


A phase 3, open-label, single-arm study of vadadustat for anemia in chronic kidney disease for Japanese patients on hemodialysis not receiving erythropoiesis-stimulating agents

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Abstract

Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor approved in Japan for the treatment of anemia in patients with chronic kidney disease (CKD). This phase 3, open-label, single-arm study evaluated the efficacy and safety of vadadustat in 24 Japanese patients with CKD-associated anemia on hemodialysis who were not receiving erythropoiesis-stimulating agents (ESAs). Patients received vadadustat for 24 weeks; the starting dose was 300 mg/day and doses were adjusted to achieve the target hemoglobin (Hb) range of 10.0–12.0 g/dL. The least squares mean of average Hb at Weeks 20 and 24 (95% confidence interval) was 10.75 g/dL (10.35, 11.14). The most common adverse event was shunt stenosis (25.0%). Adverse drug reactions (diarrhea and vomiting) occurred in two patients (8.3%) and the severity was mild. Vadadustat increased and maintained Hb levels within the target range and was generally well-tolerated in Japanese patients with anemia on hemodialysis not receiving ESAs.

KEYWORDS

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

1 | INTRODUCTION

Anemia is a common complication in patients with chronic kidney disease (CKD), and primarily develops due to insufficient production of renal erythropoietin in response to reduced hemoglobin (Hb) [1]. The frequency and severity of anemia in CKD increases with decreased kidney function [2,3]. Injectable erythropoiesis-stimulating agents (ESAs)

along with iron supplementation is currently the standard of care for anemia in CKD [1]. However, several studies have reported potential safety concerns associated with higher doses of ESAs or higher Hb targets, including an increased risk of cardiovascular events and mortality [4].

Hypoxia-inducible factors (HIFs) are transcription factors involved in regulating erythropoietin production [5,6]. Treatment with HIF prolyl hydroxylase inhibitors

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(HIF-PHIs) is expected to mimic hypoxic conditions by stabilizing HIF, which induces endogenous erythropoietin production, and results in improvements in anemia in CKD; these drugs have recently been developed as novel therapies for this condition [5,7]. Vadadustat is a HIF-PHI recently approved in Japan for the treatment of anemia in CKD [8]. Phase 3 clinical studies conducted in Japan have reported the safety and efficacy of vadadustat for the treatment of anemia associated with non-dialysis-dependent CKD (both ESA users and nonusers) [9], hemodialysis-dependent CKD (ESA users) [10], and in patients with CKD who were receiving peritoneal dialysis (both ESA users and nonusers) [11].

There are very few data available regarding the efficacy and safety of vadadustat for the treatment of anemia in Japanese patients with CKD who are on hemodialysis and not being treated with ESAs. The only available data are from a phase 2 trial of vadadustat that was conducted to determine the initial treatment dose for subsequent phase 3 trials [12]. Thus, the objective of the present study was to evaluate the efficacy and safety of vadadustat for the treatment of anemia in CKD in Japanese patients undergoing hemodialysis who were not receiving ESA treatment.

2 | PATIENTS AND METHODS

2.1 | Study design

This was a phase 3, open-label, single-arm study in patients with CKD-associated anemia undergoing hemodialysis who had not been treated with ESAs or had undergone ESA washout prior to the screening period. The study was conducted at 25 centers in Japan. The study consisted of a screening period of up to 6 weeks, a 24-week treatment period, and a 2-week follow-up observation period.

Ethical approval was obtained from the institutional review boards of all participating study sites, and the study was conducted in accordance with the Pharmaceuticals and Medical Devices Act, Good Clinical Practice (GCP), the Declaration of Helsinki, and related regulations. All patients provided written informed consent prior to study participation. The study was registered at www.clinicaltrials.gov (NCT03461146).

2.2 | Patients

Details of the inclusion and exclusion criteria are provided in the Supplementary Methods. In brief, the inclusion criteria were CKD patients aged ≥ 20 years, receiving either hemodialysis or hemodiafiltration three times per week,

average Hb level (last two measurements during screening) of ≥ 8.0 and < 10.0 g/dL, difference in final two Hb measurements during screening of < 1.5 g/dL, serum ferritin level ≥ 100 ng/mL or transferrin saturation (TSAT) of $\geq 20\%$ during screening, and not receiving ESAs for at least the following duration prior to the start of the screening period: epoetin alfa/beta/kappa, 1 week; darbepoetin alfa, 2 weeks; and epoetin beta pegol, 4 weeks.

