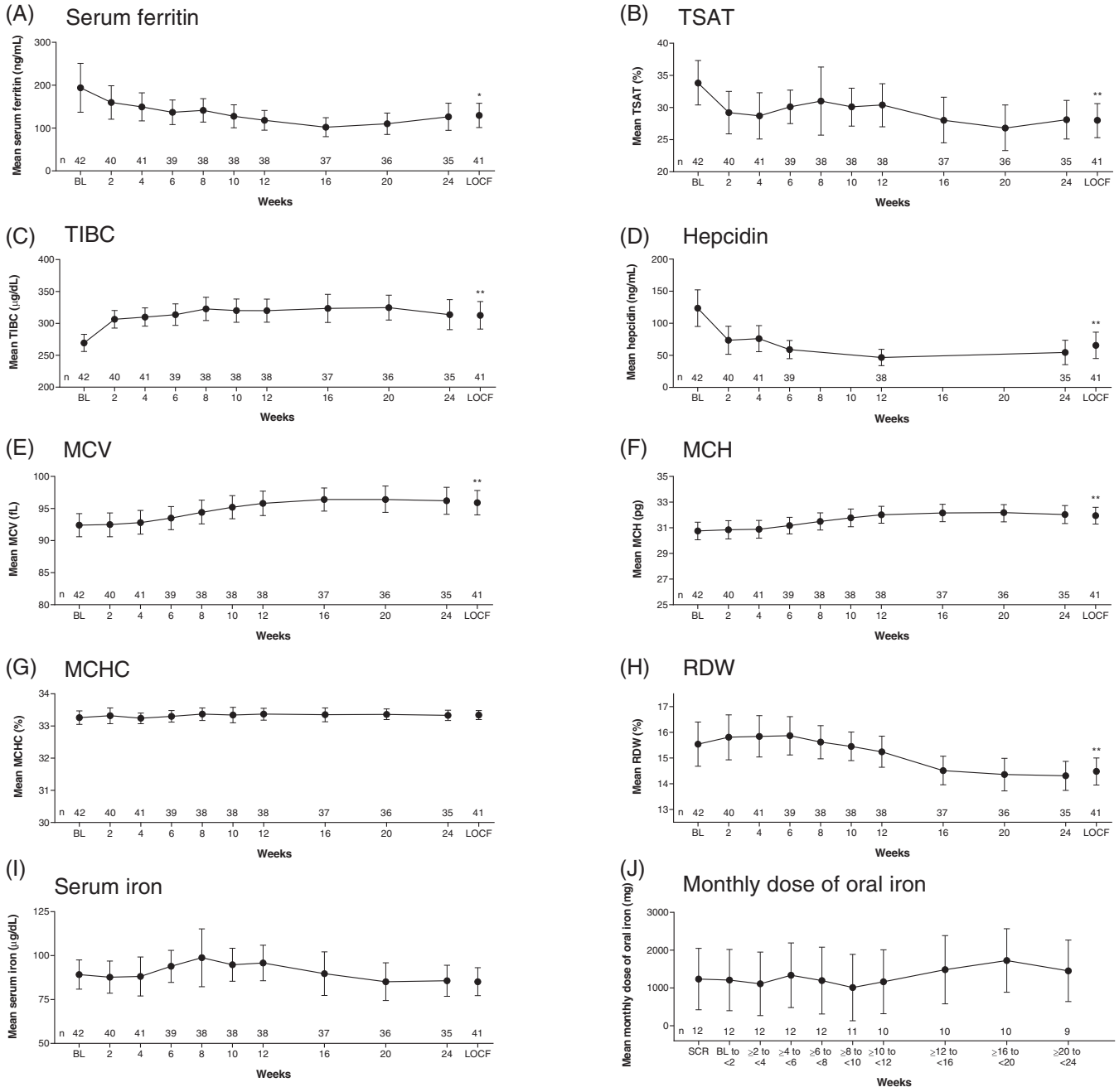


FIGURE 5 Mean iron-related parameters over 24 weeks; (A) serum ferritin, (B) TSAT, (C) TIBC, (D) hepcidin, (E) MCV, (F) MCH, (G) MCHC, (H) RDW, (I) serum iron, and (J) monthly dose of oral iron supplementation over 24 weeks (FAS). Symbols represent mean values and bars indicate 95% confidence intervals. Asterisks indicate significant difference between week 24 LOCF and baseline, except for dose of iron, which is between weeks 20 and 24 and screening (paired *t* test; $*P < .05$, $**P < .01$). BL, baseline; CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; n, number of patients; RDW, red blood cell distribution width; SCR, screening; TIBC, total iron-binding capacity; TSAT, transferrin saturation

patient who received both types of rescue therapy was withdrawn owing to low Hb that the investigator considered difficult to control. No patients received phlebotomy.

