Received: 3 February 2022 | Accepted: 24 February 2022

DOI: 10.1111/1744-9987.13820

Therapeutic Apheresis and Dialysis

WILEY

REVIEW

Treatment of anemia associated with chronic kidney disease with the HIF prolyl hydroxylase inhibitor enarodustat: A review of the evidence

Ryo Fujikawa[1] | **Yuji Nagao**[2] | **Masaki Fujioka**[1] | **Tadao Akizawa**[3]

[1]Medical Affairs Department, Torii Pharmaceutical Co. Ltd, Tokyo, Japan

[2]Pharmaceutical Division, Japan Tobacco Inc, Tokyo, Japan

[3]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Correspondence
Tadao Akizawa, Division of Nephrology, Department of Medicine, Showa University School of Medicine, Namics Shinagawa 301, 4-24-51 Takanawa, Minato-ku, Tokyo, 108-0074, Japan.
Email: akizawa@med.showa-u.ac.jp

Funding information
Torii Pharmaceutical

Abstract

Enarodustat, a newly developed hypoxia-inducible factor prolyl hydroxylase inhibitor, is used in clinical practice in Japan. Several clinical studies showed that enarodustat corrected and maintained hemoglobin (Hb) levels by stimulating endogenous erythropoietin production and improving iron utilization in anemic patients with chronic kidney disease, regardless of whether they were on dialysis. In addition, Phase III comparative studies demonstrated that enarodustat was noninferior to darbepoetin alfa in controlling Hb levels. Furthermore, enarodustat was well tolerated during the treatment. Enarodustat is currently being developed in the Republic of Korea and China and is expected to be developed worldwide. This article reviews the data on enarodustat, including the findings from preclinical studies, pharmacokinetics/pharmacodynamics, and efficacy and safety results of clinical studies.

KEYWORDS

anemia in chronic kidney disease, enarodustat, erythropoietin, HIF-PH inhibitor, iron utilization

1 | INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD), and its prevalence increases as the estimated glomerular filtration rate (eGFR) declines.[1] Anemia in CKD is caused by several factors, including decreased erythropoietin (EPO) production due to impaired kidney function and disrupted iron homeostasis.[2] It contributes to poor quality of life[2] and reportedly accelerates kidney dysfunction and increases the risk of cardiovascular disease and poor prognosis.[3–5]

Erythropoiesis-stimulating agents (ESAs) are a standard therapy for anemia in CKD. However, several patients do not respond adequately to ESAs,[6] and ESA treatment targeting a high hemoglobin (Hb) level in patients increases the risk of mortality and cardiovascular events with a high incidence of hypertension.[7–9]

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors are a new class of agents for the treatment of anemia associated with CKD. In Japan, five HIF-PH inhibitors (i.e., roxadustat, vadadustat, daprodustat, enarodustat, and molidustat) have been approved and are widely used in clinical practice. HIF-PH inhibitors mimic physiological responses to hypoxia, stabilizing HIF by regulating its degradation and leading to the expression of HIF-target genes involved in EPO production and iron metabolism (Figure 1).[10–13] Therefore, HIF-PH inhibitors

