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ORIGINAL ARTICLE

Efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese anemic patients on hemodialysis: a Phase 3, multicenter, randomized, double-blind study

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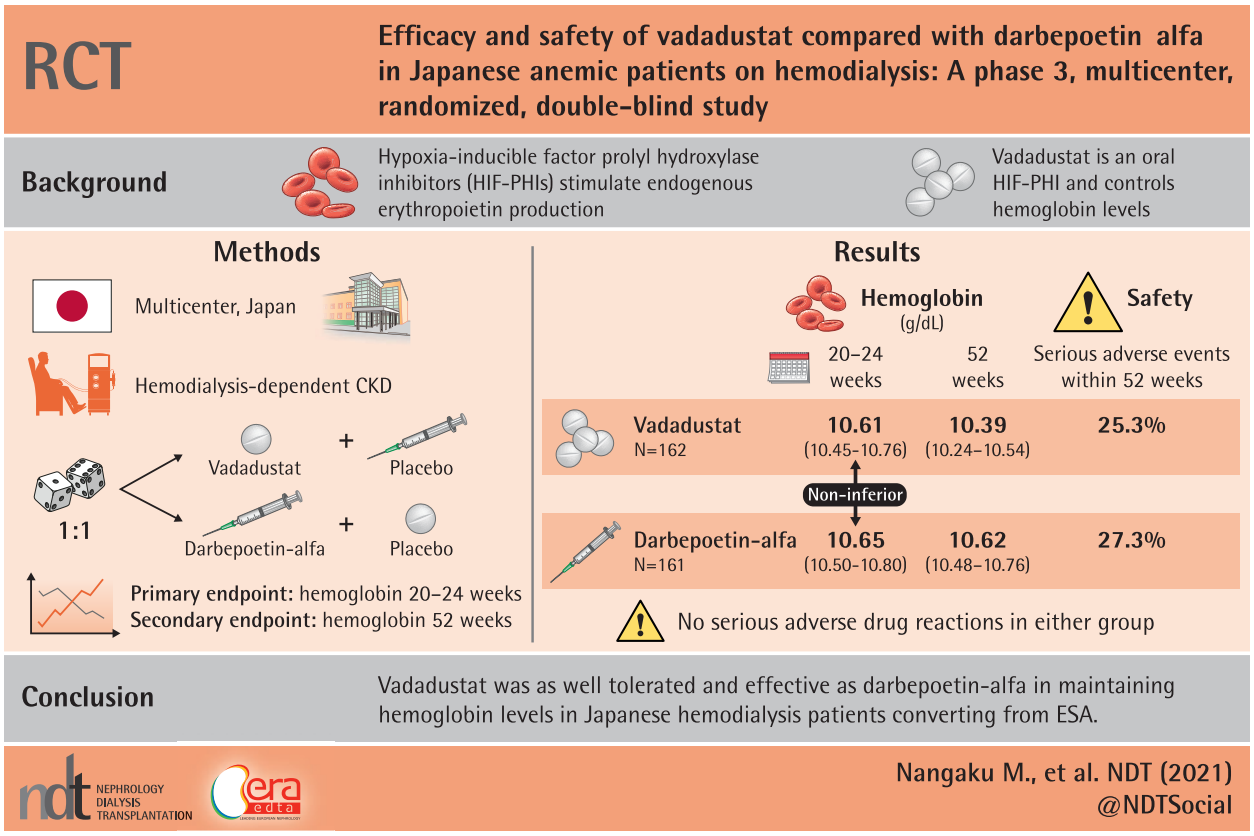
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- the injection of erythropoiesis-stimulating agents (ESAs) is the standard of care in treating renal anemia, a common complication of chronic kidney disease (CKD);
- hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), which suppress HIF degradation and increase expression of erythropoietin and its receptors, represent a new class of agents for the management of renal anemia; and
- vadadustat, an oral HIF-PHI, maintained mean hemoglobin (Hb) levels in Japanese CKD patients who were not on dialysis and those who were on hemodialysis in Phase 2 studies.

What this study adds?

- this 52-week Phase 3 study in Japanese anemic patients on hemodialysis demonstrated that the efficacy of vadadustat was noninferior to that of darbepoetin alfa as measured by average Hb levels at Weeks 20 and 24;
- in both groups, the mean Hb levels were maintained within the target range for 52 weeks. Subgroup analyses revealed that the least square means of Hb at Week 52 were within the target range in both groups, irrespective of patient's backgrounds, such as duration of hemodialysis; and
- adverse events profile in the vadadustat group was similar to that in the darbepoetin alfa group. No new safety concerns were identified.

What impact this may have on practice or policy?

- vadadustat can provide an alternative treatment of anemia in Japanese hemodialysis patients converting from ESA therapy.

ABSTRACT

Background. Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis.

Methods. The efficacy and safety of vadadustat, compared with darbepoetin alfa, was determined in a Phase 3 double-blind study in Japanese anemic patients on hemodialysis. Patients receiving erythropoiesis-stimulating agents (ESAs) were randomized and switched to either vadadustat or darbepoetin alfa for 52 weeks. Doses were adjusted to maintain a hemoglobin (Hb) level of 10.0–12.0 g/dL. The primary endpoint was average Hb level at Weeks 20 and 24.

Results. Of the 323 randomized patients, 120 and 135 completed the 52-week treatment period in the vadadustat and darbepoetin alfa groups, respectively. The average Hb levels at Weeks 20 and 24 [least square mean (LSM) and 95% confidence interval (CI)] were 10.61 (10.45–10.76) and 10.65 (10.50–10.80) g/dL in the vadadustat and darbepoetin alfa groups, respectively, demonstrating vadadustat's noninferiority to darbepoetin alfa (difference: −0.05 g/dL; 95% CI −0.26 to 0.17). In both groups, the mean Hb levels were maintained within the target range for 52 weeks. Furthermore, irrespective of patient backgrounds, the LSMs of Hb at Week 52 were within the target range. The most common adverse events were nasopharyngitis, diarrhea and shunt stenosis, which occurred at similar frequencies in both groups. No new safety concerns were identified.

Conclusions. Vadadustat was as well-tolerated and effective as darbepoetin alfa in maintaining Hb levels within the target range. The findings suggest that vadadustat can be an alternative to ESA in the management of anemia in Japanese hemodialysis patients receiving ESA (ClinicalTrials.gov, NCT03439137).

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

INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD) [1–6]. The frequency or severity of renal anemia increases as kidney dysfunction progresses primarily because the kidneys are unable to produce enough erythropoietin to compensate for the decreased hemoglobin (Hb) levels [1, 7]. If CKD progresses to end-stage kidney disease, most patients end up being treated with dialysis. The proportion of patients receiving dialysis for ≥10 years is fairly high in Japan (∼25% of dialysis patients); however, this proportion is <1% in the USA and other countries [8, 9]. Therefore, the prognosis of patients with renal anemia who are undergoing long-term dialysis should be studied, especially in Japan.