Key exclusion criteria were nonrenal causes of anemia, uncontrolled hypertension, active ocular fundus disease or 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, patients received oral vadadustat (Akebia Therapeutics Inc., Cambridge, MA) at an initial dose of 300 mg/day and a maintenance dose within a range of 150–600 mg/day, to maintain Hb levels within the predefined target range of 10.0–12.0 g/dL. The target Hb range was selected based on the 2015 guidelines of the Japanese Society for Dialysis Therapy, for patients with anemia in CKD on hemodialysis [3]. Dose adjustments were made according to the dose adjustment algorithm described in the Supplementary Methods.

Iron supplements were administered during the screening and treatment periods to maintain serum ferritin ≥ 100 ng/mL or TSAT $\geq 20\%$; dosage and administration route were determined by the investigators. In principle, new prescriptions of iron-containing phosphate binders were prohibited after the start of screening, and patients receiving an iron-containing phosphate binder at screening continued its use at the same dose until the end of the treatment period. Oral iron supplements and iron-containing phosphate binders were not to be taken within 2 h before or after administration of vadadustat, to avoid a decline in the bioavailability of vadadustat.

During the treatment period, ESAs, testosterone enanthate, mepitostane, and blood transfusions were not permitted (see the Supplementary Methods for details on prohibited medications/therapies). As rescue therapy, administration of ESAs, red blood cell transfusion, and phlebotomy were allowed at the investigator's discretion. Even if rescue therapy was given, patients could remain in the study at the discretion of the investigator.

2.4 | Outcome measures

The main efficacy endpoint was average Hb at Weeks 20 and 24. Other efficacy endpoints included Hb at each

time point, the proportion of patients within the Hb target range (10.0–12.0 g/dL), rate of Hb increase (from baseline to Week 4), mean vadadustat dose and distribution of vadadustat dose, iron dose, iron-related parameters (serum iron, total iron binding capacity [TIBC], TSAT, serum ferritin, and 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]). A central laboratory (LSI Medience Corporation, Tokyo, Japan) measured all laboratory parameters.

Safety evaluations included recording of adverse events (AEs) and adverse drug reactions. Additionally, laboratory evaluations, blood pressure measurements, plasma vascular endothelial growth factor (VEGF) measurements, and ophthalmic fundus examinations were performed. AEs of special interest were defined as those of mechanistic concern associated with the HIF-PHI and ESA drug classes, such as cardiovascular events/cardiac failure, thromboembolism, pulmonary hypertension, malignancy, retinal disorders, and hyperkalemia [13,14]. Safety outcomes also included the proportion of patients with Hb of either ≥ 12.0 or ≥ 13.0 g/dL, and the proportion of patients with a Hb increase > 2.0 g/dL within 4 weeks.

2.5 | Statistical methods

Considering the low number of patients who are non-ESA users on hemodialysis, the number of patients eligible for this study was thought to be quite limited. Therefore, the target number of patients was set at 20.

The full analysis set (FAS) included all patients who received at least one dose of vadadustat and had at least one efficacy measurement after the start of treatment. If rescue treatment was given, data from the day after the rescue treatment were not used for the main efficacy endpoint. The safety population included all patients who received at least one dose of vadadustat and had safety data available. Mixed-model repeated measures (MMRM) was used to model the average Hb at Weeks 20 and 24, which was calculated as the least squares (LS) mean with two-sided 95% confidence intervals (CIs). Visits were included as a fixed effect, baseline values as covariate effects, and patient as a random effect (covariance matrix: unstructured) in the MMRM model. For this efficacy endpoint, missing data were not imputed. Descriptive statistics were calculated from baseline or the screening period to Week 24 using the last observation carried forward (LOCF) method for other efficacy and safety endpoints, which included iron-related parameters, red blood cell indices, Hb value, dose of supplemental iron, blood

pressure, and plasma VEGF. Post hoc analyses were conducted to calculate 95% CIs for MCHC and RDW for consistency with other efficacy endpoints. Paired *t*-tests with a two-sided $\alpha = 0.05$ were used to analyze change in mean monthly iron dose from the screening period to Weeks 20–24, and to analyze changes from baseline to Week 24 (LOCF) for iron-related parameters, red blood cell indices, and blood pressure. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.; Cary, NC).

3 | RESULTS

3.1 | Demographic and baseline clinical characteristics

Patient disposition is shown in Figure 1. Of the 30 patients who provided informed consent, 24 were enrolled and received treatment, and 21 completed the study. The reasons for study discontinuation are shown in Figure 1.