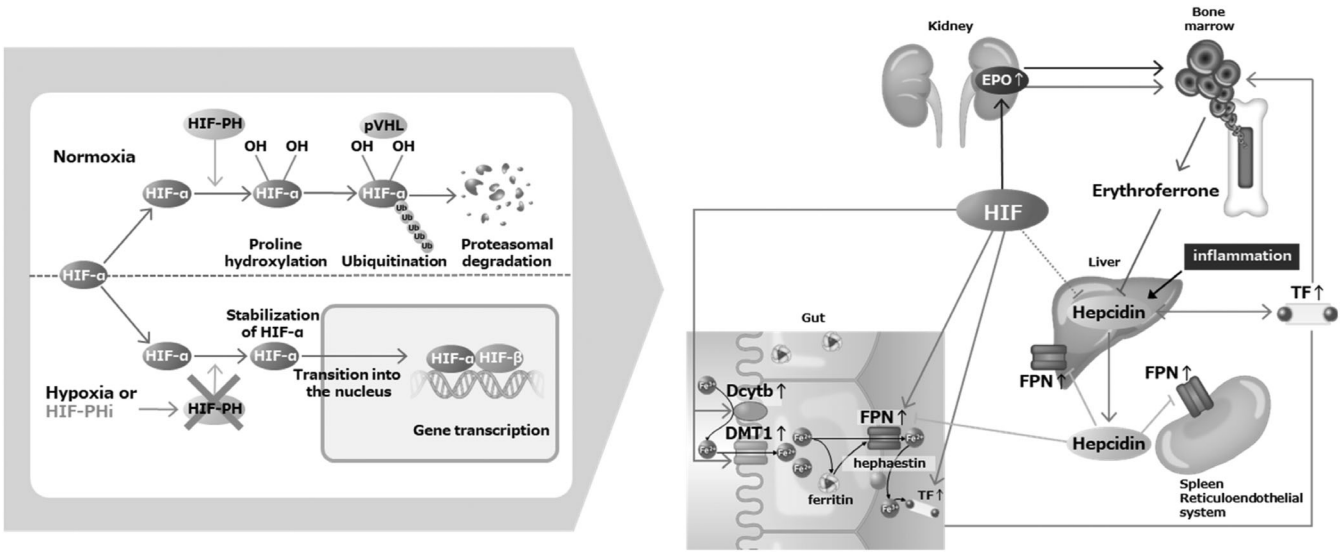

FIGURE 1 Hypoxia-inducible factor (HIF) pathway and roles of HIF in erythropoiesis and iron metabolism. Figure modified from fig. 3 in Koury et al.[12] and fig. 1 in Sugahara et al.[13] HIF-PHi, hypoxia-inducible factor prolyl hydroxylase inhibitor; pVHL, von Hippel–Lindau protein; Ub, ubiquitin; EPO, erythropoietin; TF, transferrin; Dcytb, duodenal cytochrome b; DMT1, divalent metal transporter 1; FPN, ferroportin

promote erythropoiesis with endogenous EPO production and improve iron utilization. As a result, these agents are expected to improve poor prognoses associated with high ESA doses and be effective in patients with ESA hyporesponsiveness caused by defective iron utilization or other factors.[12, 14] In addition to the genes mentioned above, HIF regulates several other factors. Therefore, HIF-PH inhibitors may induce various effects. One benefit is that they potentially protect organs against ischemic injury.[13] However, HIF-PH inhibitors also have potential safety risks associated with the expression of the vascular endothelial growth factor (VEGF), one of the HIF-target genes.[12] VEGF induces angiogenesis and vascular permeability, which are associated with pathological neovascularization in the retina and choroid[15, 16] and poor tumor prognosis.[17] Thus, HIF-PH inhibitors may increase these related risks via the expression of VEGF. In addition to HIF-mediated effects, hypertension and thrombotic events should be carefully monitored during HIF-PH inhibitor treatment because these events are related to the control of anemia with ESAs. Moreover, several diseases, such as hyperkalemia, are indicated as potential concerns in the recommendations on the appropriate use of HIF-PH inhibitors by the Asian Pacific Society of Nephrology[14] and the Japanese Society of Nephrology.[18]

Enarodustat is a once-daily, orally administered HIF-PH inhibitor developed by Japan Tobacco Inc. Enarodustat was approved in Japan in September 2020 and is currently being developed in the Republic of Korea and China for the treatment of anemia associated with CKD.[19–21] This article reviews the data on enarodustat, including the findings from preclinical studies, pharmacokinetics/pharmacodynamics, and efficacy and safety results of clinical studies.

2 | PRECLINICAL STUDIES

Enarodustat exhibited specific and potent inhibitory effects on human HIF-PH 1–3 with Ki values of 0.016, 0.061, and 0.101 μmol/L, respectively, but not on other enzymes or receptors in vitro. In Hep3B cells (a human hepatoma cell line), enarodustat stabilized HIF-α proteins and increased EPO mRNA and protein levels. In normal rats, liver and kidney EPO mRNA levels and plasma EPO concentrations were significantly increased when enarodustat was administered at doses of >1 and 3 mg/kg, respectively. In 5/6-nephrectomized rats (renal anemia model), liver EPO mRNA levels and plasma EPO concentrations were significantly increased following the administration of enarodustat at doses of >1 and 3 mg/kg, respectively. The administration of a repeated dose showed an erythropoiesis-stimulating effect in proportion to doses at ≥1 mg/kg. In addition to the once-daily dosing (QD) regimen, the effects of repeated intermittent doses (once or three times per week) showed erythropoiesis-stimulating effects; however, the dosage per day of enarodustat had to be increased when using an intermittent dosing regimen compared with the QD regimen.[22] In normal rats, enarodustat induced more efficient iron utilization compared with recombinant human