The injection of erythropoiesis-stimulating agents (ESAs) is the standard of care in treating renal anemia [7, 10, 11]. However, issues associated with the possible safety risks of ESA therapy have been reported in several clinical studies, where higher Hb targets were associated with a higher risk of mortality and cardiovascular events than those at lower target levels [12–14]. Furthermore, a meta-regression analysis of 31 clinical trials indicated that high ESA doses were associated with increased

all-cause mortality and cardiovascular complications independent of the target Hb level in patients with CKD [15]. Consequently, novel treatment options different from ESAs could benefit anemic patients.

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), which suppress HIF degradation and increase expression of erythropoietin and its receptors, represent a new class of agents for the management of renal anemia [16, 17]. Vadadustat, an oral HIF-PHI [18], maintained mean Hb levels in Japanese CKD patients who were not on dialysis and those who were on hemodialysis in Phase 2 studies [19]. We now report the results of a 52-week, Phase 3 study evaluating the efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese hemodialysis patients receiving ESA therapy. We also conducted subgroup analyses to investigate the efficacy of vadadustat in patients with many different backgrounds, including the duration of hemodialysis.

MATERIALS AND METHODS

Study design

This 52-week, Phase 3, multicenter, randomized, double-blind, active-controlled study evaluated the efficacy and safety of orally administered vadadustat in Japanese anemic CKD patients on hemodialysis who were converted from ESA therapy. The study was approved by the institutional review board of each center and conducted in compliance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice guidelines and the declaration of Helsinki. All individuals voluntarily provided their written informed consent to participate in the study.

Study population

Eligible subjects were at least 20 years of age; were diagnosed with CKD; underwent either hemodialysis or hemodiafiltration three times a week for ≥12 weeks before screening; received the same ESA therapy for ≥8 weeks before screening and had a mean Hb level of ≥9.5 to ≤12.0 g/dL, a serum ferritin level of ≥100 ng/mL or a transferrin saturation (TSAT) of ≥20% (details regarding inclusion and exclusion criteria are provided in the Supplementary data, Table S1).

Interventions

Subjects were randomly assigned in a 1:1 ratio to receive either vadadustat tablets plus darbepoetin alfa placebo infusion or vadadustat placebo tablets plus darbepoetin alfa infusion for up to 52 weeks (Supplementary data, Figure S1). Vadadustat was started at 300 mg once daily, and the dose was adjusted to 150–600 mg. The initial darbepoetin alfa dose and dosing interval were determined individually according to their previous ESA therapy; patients who had previously received darbepoetin alfa continued their usual dose and dosing interval and those on the other ESAs received darbepoetin alfa at a dose of 15–60 μg once weekly or biweekly. Vadadustat, darbepoetin alfa and their respective placebo formulations were supplied to each participating institution by Mitsubishi Tanabe Pharma Corporation (Osaka, Japan). Doses were adjusted according to the dose adjustment algorithm (Supplementary data, Table S2) to maintain Hb levels within the target range (10.0–12.0 g/dL), which is recommended as a treatment target for anemia in hemodialysis-dependent CKD by the Japanese treatment guidelines [7]. Iron supplementation was utilized to maintain a serum ferritin level of ≥100 ng/mL or TSAT of ≥20%.

Endpoints

The primary efficacy endpoint was the mean Hb levels at Weeks 20 and 24. The secondary efficacy endpoints included mean Hb levels at each point in time during the 52-week treatment period and proportions of patients with Hb levels within, above and below the target range (10.0–12.0 g/dL). Other endpoints included doses of study drugs, mean iron-related parameters, red blood cell indices and dose of iron supplementation during the 52-week treatment period.

Safety assessments included the occurrence of adverse events (AEs) and adverse drug reactions (ADRs), laboratory tests, vital signs and ophthalmoscopy tests over a 52-week period. Patients with documented Hb levels of ≥12.0 or 13.0 g/dL and those with an Hb increase rate of >2.0 g/dL over 4 weeks were evaluated. AEs of special interest were defined as those related to the HIF-PHI class and ESAs for the treatment of anemia in CKD [17, 20], including cardiovascular events/cardiac failure, retinal disorders, malignancies, hyperkalemia, pulmonary hypertension and thromboembolism.

Statistical consideration

For the primary efficacy analysis, a sample size of 300 (150 each) would yield 95% power to test the noninferiority of vadadustat to darbepoetin alfa, calculated based on the following assumptions: a mean Hb level of 11.0 g/dL at Weeks 20 and 24 for darbepoetin alfa and a difference of 0 g/dL in the mean Hb level between vadadustat and darbepoetin alfa, based on a noninferiority margin of −0.75 g/dL and standard deviation (SD) of 1.73 g/dL according to previous clinical trials of vadadustat [19].

The full analysis set included all patients with efficacy data who received at least one dose of the study drug, and the safety analysis set consisted of those who received at least one dose of the study drug and were used for statistical summarization of the safety data.

For the primary endpoint, we used a mixed-model repeated measures (MMRM) method to calculate the least square mean (LSM) of the mean Hb values and two-sided 95% confidence interval (CI) for the between-group difference at Weeks 20 and 24. The model included the treatment group, visits, interaction of the treatment group and visits as fixed effects, baseline values as covariate effects and subject as a random effect. For other endpoints, except for the dose of study drug, the paired *t*-test was used to compare between baseline or screening period and data of Week 52 using the last observation carried forward (LOCF) (significance level, two-sided P-value of 0.05).

To investigate the influence of baseline Hb levels on the efficacy of vadadustat, mean Hb and dose were stratified by tertile

Table 1. Patient characteristics at baseline (full analysis set)

Characteristics	Vadadustat ($N = 162$)		Darbepoetin alfa ($N = 161$)	
Sex (male), *n* (%)	104 (64.2)		109 (67.7)	
Age, years	66.0 ± 11.3		64.9 ± 11.7	
Body weight (dry weight), kg	58.1 ± 11.9		58.8 ± 13.8	
BMI, kg/m^2	22.4 ± 3.4		22.4 ± 4.5	
Hb, g/dL	10.73 ± 0.7		10.73 ± 0.7	
Duration of hemodialysis, years	7.4 ± 6.7		7.6 ± 7.6	
Duration of anemia from CKD, years	7.6 ± 6.2		7.6 ± 7.1	
Serum ferritin, ng/mL	144.5 ± 139.6		140.0 ± 95.3	
TSAT, %	28.6 ± 10.6		26.9 ± 9.4	
Prior ESA	*n* (%)	Weekly dose	*n* (%)	Weekly dose
Epoetin, IU	49 (30.2)	3704 ± 2118	53 (32.9)	4783 ± 3183
Darbepoetin alfa, μg	97 (59.9)	17.2 ± 12.2	90 (55.9)	18.7 ± 14.1
Epoetin beta pegol, μg	16 (9.9)	18.8 ± 12.1	18 (11.2)	22.9 ± 17.4
ERI, IU/kg/week/g/dL[a]	6.0 ± 4.0		7.0 ± 5.4	
Etiology of CKD, *n* (%)				
Diabetes	29 (17.9)		40 (24.8)	
Hypertension	20 (12.3)		22 (13.7)	
Autoimmune/glomerulonephritis/vasculitis	62 (38.3)		64 (39.8)	
Interstitial nephritis/pyelonephritis	4 (2.5)		1 (0.6)	
Cystic/hereditary/congenital disease	18 (11.1)		10 (6.2)	
Neoplasms/tumors	0 (0.0)		1 (0.6)	
Unknown	25 (15.4)		20 (12.4)	
Comorbidities, *n* (%)				
Hypertension	152 (93.8)		147 (91.3)	
Diabetes mellitus	35 (21.6)		49 (30.4)	
Dyslipidemia	59 (36.4)		79 (49.1)	