3.6 | Safety and tolerability

Overall, 38 patients (90.5%) experienced at least one AE. The common AEs were catheter site infection,

TABLE 2 Adverse events after 24 weeks of treatment (safety population)

Overview	Vadadustat (N = 42)
Patients, n (%)	
≥1 AE	38 (90.5)
≥1 adverse drug reaction	5 (11.9)
≥1 serious AE	12 (28.6)
≥1 serious adverse drug reaction	1 (2.4%)
≥1 AE leading to discontinuation	3 (7.1)
AE leading to dose reduction or interruption	2 (4.8)
Death	1 (2.4)
AEs reported in ≥5% of patients, n (%)	
Catheter site infection	10 (23.8)
Diarrhea	8 (19.0)
Nasopharyngitis	6 (14.3)
Peritonitis	5 (11.9)
Vomiting	4 (9.5)
Abdominal pain upper	3 (7.1)
Decreased appetite	3 (7.1)
Nausea	3 (7.1)
Serious AEs reported in ≥ 5% of patients, n (%)	
Peritonitis	3 (7.1)
AEs of special interest, n (%)	
Cardiovascular event, cardiac failure[a]	3 (7.1)
Cardiac failure chronic	1 (2.4)
Cerebral infarction[b]	1 (2.4)
Myocardial ischemia	1 (2.4)
Retinal disorders	4 (9.5)
Retinal hemorrhage	2 (4.8)
Macular degeneration	1 (2.4)
Macular fibrosis	1 (2.4)
Retinal vein occlusion[b]	1 (2.4)
Thromboembolism	5 (11.9)
Peripheral arterial occlusive disease	2 (4.8)
Cerebral infarction	1 (2.4)
Retinal vein occlusion	1 (2.4)
Shunt occlusion	1 (2.4)
Hyperkalemia	0
Malignancy	0
Pulmonary hypertension	0

Abbreviations: AE, adverse event.
[a]Combined data for cardiovascular events and cardiac failure.
[b]Also reported in thromboembolism.

diarrhea, nasopharyngitis, and peritonitis (Table 2); all common AEs, except for diarrhea in two patients, were considered by investigators to be unrelated to vadadustat treatment. Two patients were withdrawn from the study owing to AEs of cerebral infarction and traumatic hemothorax, and two patients had dose interruptions owing to AEs of sepsis and peripheral arterial occlusive disease, all of which were considered by investigators to be unrelated to vadadustat treatment.

TABLE 3 Ophthalmic assessments at 24 weeks of treatment (safety population)

Assessment outcome, n (%)	Vadadustat	
	Screening (n = 42)	Weeks 20 to 24 (n = 37)
Normal or abnormal, not clinically significant	38 (90.5)	32 (86.5)
Abnormal, clinically significant	4 (9.5)	5 (13.5)

Of the serious AEs in this study, a causal relationship to vadadustat could not be ruled out only for one patient who died of myocardial ischemia. The 70-year-old male had a history of myocardial infarction and died due to the event 38 days after the start of study treatment. The patient received a vadadustat dose of 450 mg/day from week 4. The mean Hb levels of the patient were 9.0, 9.0, and 8.9 g/dL at baseline, week 2, and week 4, respectively, and no rapid rise in Hb levels during the study. Ferritin levels were 82.8, 67.1, and 68.7 ng/mL with TSAT of 20%, 32%, and 26% at baseline, at week 2 and at week 4, respectively. Autopsy was not performed and the investigator was unable to identify a cause of death; therefore, a possible relationship between myocardial ischemia and vadadustat could not be excluded by the investigator.

The frequency of AEs of special interest was <5% for individual preferred terms, and a causal relationship to vadadustat was excluded except for one death owing to myocardial ischemia, described above, and one event of retinal hemorrhage. The retinal hemorrhage was mild, and the plasma VEGF of the patient at 24 weeks was not elevated (<15.6 pg/mL, ie, below the detection limit). A causal relationship to vadadustat was excluded for other retinal disorders (macular degeneration and retinal vein occlusion; Table 2). There was no vadadustat-related thromboembolism. Hyperkalemia was not reported in this study.

Mean (*SD*) plasma VEGF was 43.5 (18.6) pg/mL at baseline and 47.6 (23.9) pg/mL at week 24. There was no clear change from baseline in plasma VEGF levels. Ophthalmic assessments were normal or abnormal not clinically significant for 90.5% of patients at screening and 86.5% at Weeks 20 to 24 (Table 3). No changes from baseline to week 24 in blood pressure were observed (Figure 6A and B).