erythropoietin (rHuEPO) under conditions in which enarodustat and rHuEPO showed similar erythropoietic effects at the repeated dose. A single dose of enarodustat but not rHuEPO decreased the expression of hepcidin. In a rat model of anemia of inflammation (also known as a model with functional iron-deficiency), enarodustat showed erythropoietic effects in contrast to rHuEPO.[23]

In addition to its erythropoietic effects, the potential beneficial and detrimental effects of enarodustat were evaluated. Several preclinical studies reported that enarodustat showed renoprotective effects in models of acute and CKD (e.g., ischemia–reperfusion, diabetic kidney disease, and CKD).[24–28] Furthermore, enarodustat suppressed the transformation of renal interstitial fibroblasts, which is the terminal pathway in the progression of CKD characterized by tubulointerstitial fibrosis.[29] The potential detrimental effect on VEGF production and function of HIF-PH inhibitors were also assessed. In normal rats, enarodustat at the highest dose of 30 mg/kg significantly increased plasma VEGF concentrations, whereas this was not observed with doses ≤10 mg/kg. These results indicated that plasma VEGF concentrations are increased by enarodustat at >10-fold higher dosages than those required for endogenous EPO-mediated erythropoiesis. In addition, no increases in retinal VEGF levels were detected at the dose of 30 mg/kg, and no effects on vascular permeability were observed, even at a high dose of 300 mg/kg. Moreover, no effect of enarodustat on tumor growth was observed at the dose of 30 mg/kg, in which plasma VEGF concentration was significantly higher than those in the vehicle group in a colorectal cancer cell-inoculated mouse xenograft model.[22]

3 | PHARMACOKINETICS/PHARMACODYNAMICS

3.1 | Pharmacokinetics

The pharmacokinetic profile of enarodustat was evaluated in a single ascending-dose (1–200 mg) study with healthy Japanese subjects and a single-dose (15 mg) study with Japanese hemodialysis patients (JapicCTI-121969). Enarodustat was rapidly absorbed in both populations (time of maximum concentration [T_{max}]) of 0.5–2.5 h), and the half-life ($T_{1/2}$) was 7.7–9.1 h in healthy subjects and 11.3 h in hemodialysis patients. The maximum serum concentration (C_{max}) and area under plasma concentration-time curve from time 0 to infinity (AUC_{inf}) of enarodustat were decreased by 47% and 26%, respectively, in the fed condition compared with the fasted condition after the administration of 100 mg enarodustat. The C_{max} and AUC_{inf} of enarodustat were also decreased by 53% and 45%, respectively, when co-administered with sevelamer carbonate. However, staggered administration (enarodustat administered 3 h after or 1 h before the administration of sevelamer carbonate) substantially reduced the effect of sevelamer carbonate on both the peak (C_{max}) and total (AUC_{inf}) level of enarodustat.[30] Following the administration of 5 mg enarodustat to hemodialysis patients, more than 99% of enarodustat in plasma is mainly bound to albumin.[31] The percent distribution of enarodustat to human blood cells (in vitro) was 2.5%–6.8%. In vitro studies with hepatic microsomes and cytochrome P450 (CYP) isoenzymes showed that enarodustat was slightly metabolized, mainly by CYP2C8 and CYP2C9 with minor involvement of CYP3A4.[30] The mass balance study in which a 10 mg (100 μCi) oral dose of ^{14}C-enarodustat was administered to hemodialysis patients in the United States (NCT02805244) showed that the main component in plasma was unchanged enarodustat, and 77.1% (37.17% as unchanged enarodustat) and 10.9% (7.03% as unchanged enarodustat) of the radioactivity were excreted in feces and urine, respectively.[30, 32] A study in US hemodialysis patients (NCT01978587) showed that the hemodialysis effect on the pharmacokinetics of enarodustat was minimal. Therefore, enarodustat can be administered regardless of the dialysis schedule, and dose supplementation is not required for hemodialysis patients.[31]