[a]ERI was calculated by the following equation as a post hoc analysis. ERI (IU/kg/week/g/dL) = standardized prior ESA (IU/week)/baseline body weight (kg)/baseline Hb (g/dL). Standardized to epoetin dose (IU/week) as follows: darbepoetin alfa (μg/week) and epoetin beta pegol (μg/week) multiplied by 200, respectively. BMI, body mass index; ERI, erythropoetin resistance index. Data are mean ± SD unless otherwise indicated.

of baseline Hb levels in the vadadustat group. Subgroup analyses including Hb levels and average dose for the various patient backgrounds were conducted with respect to the efficacy. The 95% CI of mean corpuscular Hb concentration (MCHC) and red cell distribution width (RDW), and subgroup analysis based on the duration of hemodialysis were also performed as *post hoc* analyses. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient disposition and baseline characteristics

Of the 475 patients who provided their written informed consent, 323 underwent randomization, of which 162 were included in the vadadustat group and 161 in the darbepoetin alfa group. In the vadadustat group, 136 and 120 patients completed 24 and 52 weeks of treatment, respectively. In the darbepoetin alfa group, 152 and 135 completed 24 and 52 weeks of treatment, respectively. A total of 42 and 26 patients discontinued in the vadadustat and darbepoetin alfa groups, respectively, as shown in the Supplementary data, Figure S2.

The baseline characteristics were generally well-balanced between the two groups. Overall, the mean Hb level was ∼10.7 g/dL, and the mean duration of dialysis was ∼7.6 years. The mean doses of prior ESA were ∼1.1–1.3 times and erythropoietin resistance index (ERI) was ∼1.2 times numerically higher in the darbepoetin alfa group than in the vadadustat group (Table 1).

Table 2. Difference in the average Hb levels at Weeks 20 and 24 between vadadustat and darbepoetin alfa

Treatment group	*n*	Average Hb, Weeks 20 and 24	
		LSM[a]	95% CI
Vadadustat	160	10.61	10.45 to 10.76
Darbepoetin alfa	160	10.65	10.50 to 10.80
Difference between vadadustat and darbepoetin alfa		−0.05	−0.26 to 0.17

[a]The MMRM model included treatment group, visits, interaction of treatment group and visits as fixed effects; baseline values as covariate effects and subject as a random effect (covariance matric unstructured).

Hb levels and doses

The primary endpoint, the LSM (95% CI) of the average Hb levels at Weeks 20 and 24, was 10.61 (10.45–10.76) and 10.65 (10.50–10.80) g/dL in the vadadustat and darbepoetin alfa groups, respectively. The difference in the LSM (95% CI) between the two groups was −0.05 g/dL (−0.26 to 0.17), confirming that vadadustat is noninferior to darbepoetin alfa (Table 2). The mean Hb level was maintained within the target range for up to 52 weeks in both groups. A slightly decreasing trend in Hb levels was observed during the early treatment period in the vadadustat group; however, Hb levels returned to near-baseline levels at Week 16 (Figure 1a). The LSMs (95% CI) of Hb levels