Baseline characteristics are shown in Table 1. The mean (standard deviation, SD) duration of anemia in CKD was 4.5 (3.1) years and the mean (SD) duration of hemodialysis was 5.1 (4.5) years. The mean (SD) Hb at baseline was 9.2 (1.0) g/dL. Additional baseline characteristics, including history of cardiovascular disease, are shown in Table S1. A total of 19 patients underwent ESA washout and five patients were ESA nonusers at baseline. Changes in Hb during the screening period, stratified by with or without ESA washout, are shown in Table S2. Although the Hb decrease was slightly greater in patients who underwent ESA washout, a decrease in Hb was also observed in patients without ESA washout. Details on the types and doses of ESAs used before washout are shown in Table S3.

3.2 | Hb levels

The LS mean of average Hb at Weeks 20 and 24 (95% CI) was 10.75 g/dL (10.35, 11.14). The mean Hb over time is shown in Figure 2. After treatment initiation, the mean Hb increased from baseline and reached the target range at Week 8, and the mean rate of Hb increase from baseline to Week 4 was 0.05 g/dL/week (95% CI: -0.05 , 0.16). The mean Hb level was maintained within the target range from Week 8 to Week 24. At Week 24, the LS mean Hb was 10.89 g/dL (95% CI: 10.47, 11.31).

The proportion of patients within the target Hb range increased from 4/24 (16.7%) patients at baseline to 14/19 (73.7%) patients at Week 24 (Figure 3). At Week

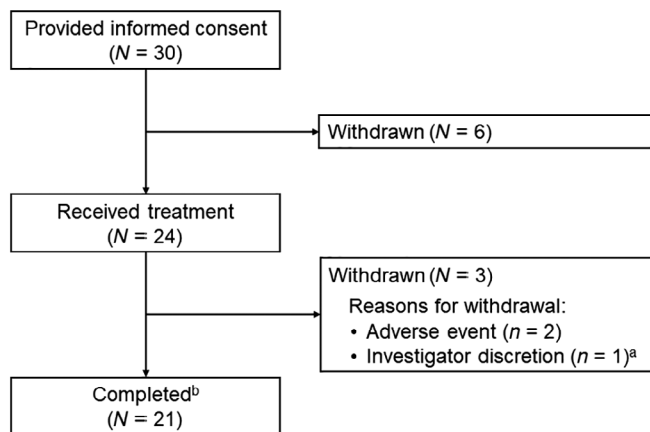


FIGURE 1 Patient flow diagram. ^a Treatment was discontinued because blood transfusion was necessary to improve hemoglobin level. ^b Although 21 patients completed the study, two of these were excluded from the efficacy analysis because they received rescue therapy

16, although the proportion of patients with Hb above the target range transiently increased (5/19 patients; 26.3%), only one patient had a Hb value >13 g/dL (13.1 g/dL). At Week 24, 3/19 (15.8%) patients had Hb measurements above the target range, but no patient exceeded a Hb level of 13 g/dL.

3.3 | Vadadustat dose

Vadadustat was started at a dose of 300 mg/day and the average dose at each time point is shown in Figure S1. The mean dose was 332.3 mg/day at Weeks 20–24. The distribution of doses at Week 20 was 5.3%, 31.6%, 26.3%, 5.3%, and 31.6% for 0, 150, 300, 450, and 600 mg vadadustat, respectively. At Week 20, although the proportion of patients receiving the 450-mg dose was low (5.3%), there was no bias toward either 150 mg or 600 mg. The proportion of patients who underwent dose adjustment was the highest between Weeks 4 and 6 (63.6%) and decreased to less than 20% after Week 10. The dose distribution at each time point is shown in Figure S2.

3.4 | Iron-related measures, red blood cell indices, and iron supplementation

Increases from baseline were seen in TIBC and RDW, whereas TSAT, serum ferritin, and hepcidin decreased from baseline at Week 24 (LOCF) (Figure 4). Mean serum iron, MCV, MCH, and MCHC did not change from baseline. Intravenous iron supplements were

TABLE 1 Baseline characteristics (full analysis set)

Characteristic	Vadadustat (N = 24)
Male sex, n (%)	19 (79.2)
Age, years	63.0 ± 12.4
Height, cm	163.6 ± 9.1
Body weight, kg	63.6 ± 13.7
Body mass index, kg/m ²	23.7 ± 4.1
Duration of anemia due to CKD, years	4.5 ± 3.1
Duration of hemodialysis, years	5.1 ± 4.5
Etiology of CKD, n (%)	
Diabetes	8 (33.3)
Autoimmune/glomerulonephritis/vasculitis	6 (25.0)
Hypertension	3 (12.5)
Unknown	7 (29.2)
Complications, n (%)	
Hypertension	22 (91.7)
Dyslipidemia	11 (45.8)
Diabetes	8 (33.3)
Hemoglobin, g/dL	9.2 ± 1.0
Serum ferritin, ng/mL	303.9 ± 194.4
Transferrin saturation, %	42.0 ± 19.3
Patients receiving intravenous iron, n (%)	2 (8.3)
Patients receiving iron-containing phosphate binder, n (%)	7 (29.2)