3.2 | Pharmacodynamics

A multiple ascending-dose (2, 5, 10, and 15 mg enarodustat and placebo) study in US hemodialysis patients (NCT01971164) showed that 5–15 mg enarodustat slightly, transiently, and dose-dependently increased the EPO concentration, and no EPO accumulation was observed following repeated daily doses.[33] Phase IIb studies with Japanese hemodialysis patients (JapicCTI-152892) and nondialysis patients (JapicCTI-152881) also reported dose-related increases in EPO concentrations in response to enarodustat treatment, and EPO concentrations remained within the physiological range during treatment with enarodustat.[34, 35]

4 | CLINICAL EFFICACY AND SAFETY

The Phase IIb and Phase III studies that assessed the efficacy and safety of enarodustat in anemic patients with CKD are listed in Table 1. In this section, the efficacy and safety of enarodustat are summarized based on the published Japanese data.

TABLE 1 Phase IIb and phase III clinical trials for enarodustat (global)

Phase	Study identifier [study name]	Location	Patient type	Design	n Intervention	n Control	Period (week)	Primary end point
IIb	JapicCTI-152881	Japan	ND ESA-naïve ND ESA-treated	Randomized, double-blind, placebo-controlled, parallel-arm	71 80	23 26	30	Hb level increase rate per week The percentage of subjects with a change in the Hb level within ±1.0 g/dl from baseline to the evaluation point
IIb	JapicCTI-152891	Japan	HD ESA-naïve	Randomized, double-blind, uncontrolled, parallel-arm	71	—	30	Hb level increase rate per week
IIb	JapicCTI-152892	Japan	HD ESA-treated	Randomized, double-blind, placebo-controlled, parallel-arm	63	22	30	The percentage of subjects with a change in the Hb level within ±1.0 g/dl from baseline to the evaluation point
III	JapicCTI-173699 [SYMPHONY ND-Long]	Japan	ND ESA-naïve and ESA-treated	Open-label, uncontrolled, intraindividual dose adjustment	132	—	52	Adverse events, laboratory tests, vital signs, standard 12-lead electrocardiogram, chest X-ray, and fundoscopy
III	JapicCTI-173700 [SYMPHONY HD-Long]	Japan	HD ESA-treated	Open-label, uncontrolled, intraindividual dose adjustment	136	—	52	Adverse events, laboratory tests, vital signs, standard 12-lead electrocardiogram, chest X-ray, and fundoscopy
III	JapicCTI-173701 [SYMPHONY PD]	Japan	PD ESA-naïve and ESA-treated	Open-label, uncontrolled, intraindividual dose adjustment	42	—	52	Mean Hb level during the evaluation period or end of administration (week 24)
III	JapicCTI-183870 [SYMPHONY ND]	Japan	ND ESA-naïve and ESA-treated	Randomized, open-label, active controlled, parallel-arm	107	109	24	Difference in the mean Hb level between enatodustat arm and DA arm during the evaluation period
III	JapicCTI-183938 [SYMPHONY HD]	Japan	HD ESA-treated	Active-controlled, randomized, double-blind, and parallel-arm	87	86	24	Difference in the mean Hb level between enatodustat arm and DA arm during the evaluation period
III	JapicCTI-173702 [SYMPHONY HD-naïve]	Japan	HD ESA-naïve	Open-label, uncontrolled, intraindividual dose adjustment	34	—	24	Hb level increase rate per week

TABLE 1 (Continued)

Study identifier		Location	Patient type	Design	n		Period (week)	Primary end point
Phase	[study name]				Intervention	Control		
III	NCT04027517	Korea	HD ESA-treated	Randomized, open-label, active-controlled, parallel-group	172		24	• Difference in mean Hb level change during the evaluation period from baseline between enarodustat arm and DA arm • Difference in the mean Hb level between enatodustat arm and DA arm during the evaluation period
III	ChiCTR2000040431	China	ND ESA-naïve	Randomized, double-blind, placebo-controlled, parallel-arm during first 8-week treatment + open-label treatment for subsequent 16 weeks	100[a]	50[a]	24	The difference between the mean Hb concentration level at week 7–9 and the baseline

Abbreviations: DA, darbepoetin alfa; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HD, hemodialysis; ND, nondialysis; PD, peritoneal dialysis.
[a]Target number of subjects.