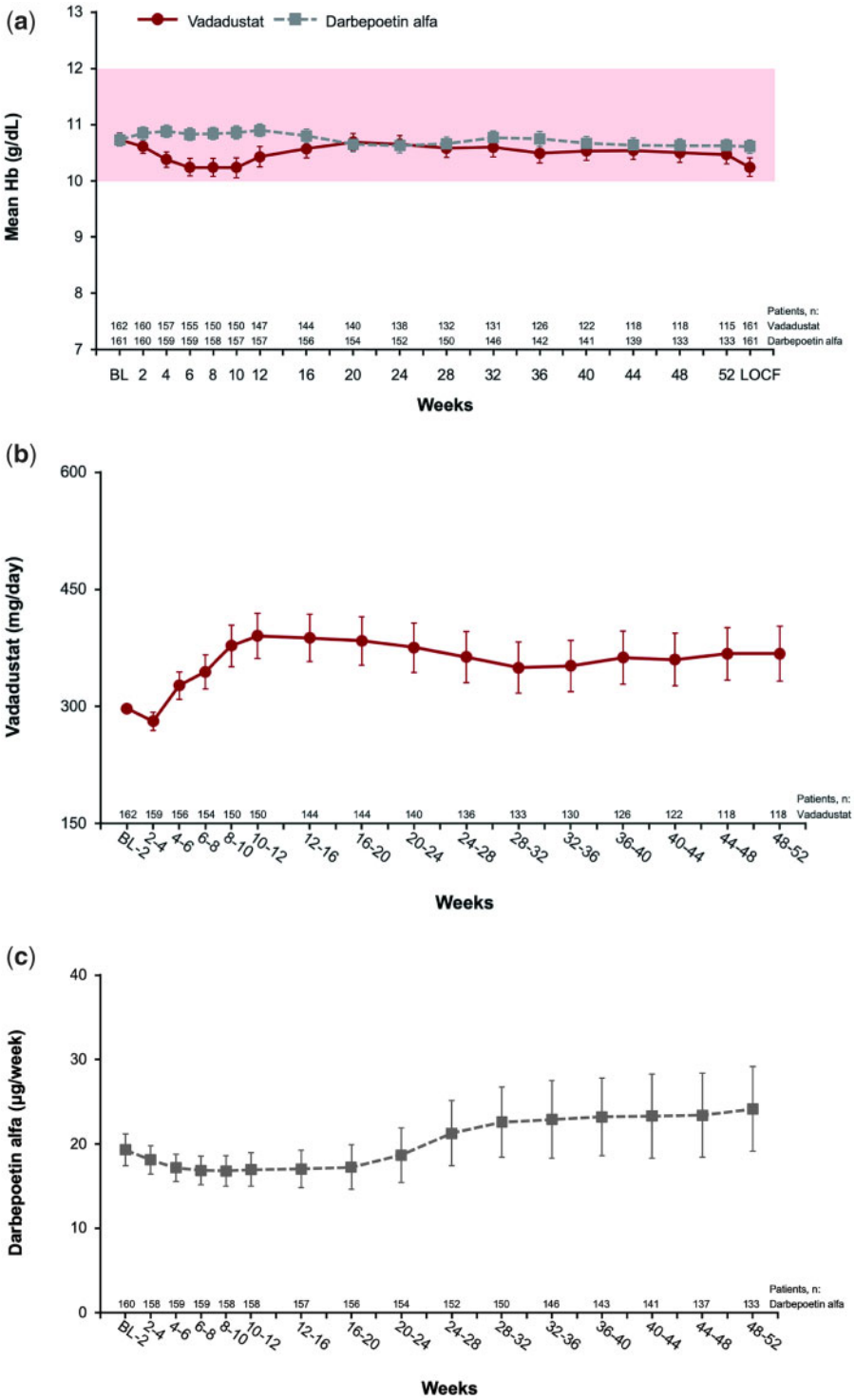


FIGURE 1: Mean Hb levels and dose of study drug over time. (**a**) Mean Hb levels, (**b**) mean daily doses of vadadustat and (**c**) mean weekly doses of darbepoetin alfa. Data represent mean and 95% CI. BL, baseline.

at Week 52 were 10.39 (10.24–10.54) and 10.62 (10.48–10.76) g/dL in the vadadustat and darbepoetin alfa groups, respectively. The mean (95% CI) doses during Weeks 48–52 of vadadustat and darbepoetin alfa were 367.65 (331.91–403.39) mg/day (Figure 1b) and 24.15 (19.12–29.18) µg/week (Figure 1c), respectively. In the vadadustat group, there was no decreasing trend in Hb levels during the early treatment period in patients with a baseline Hb level of <10.4 g/dL. In contrast, in the subgroup of patients with a baseline Hb level of ≥10.4 to <11.0 g/dL and those with an Hb level of ≥11.0 g/dL, a decreasing trend in Hb levels in the early treatment period was observed (Figure 2a). The mean vadadustat doses in patients with each baseline Hb level are shown in Figure 2b.

At Weeks 24 and 52, 75.4 and 75.7% of patients in the vadadustat group and 75.7 and 86.5% of patients in the darbepoetin alfa group were within the target Hb levels of 10.0–12.0 g/dL,

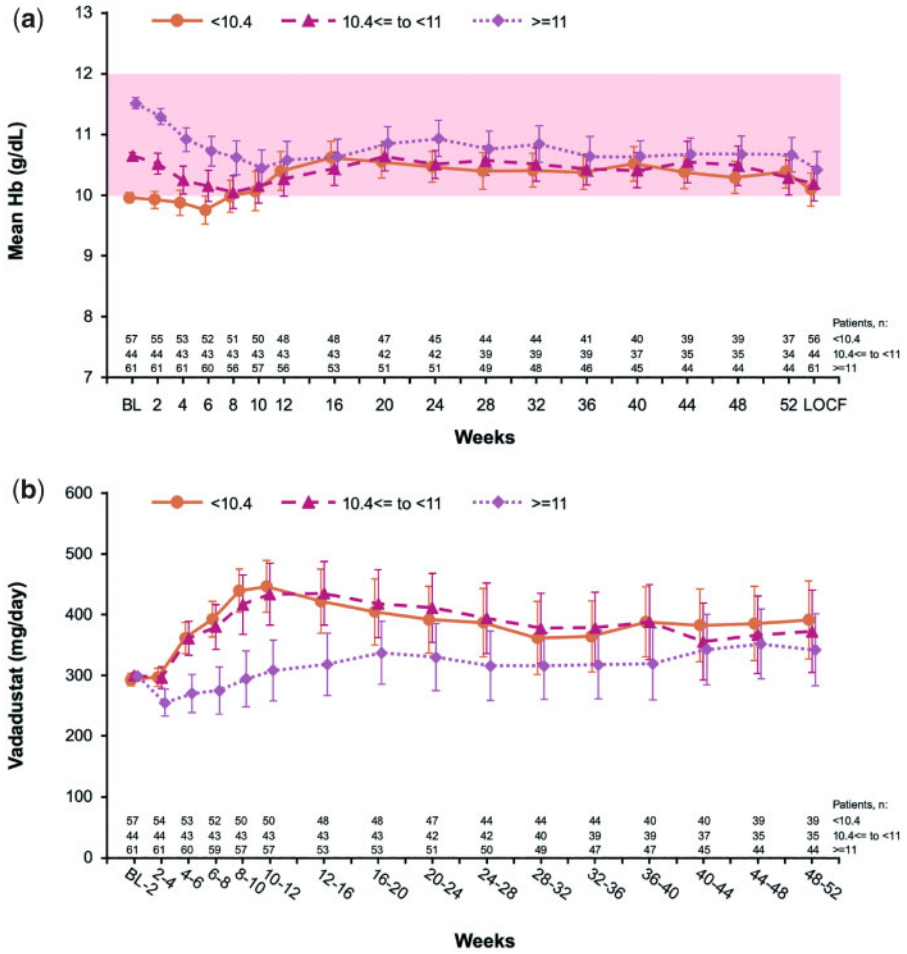


FIGURE 2: Mean Hb levels and dose in vadadustat-treated subgroups stratified by baseline Hb. (**a**) Mean Hb levels and (**b**) mean daily doses of vadadustat. Data represent mean and 95% CI. BL, baseline.

respectively (Supplementary data, Figure S3). The proportions of patients with Hb excursions of ≥12 and ≥13 g/dL were 25.3 and 3.7% in the vadadustat group and 29.8 and 3.1% in the darbepoetin alfa group, respectively. No patients in either group exhibited a rapid rise in Hb levels (>2.0 g/dL/4 weeks) during the 52-week treatment period.

Iron-related parameters

There were no significant differences in serum ferritin and TSAT at Week 52 (LOCF) compared with baseline in both groups (Figure 3a and b). The total iron-binding capacity (TIBC) increased at Week 52 (LOCF) from baseline in the vadadustat group and remained almost stable in the darbepoetin alfa group (Figure 3c). The hepcidin level decreased from baseline at Week 52 (LOCF) in the vadadustat group and remained unchanged in the darbepoetin alfa group, but no obvious differences were found between the two groups (Figure 3d). The changes in red blood cell parameters are shown in Figure 3e–h. The mean corpuscular volume (MCV) and mean corpuscular Hb (MCH) levels increased from baseline at Week 52 (LOCF) only in the vadadustat group (Figure 3e and f), whereas MCHC level increased from baseline at Week 52 in both groups (Figure 3g). The RDW decreased from baseline at Week 52 (LOCF) in the vadadustat group but increased in the darbepoetin alfa group (Figure 3h). No significant differences were noted in the mean monthly dose of intravenous (IV) iron from the screening period to Weeks 48–52 in both groups (Figure 3i). The proportion of patients receiving IV iron during Weeks 48–52 was 30.9% in the vadadustat group and 33.3% in the darbepoetin alfa group. The proportion of patients receiving oral iron during Weeks 48–52 was 3.3% in the vadadustat group and 2.2% in the darbepoetin alfa group.