Notes: Data are means ± standard deviations, unless otherwise stated. Abbreviation: CKD, chronic kidney disease.

administered in 8/24 (33.3%) patients and oral iron supplements were not used throughout the treatment duration. Mean intravenous iron doses during the screening period and Weeks 20–24 were 64.7 mg/month and 112.9 mg/month, respectively. Seven patients were taking iron-containing phosphate binders prior to the start of screening and each patient maintained their dosage throughout the study period. No patients initiated iron-containing phosphate binder therapy during the study period. The mean dosages were 3250 and 3938 mg/day for ferric citrate hydrate and sucroferric oxyhydroxide, respectively.

3.5 | Safety and tolerability

AEs occurred in 23/24 (95.8%) patients; common AEs (occurring in ≥5% of patients) were shunt stenosis, nasopharyngitis, diarrhea, skin abrasion, and vomiting. Adverse drug reactions (diarrhea and vomiting) occurred

FIGURE 2 Average hemoglobin over time (full analysis set). Data are means with 95% confidence intervals. The shaded area indicates the target range. LOCF, last observation carried forward

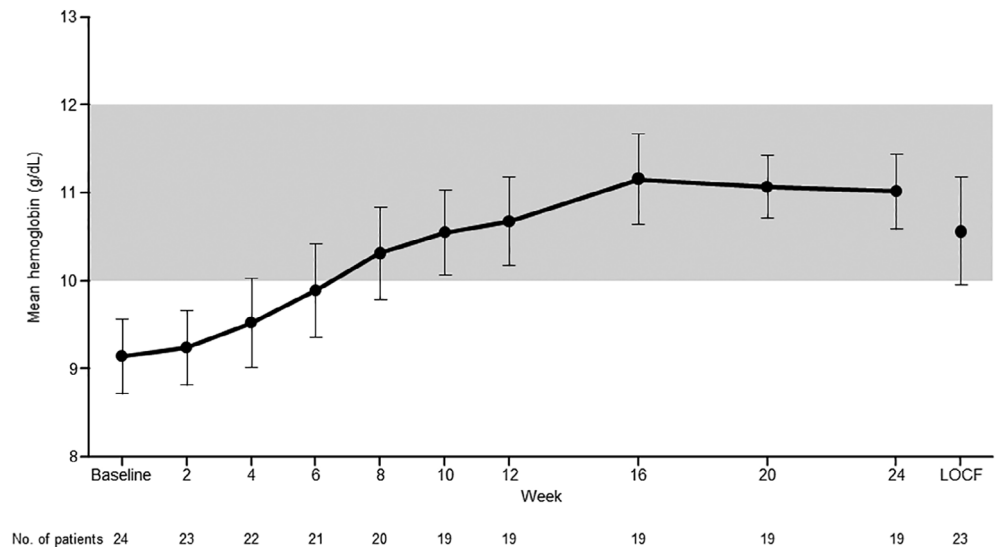
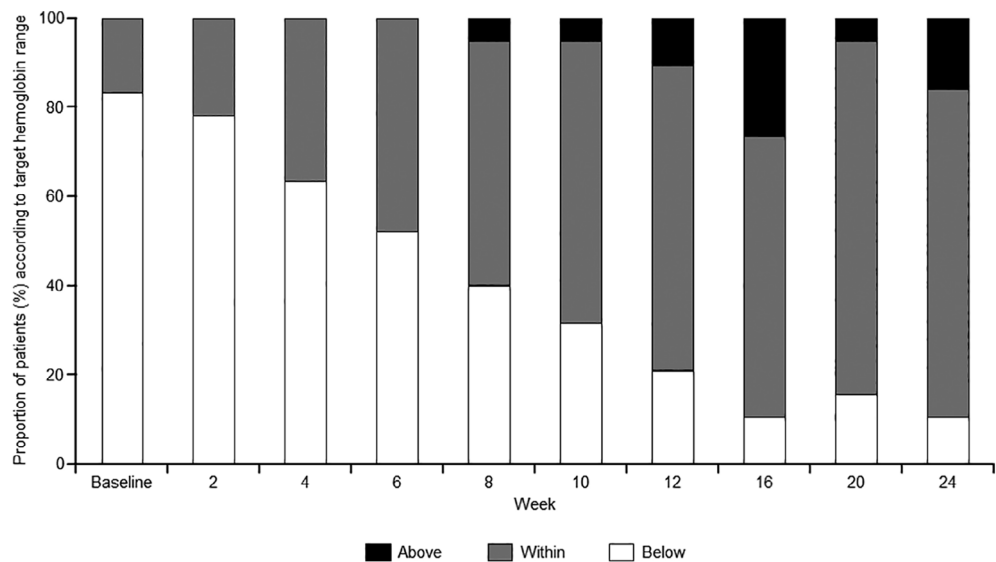