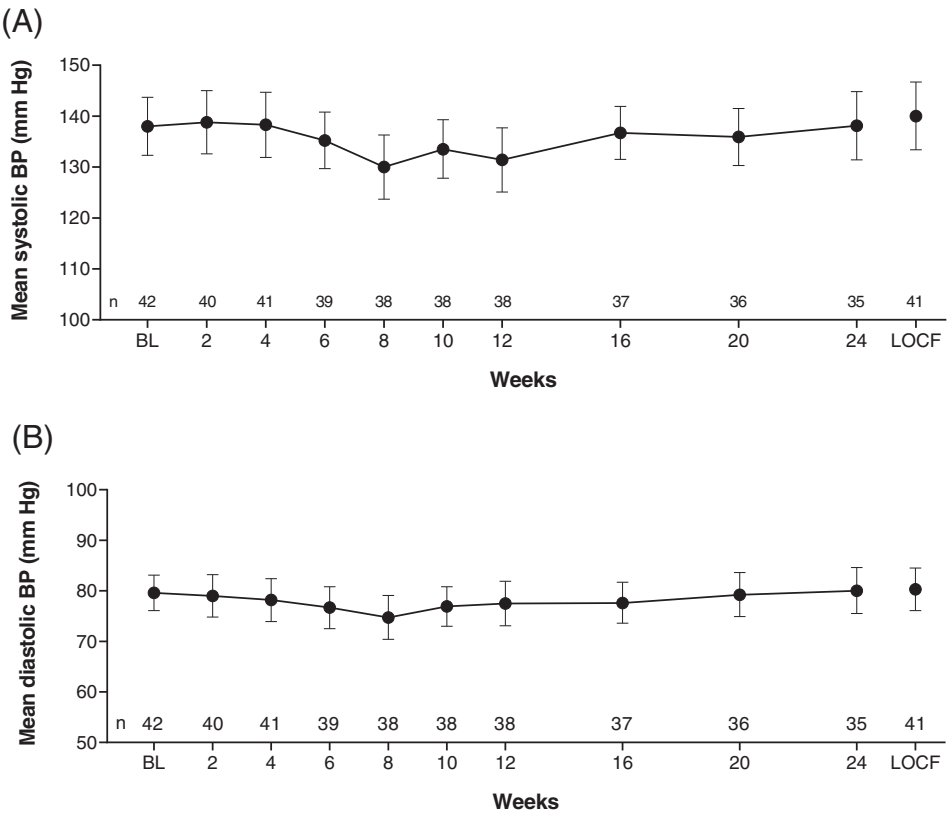


FIGURE 6 Mean (A) systolic blood pressure and (B) diastolic blood pressure over 24 weeks (FAS). Symbols represent mean values and bars indicate 95% confidence intervals. BL, baseline; BP, blood pressure; FAS, full analysis set; LOCF, last observation carried forward; n, number of patients

4 | DISCUSSION

This is the first phase 3 study evaluating the efficacy and safety of vadadustat in Japanese patients with anemia in CKD receiving peritoneal dialysis. All patients started on a 300 mg dose of vadadustat, regardless of Hb level, and were individually titrated to an optimal dose. The LS mean of average Hb at Weeks 20 and 24 was within the predefined target range of 11.0 to 13.0 g/dL in the FAS.

In ESA users with screening Hb <11.0 g/dL, mean Hb levels achieved target range at 16 weeks. The fact that it took time for average Hb to enter the target Hb range may be due to the dose adjustment algorithm applied in this study, which permitted dose increases no more frequently than every 4 weeks. The time when average Hb entered the target range coincided with the time when the average dose of vadadustat increased by about 1 dose. The proportion of patients whose Hb entered the target range increased from 22.2% at baseline to 61.5% at 24 weeks.

In ESA users with screening Hb ≥11.0 g/dL, mean Hb levels were maintained within the target range throughout the treatment period. The proportion of these patients with Hb within the target range was 90.9% at baseline and 70.0% at week 24, a decrease of 20.9% ($P = 0.157$) compared with baseline. The number of patients with Hb outside the target range at 24 weeks increased by 4 (above range: 2; below range: 4) compared with baseline (below range: 2). This numerical decrease in the proportion of patients with Hb within the target range may have been affected by the small sample size in the subgroup of ESA users with screening Hb ≥11.0 g/dL and is not considered to reflect an insufficient Hb maintenance effect with vadadustat. It therefore appears possible to control Hb within the target range with vadadustat treatment in ESA users, regardless of the baseline Hb level.