Subgroup analysis

Subgroup analyses based on patient background revealed that the LSMs of Hb levels at Week 52 were within the target range of 10.0–12.0 g/dL in both groups, irrespective of patients' backgrounds, including the duration of hemodialysis, duration of anemia, CKD etiology, comorbidities and baseline C-reactive protein (CRP) levels (Figure 4).

Safety

A similar proportion of patients reported at least one AE during the 52-week treatment period: 95.1% (154 of 162 patients) and 98.1% (158 of 161 patients) in the vadadustat and darbepoetin alfa groups, respectively, as presented in Table 3. During the 52-week treatment period, 11.1% and 3.7% of patients in the vadadustat and darbepoetin alfa groups,

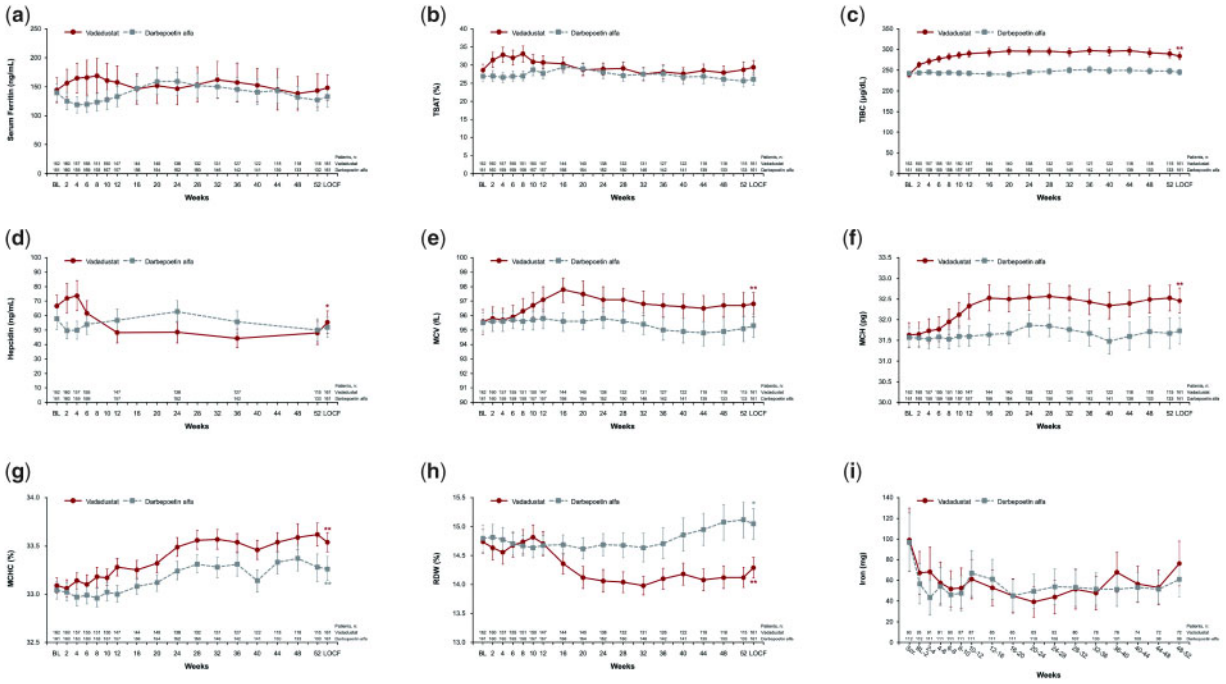


FIGURE 3: Iron-related parameters. (**a**) Serum ferritin, (**b**) TSAT, (**c**) TIBC, (**d**) hepcidin, (**e**) MCV, (**f**) MCH, (**g**) MCHC, (**h**) RDW and (**i**) monthly dose of IV iron. Data represent mean and 95% CI. Asterisks indicate significant differences between Week 52 LOCF and baseline, except for monthly dose of IV iron, which is between Weeks 48–52 and screening (paired *t*-test; *P < 0.05, **P < 0.01). BL, baseline.

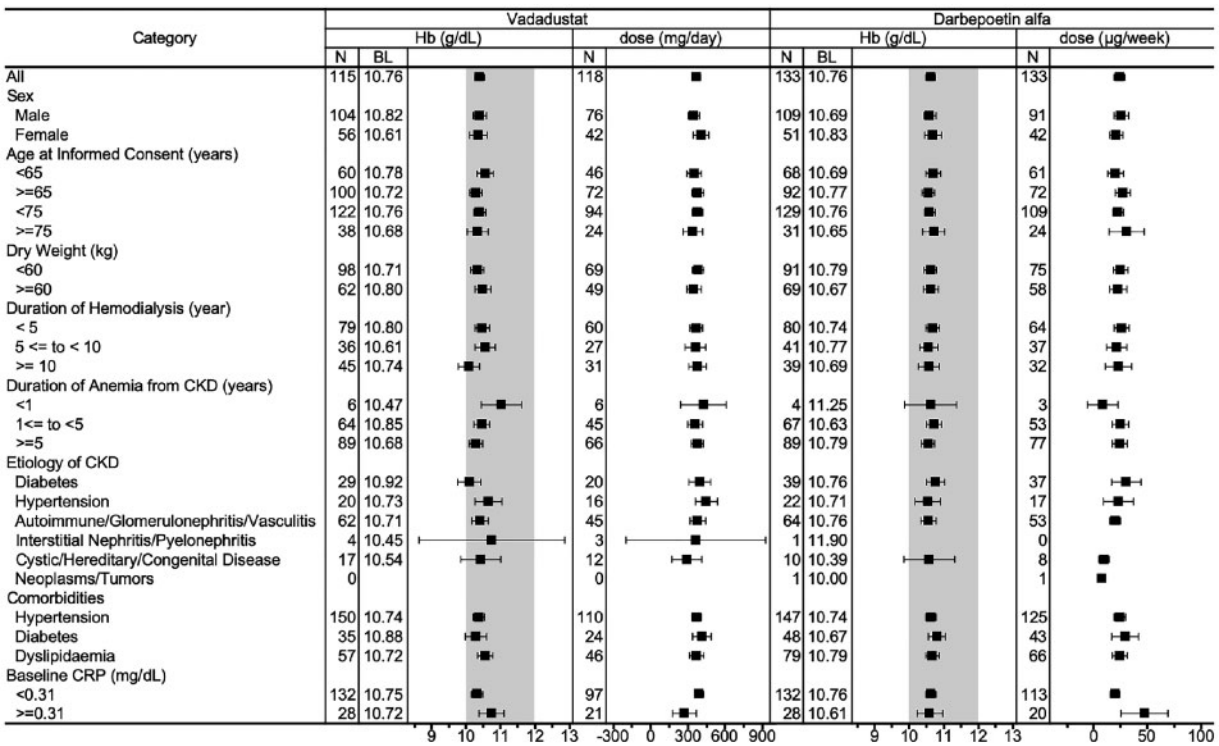


FIGURE 4: Subgroup analyses for LSM Hb at Week 52 and dose of study drug during Weeks 48–52. The results of a prespecified subgroup analysis with respect to the efficacy are shown. Error bars indicate 95% CI. BL, baseline.