4.1 | Clinical efficacy

4.1.1 | Nondialysis CKD patients

The Phase IIb study (JapicCTI-152881) assessed short-term efficacy during the first 6 weeks of the treatment period (Period 1) and maintenance doses of enarodustat during the subsequent 24 weeks (Period 2) for Japanese anemic patients with CKD not on dialysis. During Period 1, 94 ESA-naïve subjects (correction group) and 107 ESA-treated subjects (conversion group) were randomized to enarodustat 2, 4, or 6 mg once daily or placebo under double-blind conditions. During Period 2, all patients received enarodustat titrated 2–8 mg/day to maintain Hb levels within the target range (10–12 g/dl). In the correction group, the increase rate in Hb levels per week estimated using the mixed effects model increased in a dose-dependent manner (least-squares mean ± standard error: −0.023 ± 0.034 g/dl/week in the placebo arm; 0.137 ± 0.034, 0.193 ± 0.034, and 0.440 ± 0.037 g/dl/week in the enarodustat 2-, 4-, and 6-mg arms, respectively). In the conversion group, the proportion of subjects who maintained Hb levels within baseline ±1.0 g/dl did not differ between each enarodustat arm and the placebo arm during Period 1 (54.2% of subjects in the placebo arm; 80.8%, 70.4%, and 50.0% in the enarodustat 2-, 4-, and 6-mg arms, respectively). Over 70% of subjects in both groups maintained Hb levels within the target range at the end of treatment (EOT) during Period 2.[34]

The Phase III SYMPHONY ND study (JapicCTI-183870) compared the efficacy (noninferiority to darbepoetin alfa [DA]) and safety of enarodustat in Japanese anemic patients with CKD not on dialysis. This open-label study consisted of a 4-week screening period, 24-week treatment period, and 2-week follow-up period. The treatment period consisted of an initial 4-week treatment period with a fixed starting dose of 2 mg/day and a 20-week maintenance treatment period with dose adjustments (1–8 mg/day) to maintain Hb levels within the target range (10–12 g/dl). In this study, 216 subjects (102 ESA-naïve and 114 ESA-treated subjects) were randomly assigned to the enarodustat arm ($n = 107$; 50 ESA-naïve and 57 ESA-treated subjects) or DA arm ($n = 109$; 52 ESA-naïve and 57 ESA-treated subjects). The primary endpoint analysis demonstrated that the mean Hb level during the evaluation period (defined as the mean Hb level at weeks 20, 22, and 24 or discontinuation corresponding to week 24) in the enarodustat arm was 10.96 g/dl (95% confidence interval [CI]: 10.84, 11.07) with a difference of 0.09 g/dl (95% CI: 0.07, 0.26) between arms, establishing its noninferiority to DA. During the initial 4-week treatment period in ESA-naïve subjects, the mean change in Hb levels at week 4 from week 0 was 0.32 g/dl (95% CI: 0.13, 0.51) with no evidence of a rapid Hb increase

(i.e., >2.0 g/dl in 4 weeks). The increase rate in Hb levels estimated using the mixed effects model was 0.079 g/dl per week (95% CI: 0.033, 0.125). In ESA-treated subjects, the proportion of subjects who achieved a Hb level within the range of week 0 ± 1.0 g/dl at week 4 was 87.7% (95% CI: 76.3, 94.9), with a stable Hb level after switching from existing ESA therapy. During the 20-week maintenance treatment period, Hb levels were maintained within the target range (Figure 2). The proportion of patients who achieved a mean Hb level within the target range during the EOT period was 88.6% (95% CI: 80.9, 94.0). During the overall treatment period, the mean prescribed dose of enarodustat was 2.68 mg/day, which was comparable to the starting dose (2 mg/day).[36]