In this study, there were only 2 cases of ESA nonusers, and increases in Hb levels were observed in both patients. It is difficult to conclude efficacy of vadadustat in ESA nonusers receiving peritoneal dialysis based on these results alone. In a study of ESA nonusers receiving hemodialysis, the proportion of patients in the target Hb range increased from 16.7% at baseline to 73.7% at 24 weeks of vadadustat treatment (study J04, NTC03461146; unpublished data). A similar increase was seen in nondialysis-dependent ESA nonusers, from 15.5% at baseline to 69.7% at 24 weeks of vadadustat treatment.[23] Taken together, these results suggest that vadadustat can be expected to effectively manage Hb levels in ESA nonusers receiving peritoneal dialysis.

Until now, nothing had been reported about the changes in iron-related parameters in peritoneal dialysis patients treated with vadadustat. In the present study, decreases in serum ferritin, TSAT, and hepcidin and an increase in TIBC from baseline to the end of the study

period were observed. These changes in the iron-related parameters are consistent with results of the previous phase 2 studies with hemodialysis patients.[20] Hence, the effects of vadadustat on iron-related parameters are suggested to be similar in both peritoneal dialysis and hemodialysis patients.

It is known that peritoneal dialysis is often associated with complications that arise from contamination of the peritoneal catheter, resulting in peritonitis and related symptoms such as abdominal pain.[29] Many of the most common AEs and serious AEs in our study, including catheter site infection and peritonitis, are consistent with those related to peritoneal dialysis. The incidence of peritonitis in this study was 1 episode every 40.5 patient-months, which is similar to a previous registry study (1 episode every 42.8 patient-months) of peritoneal dialysis patients in Japan.[30] In the case of long-acting ESA clinical trials, adverse reactions of hypertension are reported in 6% (epoetin beta pegol) and 11.1% (darbepoetin alfa) of treated patients.[31] No hypertension and no increases in mean diastolic or systolic blood pressure were observed with vadadustat in our study. In accordance with the available safety data on vadadustat in phase 2 clinical trials,[19–22] vadadustat was generally safe and well tolerated in peritoneal dialysis patients in this study.

The 2015 guidelines of the Japanese Society for Dialysis Therapy referenced in the present study state that a rapid rise in Hb level is a risk factor for cardiovascular-related events in the treatment of renal anemia.[27] Iron supplementation is also recommend if ferritin is <100 ng/mL and TSAT is <20%[32] in the guideline, and iron deficiency reported to be associated with thrombotic event.[33] In addition, the Recommendations on the proper use of HIF-PH inhibitors released in September 2020 by the Japanese Society of Nephrology (https://jsn.or.jp/data/HIF-PH_recommendation.pdf) state that patients should be managed to avoid iron deficiency as precautions for thromboembolism. In this study, one cardiovascular event for which a causal relationship to the drug could not be ruled out occurred in one patient, who died of myocardial ischemia and had a history of myocardial infarction. The Hb level in this patient remained at the baseline level throughout the study period, and did not increase rapidly, which might suggest that changes in Hb levels were not associated with the recurrence of myocardial ischemia. For the iron status during the period from baseline to week 4, ferritin levels remained <100 ng/mL, but TSAT tended to increase. Therefore, it is unlikely that vadadustat aggravated the iron status, which caused the recurrence of myocardial infarction.

No malignancy cases were observed in the present study; however, HIF regulates VEGF, an angiogenic growth factor, and increased VEGF expression has been shown to enhance malignancy and metastatic potential.[21,34,35] Some authors have reported a direct relationship between HIF and malignancy.[36,37] However, malignant tumors and elevated plasma VEGF were not observed with vadadustat in this study, although blood VEGF values may not reflect local VEGF.[38,39] These results are consistent with previous Japanese trials in which vadadustat-related malignancy was not observed.[20,23,24] However, the relationship between HIF-PHI class and AEs of special interest, especially malignancy, needs to be further investigated.

The small sample size, open-label design, lack of a control group and short treatment duration are limitations of this study.

5 | CONCLUSIONS

In Japanese patients with anemia in CKD undergoing peritoneal dialysis, including ESA users and nonusers, average Hb was within the target range at 20 and 24 weeks of vadadustat treatment. Vadadustat was well tolerated and no new safety concerns were observed. These results support the use of vadadustat as an effective and safe treatment for anemia in patients with CKD who are undergoing peritoneal dialysis.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION STATEMENT

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. Masaomi Nangaku, Kazuoki Kondo, Genki Kaneko, Makiko Otsuka, Yutaka Kawaguchi, and Yasuhiro Komatsu were involved in the study design, and Yutaka Kawaguchi conducted the statistical analysis.

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