respectively, reported at least one ADR, and 25.3 and 27.3% of those in the vadadustat and darbepoetin alfa groups, respectively, reported at least one serious AE; however, none of the serious events was considered to be related to study treatment. AEs leading to discontinuation occurred in 9.9 and 8.7% of patients in the vadadustat and darbepoetin alfa groups, respectively, while 8.0 and 2.5% of those in the vadadustat and darbepoetin alfa groups, respectively, reported dose reduction or

Table 3. Safety results, 52 weeks (safety analysis set)

Overview	Vadadustat ($N=162$) n (%)	Darbepoetin alfa ($N=161$) n (%)
Summary		
Subjects with at least one AE	154 (95.1)	158 (98.1)
ADR	18 (11.1)	6 (3.7)
Serious AEs	41 (25.3)	44 (27.3)
Serious ADR	0 (0.0)	0 (0.0)
Discontinuation due to AEs	16 (9.9)	14 (8.7)
Dose reduction or interruption of study drug due to AEs	13 (8.0)	4 (2.5)
AEs leading to rescue therapy	6 (3.7)	2 (1.2)
Deaths due to AEs	2 (1.2)	1 (0.6)
AEs reported in ≥5% of patients in either group		
Nasopharyngitis	74 (45.7)	73 (45.3)
Diarrhea	25 (15.4)	24 (14.9)
Shunt stenosis	23 (14.2)	26 (16.1)
Contusion	21 (13.0)	19 (11.8)
Retinal hemorrhage	16 (9.9)	10 (6.2)
Back pain	15 (9.3)	11 (6.8)
Headache	13 (8.0)	5 (3.1)
Pain in extremity	13 (8.0)	4 (2.5)
Pruritus	12 (7.4)	9 (5.6)
Gastroenteritis	12 (7.4)	1 (0.6)
Conjunctivitis	11 (6.8)	4 (2.5)
Vomiting	10 (6.2)	17 (10.6)
Arthralgia	10 (6.2)	11 (6.8)
Eczema	10 (6.2)	8 (5.0)
Wound	10 (6.2)	7 (4.3)
Nausea	10 (6.2)	2 (1.2)
Skin abrasion	9 (5.6)	15 (9.3)
Influenza	9 (5.6)	12 (7.5)
Myalgia	9 (5.6)	5 (3.1)
Decreased appetite	9 (5.6)	4 (2.5)
Constipation	7 (4.3)	12 (7.5)
Upper respiratory tract infection	7 (4.3)	8 (5.0)
Musculoskeletal pain	7 (4.3)	8 (5.0)
Seasonal allergy	4 (2.5)	12 (7.5)

Administration of ESAs, red blood cell transfusion or phlebotomy was permitted as rescue therapy at the investigators' discretion.

Table 4. AEs of special interest

Category	Vadadustat ($N=162$) n (%)	Darbepoetin alfa ($N=161$) n (%)
Cardiovascular event, cardiac failure	13 (8.0)	15 (9.3)
Cerebral infarction	1 (0.6)	5 (3.1)
Carotid artery stenosis	1 (0.6)	1 (0.6)
Cerebellar infarction	1 (0.6)	1 (0.6)
Intracranial aneurysm	1 (0.6)	0 (0.0)
Lacunar infarction	1 (0.6)	0 (0.0)
Thrombotic cerebral infarction	1 (0.6)	0 (0.0)
Subarachnoid hemorrhage	0 (0.0)	1 (0.6)
Cardiac failure congestive	2 (1.2)	0 (0.0)
Angina pectoris	1 (0.6)	3 (1.9)
Coronary artery stenosis	1 (0.6)	2 (1.2)
Myocardial ischemia	1 (0.6)	1 (0.6)
Angina unstable	1 (0.6)	0 (0.0)
Arteriosclerosis coronary artery	1 (0.6)	0 (0.0)
Cardiac failure	1 (0.6)	0 (0.0)
Pulmonary edema	2 (1.2)	1 (0.6)
Subdural hematoma	1 (0.6)	0 (0.0)
Coronary artery restenosis	0 (0.0)	1 (0.6)
Retinal disorder	21 (13.0)	16 (9.9)
Retinal hemorrhage	16 (9.9)	10 (6.2)
Diabetic retinopathy	2 (1.2)	1 (0.6)
Macular edema	1 (0.6)	3 (1.9)
Retinal edema	1 (0.6)	0 (0.0)
Retinal vein occlusion	1 (0.6)	0 (0.0)
Vitreous floaters	1 (0.6)	0 (0.0)
Cystoid macular edema	1 (0.6)	0 (0.0)
Chorioretinopathy	1 (0.6)	0 (0.0)
Retinal detachment	0 (0.0)	1 (0.6)
Retinal vascular disorder	0 (0.0)	1 (0.6)
Vitreous detachment	0 (0.0)	1 (0.6)
Vitreous hemorrhage	0 (0.0)	1 (0.6)
Retinal aneurysm	0 (0.0)	1 (0.6)
Age-related macular degeneration	0 (0.0)	1 (0.6)
Malignancy	7 (4.3)	9 (5.6)
Breast cancer	1 (0.6)	1 (0.6)
Gastric cancer	1 (0.6)	1 (0.6)
Seborrhoeic keratosis	1 (0.6)	1 (0.6)
Cholesteatoma	1 (0.6)	0 (0.0)
Laryngeal papilloma	1 (0.6)	0 (0.0)
Squamous cell carcinoma of skin	1 (0.6)	0 (0.0)
Uterine leiomyoma	1 (0.6)	0 (0.0)
Pyogenic granuloma	0 (0.0)	1 (0.6)
Thymoma	0 (0.0)	1 (0.6)
Prostate cancer	0 (0.0)	1 (0.6)
Pancreatic neoplasm	0 (0.0)	1 (0.6)
Urethral neoplasm	0 (0.0)	1 (0.6)
Renal cell carcinoma	0 (0.0)	1 (0.6)
Gastrointestinal submucosal tumor	0 (0.0)	1 (0.6)
Hyperkalemia	1 (0.6)	1 (0.6)
Thromboembolism	12 (7.4)	14 (8.7)
Cerebral infarction	1 (0.6)	5 (3.1)
Cerebellar infarction	1 (0.6)	1 (0.6)
Lacunar infarction	1 (0.6)	0 (0.0)
Thrombotic cerebral infarction	1 (0.6)	0 (0.0)
Retinal vein occlusion	1 (0.6)	0 (0.0)
Peripheral arterial occlusive disease	3 (1.9)	3 (1.9)
Thrombophlebitis	0 (0.0)	1 (0.6)
Peripheral artery occlusion	0 (0.0)	1 (0.6)
Shunt occlusion	4 (2.5)	4 (2.5)
Shunt thrombosis	1 (0.6)	0 (0.0)
Arteriovenous fistula thrombosis	0 (0.0)	1 (0.6)
Pulmonary hypertension	0 (0.0)	0 (0.0)