The Phase III SYMPHONY ND-Long study (JapicCTI-173699) evaluated the long-term (52-week) safety and efficacy of enarodustat in Japanese anemic patients with CKD not on dialysis. The study consisted of a 2- or 4-week screening period, 52-week treatment period, and 2-week follow-up period, with 132 subjects (42 ESA-naïve and 90 ESA-treated subjects) evaluated during the treatment period. The treatment period consisted of an initial 4-week treatment period with a fixed starting dose of 2 mg/day and a 48-week maintenance treatment period with dose adjustments (1–8 mg/day) to maintain Hb levels within the target range (10–12 g/dl). The mean Hb levels and 95% CI for each visit were maintained within the target range over the treatment period. The proportion of participants who achieved a mean Hb level within the target range during the EOT period was 79.2%. During the evaluation period for 24- and 52-week treatments, the mean prescribed doses of enarodustat were 2.84 mg/day during weeks 20–24 and 3.02 mg/day during weeks 48–52. The mean number of dose adjustments was 1.1 from week 0 to 24 and 1.5 from week 24 to 52.[37]

4.1.2 | Hemodialysis patients

The Phase IIb study (JapicCTI-152892) assessed the dose–response of enarodustat during the first 6 weeks of the treatment period (Period 1) and maintenance doses during the subsequent 24 weeks (Period 2) for Japanese anemic patients with CKD on hemodialysis. During Period 1, 85 ESA-treated subjects were randomized to enarodustat 2, 4, or 6 mg once daily or placebo under double-blind conditions. During Period 2, all subjects received enarodustat titrated 2–8 mg/day to maintain Hb levels within the target range (10–12 g/dl). The proportion of subjects who maintained Hb levels within baseline ±1.0 g/dl in the enarodustat arms tended to be higher than that in the placebo arm during Period 1 (27.3% of subjects in the placebo arm; 63.2%, 60.0%, and 52.4% in the enarodustat 2-, 4-, and 6-mg arms, respectively). Furthermore, 65.1% of subjects maintained Hb levels within the target range at the EOT in Period 2.[35]

The Phase III SYMPHONY HD study (JapicCTI-183938) compared the efficacy (noninferiority to DA) and safety of enarodustat with double-blind and double-dummy procedures in Japanese anemic patients with CKD on hemodialysis. The study consisted of a 4-week screening period, 24-week treatment period, and 2-week follow-up period. The treatment period consisted of an initial 4-week treatment period with a fixed starting dose of 4 mg/day and a 20-week maintenance treatment period with dose adjustments (1–8 mg/day) to maintain Hb levels within the target range (10 to <12 g/dl). In this study, 173 ESA-treated subjects were randomly assigned to the enarodustat arm ($n = 87$) or DA arm ($n = 86$). The primary endpoint analysis demonstrated that the mean Hb level during the evaluation period (defined as the mean Hb level at weeks 20, 22, and 24 or discontinuation corresponding to week 24) in the enarodustat arm was 10.73 g/dl (95% CI: 10.56, 10.91) with a difference of −0.12 g/dl (95% CI: −0.33, 0.10) between arms, establishing its noninferiority to DA. During the initial 4-week treatment period, the proportion of subjects who achieved a Hb level within the range of week 0 ± 1.0 g/dl at week 4 was 80.2% (95% CI: 70.2, 88.0), with a stable Hb level after switching from existing ESA therapy. During the 20-week maintenance treatment period, Hb levels were appropriately maintained within the target range (Figure 3). The proportion that achieved a mean Hb level within the target range during the EOT period was 77.9% (95% CI: 67.7, 86.1). During the overall treatment period, the mean prescribed dose of enarodustat was 3.95 mg/day, which was comparable to the starting dose (4 mg/day).[38]

The Phase III SYMPHONY HD-Long study (JapicCTI-173699) evaluated the long-term (52-week) safety and efficacy of enarodustat in Japanese anemic patients with CKD on hemodialysis. The study consisted of a 2- or 4-week screening period, 52-week treatment period, and 2-week follow-up period. The treatment period consisted of an initial 4-week treatment period with a fixed starting dose of 4 mg/day and a 48-week maintenance treatment period with dose adjustments (1–8 mg/day) to maintain Hb levels within the target range (10 to <12 g/dl), with 136 ESA-treated subjects evaluated during the treatment period. The mean Hb levels and 95% CI for each visit were maintained within the target range over the treatment period. The proportion that achieved a mean Hb level within the target range during the EOT period was 76.5%. During the evaluation period for 24- and 52-week treatments, the mean prescribed doses of