FIGURE 3 Proportion of patients at each visit with hemoglobin levels above, within, or below the target range (full analysis set)



in 2/24 (8.3%) patients and were rated as mild (Table 2). Serious AEs occurred in 7/24 (29.2%) patients; none were considered related to the study treatment and all were recovered (Table 2). Two patients discontinued due to AEs. However, these events were considered to be unrelated to the study drug. AEs of special interest included cardiac dysfunction in one patient and thromboembolism in two patients (arteriovenous fistula occlusion and peripheral arterial occlusion).

One of 24 patients (4.2%) experienced a rapid increase in Hb (0.625 g/dL/week), exceeding the criteria of a rapid increase (0.5 g/dL/week). The patient's Hb increased from a baseline level of 8.2 to 10.7 g/dL at Week 4 with a vadadustat dose of 300 mg; Hb was maintained in the target range from Weeks 4–24 without any further rapid increases. During the treatment period, 7/24 patients (29.2%) had a Hb measurement ≥ 12 g/dL. One of these patients had a Hb

measurement ≥ 13 g/dL at a vadadustat dose of 450 mg. After stopping administration of the study drug, the patient's Hb returned to within the target range at the next visit, 4 weeks later. There were no clinically significant exacerbations noted in ophthalmic fundus examinations during the study. Blood pressure did not increase significantly at Week 24 compared with baseline; respective mean (SD) at baseline and Week 24 values were 140.8 (17.1) and 144.8 (20.8) mm Hg for systolic blood pressure and 78.2 (9.8) and 80.7 (10.4) mm Hg for diastolic blood pressure. The mean (SD) plasma VEGF levels were 51.0 (20.7) pg/mL at baseline and 54.0 (25.9) pg/mL at Week 24.

4 | DISCUSSION

This was the first phase 3 study to evaluate the efficacy and safety of vadadustat in Japanese patients with CKD-