treatment interruption due to AEs. Three deaths were reported during the study. One patient died of pneumonia and another died from a complication of CKD in the vadadustat group, and one died of rupture of a peripheral aneurysm in the darbepoetin alfa group; however, causality with the study drug was not considered reasonable for all these events. The most frequently reported AEs were nasopharyngitis, diarrhea and shunt stenosis, which occurred similarly between the treatment groups: 45.7, 15.4 and 14.2%, respectively, in the vadadustat group and 45.3, 14.9 and 16.1%, respectively, in the darbepoetin alfa group.

As presented in Table 4, there was no apparent difference in the proportion of patients who reported AEs of special interest between the vadadustat and darbepoetin alfa groups: cardiovascular event/cardiac failure (8.0% versus 9.3%), retinal disorder (13.0% versus 9.9%), malignancy (4.3% versus 5.6%),

hyperkalemia (0.6% versus 0.6%), pulmonary hypertension (0.0% versus 0.0%) and thromboembolism (7.4% versus 8.7%). Retinal hemorrhage occurred more often in the vadadustat group than in the darbepoetin alfa group; however, causality with the study drug was not considered reasonable. The plasma vascular endothelial growth factor (VEGF) levels [median (min–max)] at baseline and closest to the time of retinal hemorrhage in patients with retinal hemorrhage were 44.6 (15.6–80.0) and 47.4 (15.6–70.0) in the vadadustat group and 55.4 (33.2–329.0) and 50.2 (29.5–92.7) in the darbepoetin alfa group, respectively.

DISCUSSION

This 52-week Phase 3 study demonstrated that the efficacy of vadadustat was noninferior to that of darbepoetin alfa as measured by average Hb level at Weeks 20 and 24. The mean Hb level was maintained within the target range throughout the 52-week treatment period, and proportions of patients within the range at Weeks 24 and 52 were ∼80% each of the patients in the vadadustat group, similar to those in the darbepoetin alfa group. Overall, this study confirmed that oral vadadustat was as effective as darbepoetin alfa injection in maintaining Hb levels within the target range in Japanese anemic patients on hemodialysis.

In this study, there were more patients who discontinued from the study in the vadadustat group than in the darbepoetin alfa group [16% (26 of 162 patients) versus 6% (9 of 161 patients)]. However, since the primary endpoint was analyzed by the MMRM method, this imbalance is unlikely to have affected the study outcome. The MMRM method minimizes the impacts of missing data by assuming that all missing data are missing at random and that all withdrawals would behave similarly to other patients who had not discontinued in the same treatment group [21, 22]. Furthermore, a sensitivity analysis assuming that all missing data were not at random showed that vadadustat remained noninferior to darbepoetin alfa (data not shown). Although the baseline ESA dose and ERI differed slightly between the groups numerically, noninferiority was confirmed even after adjustment of the primary endpoint of mean Hb levels at Weeks 20 and 24 by adding ERI as a covariate (data not shown). Therefore, the number of withdrawals and baseline ERI are unlikely to affect the efficacy (primary endpoint) of vadadustat compared with darbepoetin alfa.

In the vadadustat group, although within a target range, there was a decreasing trend in mean Hb levels in the early treatment period after switching from ESA; however, the Hb levels returned to baseline levels with the increase in the dose according to the study protocol. It is likely that the temporal decreasing tendency of Hb levels is attributed to the treatment protocol, where the start dose of vadadustat was 300 mg to avoid Hb overshoot and dose increase was allowed only when the Hb level dropped $<$10 g/dL over a 4-week interval. In addition, the Hb levels were almost stable in the early treatment period in patients with baseline Hb levels of $<$10.4 g/dL. Therefore, although the transient Hb decreasing tendency observed in this study is unlikely to be of clinical concern, monitoring Hb levels is recommended until Hb levels have stabilized after initiation of vadadustat treatment.

Among iron-related parameters and red blood cell indices, TIBC, MCV and MCH increased from the baseline level at the end of the treatment in the vadadustat group, unlike in the darbepoetin alfa group, in this study. However, the serum ferritin level, which indicates the amount of stored iron [23], was almost stable, and hepcidin, which negatively regulates iron metabolism [23], marginally decreased from baseline at Week 52 (LOCF) by the vadadustat treatment; no remarkable differences between treatment groups were observed. Taken together, these results are insufficient to conclude whether vadadustat improved iron utilization in patients with renal anemia on hemodialysis, and further investigations are required.

Subgroup analyses revealed that the LSMs of Hb at Week 52 were within the target range in both groups, irrespective of patients' backgrounds, such as duration of hemodialysis, duration of renal anemia, CKD etiology, comorbidities and baseline CRP, as shown in Figure 4. Although the average dialysis period is longer in Japan than in the USA and other countries [8, 9], there are few reports on the effect of vadadustat in patients with renal anemia under long-term hemodialysis. Of note, although the sample size was limited in this study, the effect of vadadustat on the maintenance Hb levels in patients undergoing hemodialysis for $\geq$10 years was similar to those in undergoing hemodialysis for $<$5 years and for $\geq$5 to $<$10 years, providing preliminary evidence that vadadustat has a stable effect regardless of the duration of hemodialysis. Bernhardt *et al.* reported that an HIF-PHI increased erythropoietin production even in anephric patients receiving hemodialysis, which is likely due to hepatic erythropoietin production [24]. It is not known to what extent erythropoietin-producing cells in the kidneys were impaired in patients receiving hemodialysis for $>$10 years in the current study, but the similar efficacy of vadadustat compared with patients receiving hemodialysis for $<$5 years may have been partially compensated by the production of erythropoietin from the liver.