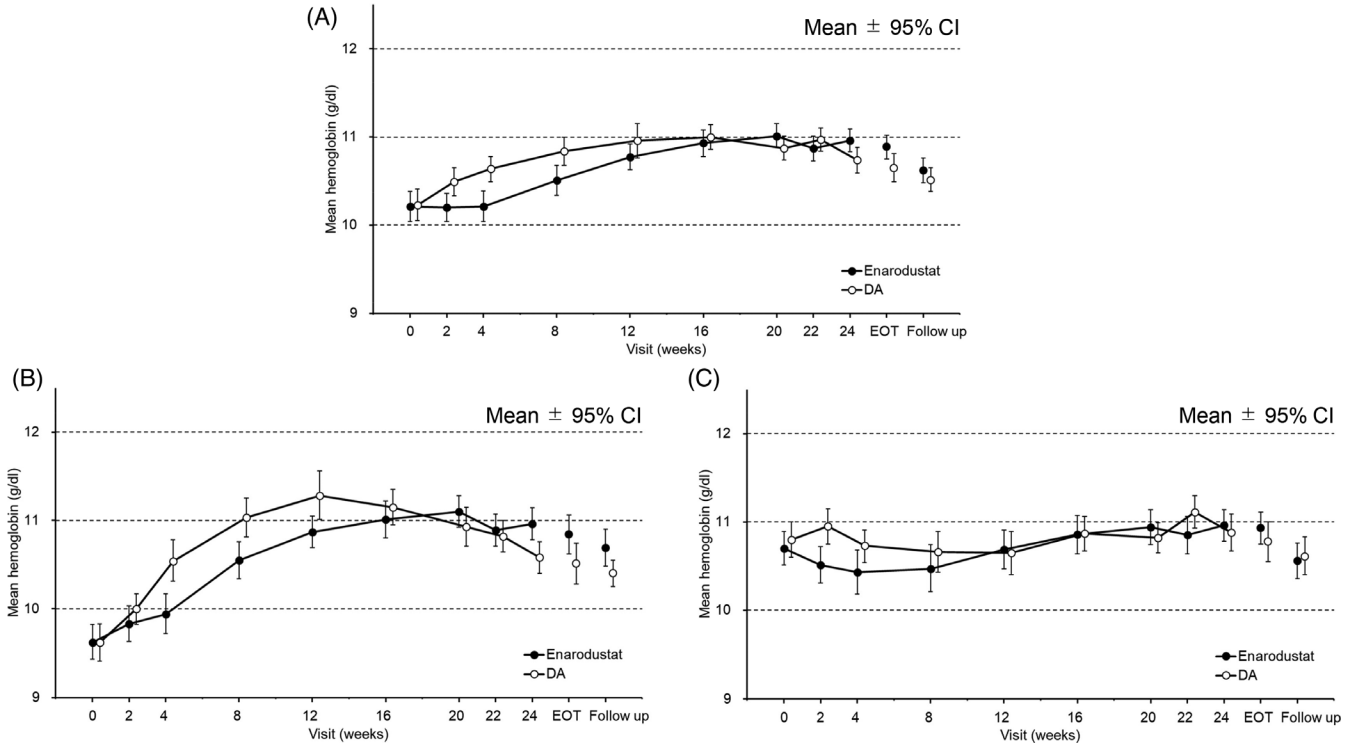

FIGURE 2 Time course of Hb levels over time (full analysis set). (A) All subjects. (B) ESA-naïve subjects. (C) ESA-treated subjects. Each point indicates the mean Hb level in each treatment arm, and bars indicate the 95% confidence interval. Figures adapted from fig. 1a, b, and c in Akizawa et al.[36] Hb, hemoglobin; ESA, erythropoiesis-stimulating agent; CI, confidence interval; DA, darbepoetin alfa; EOT, end of treatment