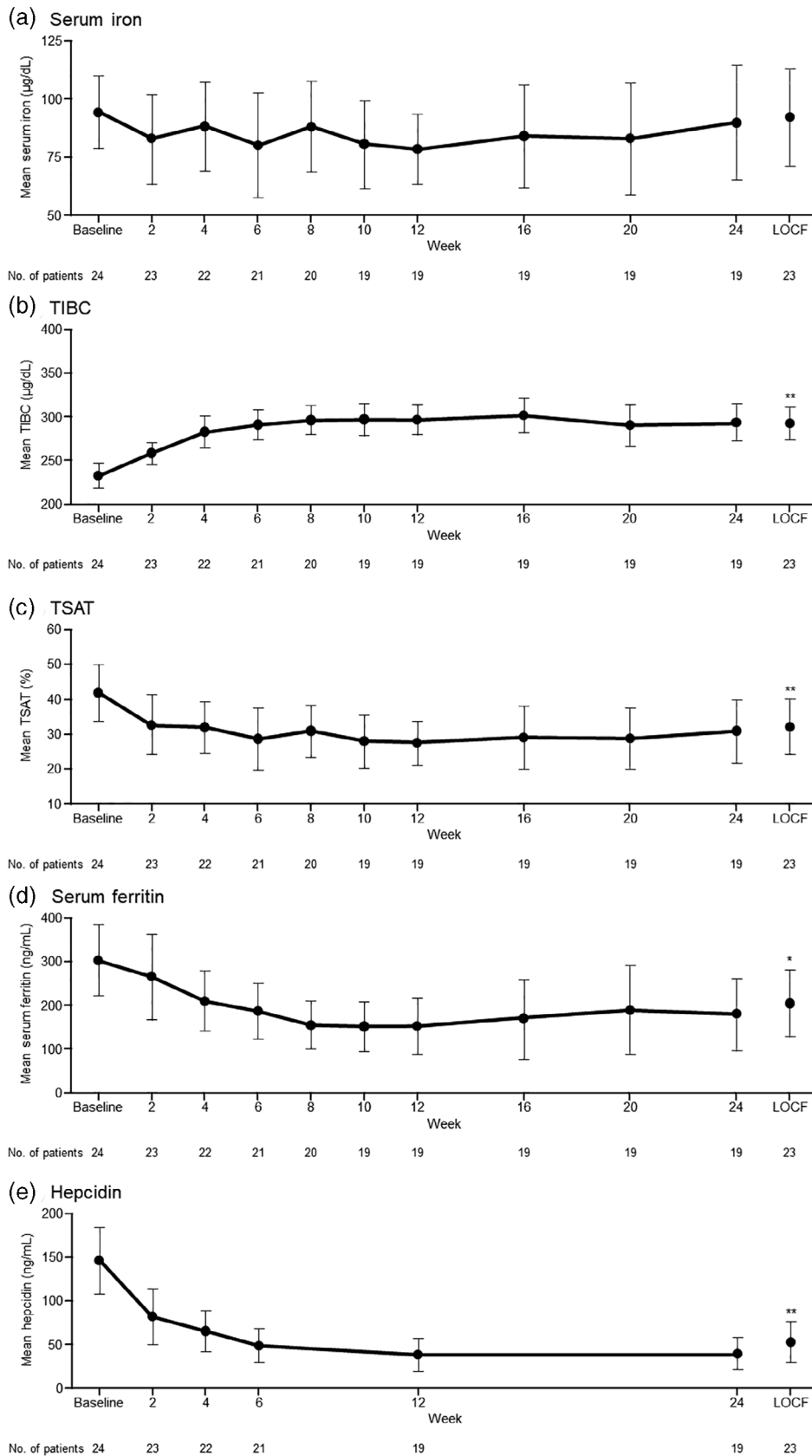


FIGURE 4 Change in iron-related measures and red blood cell indices over time (full analysis set). (a) Serum iron, (b) TIBC, (c) TSAT, (d) serum ferritin, (e) Hepcidin, (f) MCV, (g) MCH, (h) MCHC, (i) RDW, (j) IV iron. Asterisks indicate a significant difference from baseline (paired *t*-test; **p* < 0.05; ***p* < 0.01). Data are means with 95% confidence intervals. BL, baseline; IV, intravenous; LOCF, last observation carried forward; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width; TIBC, total iron binding capacity; TSAT, transferrin saturation; WK, week