The AE profile in the vadadustat group was almost similar to that in the darbepoetin alfa group. Common AEs included nasopharyngitis, diarrhea and shunt stenosis, and their frequencies were similar to those observed in the darbepoetin alfa group and in the previous Phase 2 study involving anemic patients on hemodialysis [19]. ADRs, such as diarrhea and nausea, were more common in the vadadustat group, although not serious. The incidence of AEs of special interest, including cardiovascular event/cardiac failure, retinal disorder, malignancy, hyperkalemia and thromboembolism, was almost similar in the vadadustat and darbepoetin alfa groups. The incidence of retinal hemorrhage was slightly higher in the vadadustat group than in the darbepoetin alfa group (9.9% versus 6.2%); however, all these events were mild in severity and not considered to be related to the study drugs. Furthermore, no significant changes in plasma VEGF levels were observed in patients with retinal hemorrhage. Hyperkalemia has been reported in a clinical study of another HIF-PHI [20], and thromboembolic complications were reported as a safety concern of HIF-PHIs [17]; however,

no higher risk of these events was noted in our study. We observed no new safety concerns in the present safety analysis compared with previous studies of vadadustat [18, 19]. In this study, progression of renal cysts was not monitored in patients with concomitant renal cysts, but no AEs with the suspected progression of renal cyst were observed in the vadadustat group (data not shown). Since it has been reported that HIF-1α is associated with the progression of advanced renal cyst in autosomal dominant polycystic kidney disease (ADPKD) model animals [25], the post-marketing surveillance of vadadustat is planned to evaluate the progression of renal cysts in patients with ADPKD.

In terms of sample size and study period, this study does not seem to have adequate power to draw conclusions regarding the long-term safety of vadadustat, especially regarding AEs of special interest, including cardiovascular events, and further investigation will be required to establish the long-term safety profile of vadadustat. The large, long-term Phase 3 trials (such as NCT02865850 and NCT02892149) should confirm the long-term safety.

In conclusion, oral vadadustat was as effective as darbepoetin alfa injection in maintaining mean Hb levels within the target range for up to 52 weeks in Japanese anemic patients on hemodialysis who were previously receiving ESAs in this Phase 3 study. Vadadustat was well tolerated, and no new safety concerns were identified. These findings suggest that vadadustat can provide an alternative treatment of anemia in Japanese hemodialysis patients converting from ESA therapy.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

All authors participated in the interpretation of the study results, draft manuscripts, critical revisions and approval of the final version of the manuscript. M.N., K.K., G.K., H.M., Y.Kawaguchi and Y.Komatsu were involved in the study design; M.N. and K.K. were investigators in the study, and Y.Kawaguchi conducted the statistical analysis.

CONFLICT OF INTEREST STATEMENT

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(See related article by Locatelli and Vecchio. A new paradigm in treating patients with chronic kidney disease and anaemia after a journey lasting more than 35 years. *Nephrol Dial Transplant* 2021; 36: 1559–1563)

DATA AVAILABILITY STATEMENT

The deidentified datasets generated and/or analyzed during the current study, protocols, annotated case report form, dataset specifications, and clinical study report may be available from Mitsubishi Tanabe Pharma Corporation upon reasonable request from qualified researchers at https://vivli.org. For the Mitsubishi Tanabe Pharma Corporation criteria on data sharing, see https://vivli.org/ourmember/mitsubishi-tanabe-pharma/.

REFERENCES

1. Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. *Nat Rev Nephrol* 2015; 11: 394–410
2. KDOQI; National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis* 2006; 47 (5 Suppl 3): S11–S145
3. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One* 2014; 9: e84943
4. Astor BC, Muntner P, Levin A *et al.* Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med* 2002; 162: 1401–1408
5. Covic A, Jackson J, Hadfield A *et al.* Real-world impact of cardiovascular disease and anemia on quality of life and productivity in patients with non-dialysis-dependent chronic kidney disease. *Adv Ther* 2017; 34: 1662–1672
6. Hörl WH. Anaemia management and mortality risk in chronic kidney disease. *Nat Rev Nephrol* 2013; 9: 291–301
7. Yamamoto H, Nishi S, Tomo T *et al.* 2015 Japanese society for dialysis therapy: guidelines for renal anemia in chronic kidney disease. *Ren Replace Ther* 2017; 3: 36
8. Kimata N, Tsuchiya K, Akiba T *et al.* Differences in the characteristics of dialysis patients in Japan compared with those in other countries. *Blood Purif* 2015; 40: 275–279
9. Robinson BM, Akizawa T, Jager KJ *et al.* Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet* 2016; 388: 294–306
10. McMurray J, Parfrey PS, Adamson JW *et al.* Kidney disease: Improving Global Outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012; 2: 279–335

11. Mercadal L, Metzger M, Casadevall N *et al.*; on behalf of the NephroTest Study Group. Timing and determinants of erythropoietin deficiency in chronic kidney disease. *Clin J Am Soc Nephrol* 2012; 7: 35–42
12. Singh AK, Szczech L, Tang KL *et al.*; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; 355: 2085–2098
13. Drüeke TB, Locatelli F, Clyne N *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; 355: 2071–2084
14. Bradbury BD, Danese MD, Gleeson M *et al.* Effect of epoetin alfa dose changes on hemoglobin and mortality in hemodialysis patients with hemoglobin levels persistently below 11 g/dL. *Clin J Am Soc Nephrol* 2009; 4: 630–637
15. Koulouridis I, Alfayez M, Trikalinos TA *et al.* Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. *Am J Kidney Dis* 2013; 61: 44–56
16. Hasegawa S, Tanaka T, Nangaku M. Hypoxia-inducible factor stabilizers for treating anemia of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2018; 27: 331–338
17. Sanghani NS, Haase VH. Hypoxia-inducible factor activators in renal anemia: current clinical experience. *Adv Chronic Kidney Dis* 2019; 26: 253–266
18. Pergola PE, Spinowitz BS, Hartman CS *et al.* Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. *Kidney Int* 2016; 90: 1115–1122
19. Nangaku M, Farag YMK, deGoma E *et al.* Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, for treatment of anemia of chronic kidney disease: two randomized Phase 2 trials in Japanese patients. *Nephrol Dial Transplant* 2020; doi: 10.1093/ndt/gfaa060
20. Chen N, Hao C, Liu BC *et al.* Roxadustat treatment for anemia in patients undergoing long-term dialysis. *N Engl J Med* 2019; 381: 1011–1022
21. Prakash A, Risser RC, Mallinckrodt CH. The impact of analytic method on interpretation of outcomes in longitudinal clinical trials. *Int J Clin Pract* 2008; 62: 1147–1158
22. Siddiqui O, Hung HM, O'Neill R. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. *J Biopharm Stat* 2009; 19: 227–246
23. Anderson GJ, Frazer DM. Current understanding of iron homeostasis. *Am J Clin Nutr* 2017; 106: 1559s–1566s
24. Bernhardt WM, Wiesener MS, Scigalla P *et al.* Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *J Am Soc Nephrol* 2010; 21: 2151–2156
25. Kraus A, Peters DJM, Klanke B *et al.* HIF-1α promotes cyst progression in a mouse model of autosomal dominant polycystic kidney disease. *Kidney Int* 2018; 94: 887–899

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