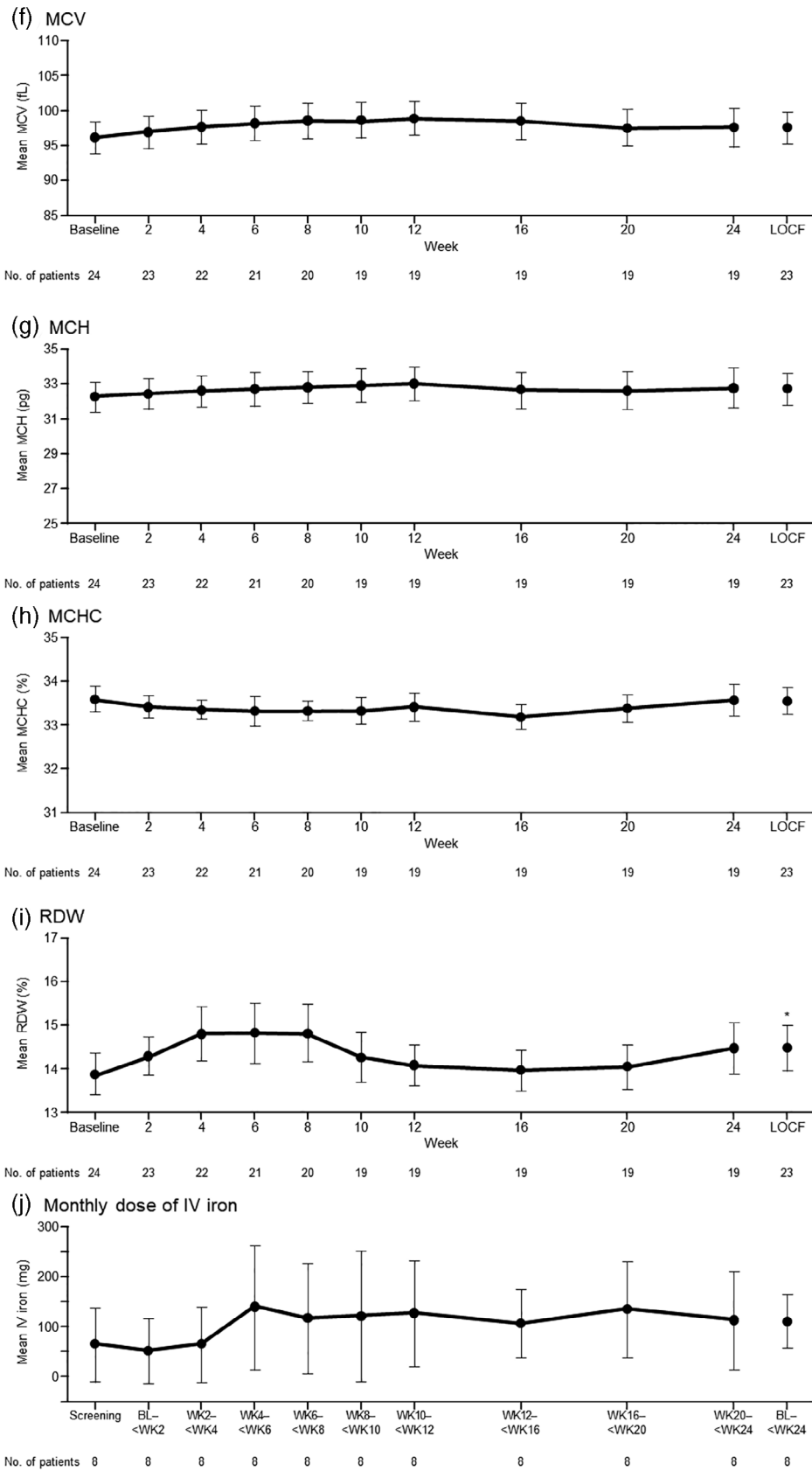


FIGURE 4 (Continued)

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

Overview	Vadadustat (N = 24)
Patients, <i>n</i> (%)	
≥1 AE	23 (95.8)
≥1 adverse drug reaction	2 (8.3)
≥1 serious AE	7 (29.2)
≥1 serious adverse drug reaction	0 (0.0)
≥1 AE leading to discontinuation	2 (8.3)
AE leading to dose reduction or interruption	1 (4.2)
Death	0 (0.0)
AEs reported in ≥5% of patients, <i>n</i> (%)	
Shunt stenosis	6 (25.0)
Nasopharyngitis	5 (20.8)
Diarrhea	4 (16.7)
Skin abrasion	3 (12.5)
Vomiting	2 (8.3)
Serious AEs, <i>n</i> (%)	
Pneumonia	1 (4.2)
Aneurysm	1 (4.2)
Peripheral arterial occlusive disease	1 (4.2)
Duodenal ulcer hemorrhage	1 (4.2)
Clavicle fracture	1 (4.2)
Arteriovenous fistula occlusion	1 (4.2)
Shunt stenosis	1 (4.2)
Pelvic fracture	1 (4.2)
Vascular access malfunction	1 (4.2)

Abbreviation: AE, adverse event.

associated anemia who were on hemodialysis and were not receiving ESA treatment. Hb levels increased to within the target range and were maintained for up to 24 weeks, and no major safety concerns were identified. These results indicate that vadadustat may be useful for treating anemia in CKD patients on hemodialysis not receiving ESAs.

In our study, the mean Hb reached the target range and was maintained within the range up to the end of the study, and the LS mean Hb and 95% CI at Week 24 were also within the target range, suggesting the effectiveness of vadadustat in patients with baseline Hb levels below the target range. The results of the present study are consistent with those of a Japanese phase 2 study (CI-0022), which also targeted hemodialysis patients who were not using ESAs [12]. A recent phase 3 study reported that vadadustat was effective for maintaining

Hb levels within the target range in hemodialysis patients using ESAs [10]. Taken together, these studies suggest that vadadustat is effective in hemodialysis patients, regardless of ESA treatment status.

In the present study, we observed decreases in serum ferritin and hepcidin, and an increase in TIBC from baseline to the end of the study period. These changes in iron parameters were similar to the results of the phase 2 study in Japanese hemodialysis patients not using ESAs [12]. On the other hand, no remarkable decreases in ferritin or hepcidin were observed in the phase 3 study in Japanese hemodialysis patients using ESAs [10]. The differences in the changes of iron-related parameters between the studies may be related to conditions such as the prior use or nonuse of ESAs and/or the degree of Hb improvement during the study period. Further study is needed to clarify the influences of vadadustat on iron-related parameters.

AEs that occurred in ≥5% of patients in our study included shunt stenosis, nasopharyngitis, diarrhea, and skin abrasions; these AEs were also reported in the phase 3 study of vadadustat, which targeted hemodialysis patients using ESAs [10]. The occurrence of shunt stenosis was relatively high in the present study (25.0%). Thromboembolism may be involved in shunt stenosis, and an increase of blood viscosity caused by rapid Hb rise and iron deficiency has been reported to be a risk factor for thromboembolism [15,16]. To avoid iron deficiency, the current study protocol specified that iron supplementation should be initiated and titrated if ferritin was <100 ng/mL or TSAT was <20%, according to the 2015 guidelines of the Japanese Society for Dialysis Therapy [3]. In five of the six patients who developed shunt stenosis in our study, their ferritin or TSAT levels were not below those required for iron supplementation prior to stenosis onset. Therefore, it is unlikely that vadadustat induced iron deficiency leading to shunt stenosis. In addition, although one of the six patients with shunt stenosis had a Hb level ≥12 g/dL at the onset of the event, there was no rapid increase in Hb before the onset of disease in any of the patients, suggesting that rapid Hb rise was unlikely to be associated with shunt stenosis. Although a relationship between high ESA dose and thrombotic events, including dialysis vascular access-related thrombotic events, has been reported [17], we found no association between the dose of vadadustat and the development of shunt stenosis. As with all of the commonly occurring AEs in the present study, none of the cases of shunt stenosis were judged by the study investigators to be related to the study drug. In the Japanese phase 3 study [10] of vadadustat, which targeted hemodialysis patients using ESAs, the incidence of shunt stenosis was similar (~15%) in the vadadustat and control (darbepoetin alfa) groups. Nevertheless, because of the

small number of patients recruited in the present study, the potential relationship of shunt stenosis with vadadustat administration in this population should be further evaluated in post-marketing surveillance studies.

In the present study, two patients discontinued due to AEs (decreased Hb and duodenal ulcer hemorrhage). Regarding the case of decreased Hb, Hb levels at two measurements during the screening period and at baseline were 10.6, 9.3, and 9.0 g/dL, respectively. Two weeks after starting vadadustat treatment, the Hb level was 7.6 g/dL, and the patient was withdrawn from the study and received ESA rescue therapy. In the case of duodenal ulcer, the patient discontinued the study owing to ulcer-related bleeding and subsequently received a blood transfusion. It was considered that there was no causal relationship between these AEs and vadadustat. No deaths were reported in the present study and the safety data are in line with those reported in previous clinical trials of vadadustat [12–14,18]. No new safety concerns were identified in the present study.

AEs of special interest occurred in two patients: cardiac failure (cardiac dysfunction, $n = 1$) and thromboembolism ($n = 2$; arteriovenous fistula occlusion and peripheral arterial occlusive disease). Cardiac dysfunction and peripheral arterial occlusive disease developed in the same patient. This patient had a history of chronic heart failure and atherosclerosis obliterans in the lower extremities. For the second case of thromboembolism, the patient discontinued the study at the discretion of the investigator. Vadadustat was administered for only 2 days, and arteriovenous fistula occlusion developed 12 days after the discontinuation. All these events were considered to be unrelated to vadadustat. Hyperkalemia has been reported in clinical studies for other HIF-PHIs [19]; but was not reported in the present study. Increased VEGF expression has been associated with retinal disorder, enhanced malignancy and metastatic potential [18,20,21], and there are reports of a direct relationship between HIF and malignancy [22,23]. HIF upregulates VEGF; therefore, HIF-PHIs may influence VEGF levels. Although plasma VEGF values do not necessarily reflect local VEGF concentrations [24], there were no incidences of malignant tumors, elevated plasma VEGF, or retinal hemorrhage in the present study. However, larger, long-term studies are required to fully investigate the safety of vadadustat, including AEs with relatively low incidence rates and those of special interest. The results of ongoing global phase 3 studies are expected to address the issue of long-term vadadustat safety (NCT02648347, NCT02680574, NCT02865850, and NCT02892149).

The present study had several limitations, which included the small sample size, the open-label design, the lack of comparator, and the short study duration.

5 | CONCLUSIONS

The results of our study suggest that vadadustat can be used effectively and safely to treat anemia in chronic kidney disease patients not receiving erythropoiesis-stimulating agents and who are undergoing hemodialysis.


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CONFLICT OF INTEREST

Masaomi Nangaku has received honoraria, advisory fees, or research funding from Akebia, Alexion, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Dai-ichi Sankyo, GSK, JT, Kyowa Hakko Kirin, Mitsubishi Tanabe, Ono, Takeda, and Torii. Yasuhiro Komatsu has received honoraria from Baxter, Chugai, and Kyowa Hakko Kirin. Kazuoki Kondo, Souichirou Takabe, Kiichiro Ueta, Tsubasa Tandai, and Yutaka Kawaguchi are employees of Mitsubishi Tanabe Pharma Corporation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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