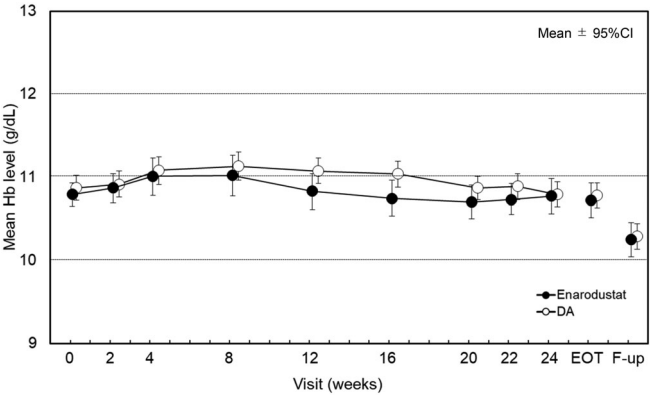

FIGURE 3 Hb levels over time and mean dose of enarodustat and DA (full analysis set). Each point indicates the mean Hb level in each arm (closed circles: enarodustat arm; open circles: DA arm), and bars indicate the 95% confidence interval. Figure modified from fig. 1 in Akizawa et al.[38] Hb, hemoglobin; EOT, end of treatment; CI, confidence interval; DA, darbepoetin alfa; F-up, follow-up

enarodustat were 3.73 mg/day during weeks 20–24 and 3.29 mg/day during weeks 48–52. The mean number of dose adjustments was 1.7 from week 0 to 24 and 1.5 from week 24 to 52.[37]

The Phase III SYMPHONY HD-naïve study (JapicCTI-173702) assessed the efficacy and safety of enarodustat in ESA-naïve Japanese anemic patients with CKD on hemodialysis (n = 34). The starting dose of enarodustat was 4 mg/day, and the dose was adjusted as appropriate in the range of 1–8 mg/day to maintain Hb levels within the target range (10 to <12 g/dl). As a result, the estimated increase rate in Hb levels per week from week 0–4 [95% CI] was 0.302 [0.239, 0.365] g/dl/week, and Hb levels were maintained within the target range after week 8 (Figure 4).[30]

4.1.3 | Peritoneal dialysis patients

The Phase III SYMPHONY PD study assessed the efficacy and safety of enarodustat in anemic patients with CKD on peritoneal dialysis (n = 42). The starting dose of enarodustat was 2 mg/day, and the dose was adjusted as appropriate in the range of 1–8 mg/day to maintain Hb levels within the target range (10–12 g/dl). As a result, the Hb level (mean ± standard deviation) was 11.01 ± 0.81 g/dl at baseline and 10.78 ± 0.69 g/dl at the EOT, and the Hb level was maintained within the target range over the treatment period (Figure 5).[30]

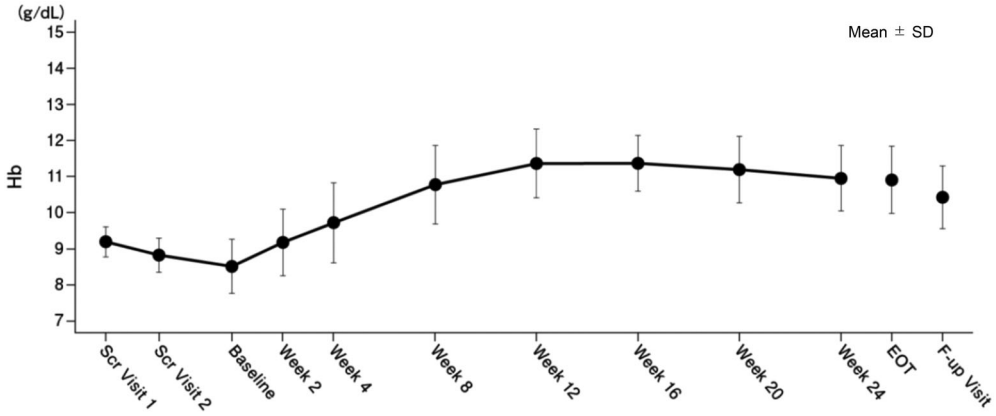

FIGURE 4 Time course of Hb levels over time (full analysis set). Each point indicates the mean Hb level in enarodustat, and bars indicate the standard deviation. Hb, hemoglobin; SD, standard deviation; Scr visit, screening visit; EOT, end of treatment; F-up Visit; follow-up visit

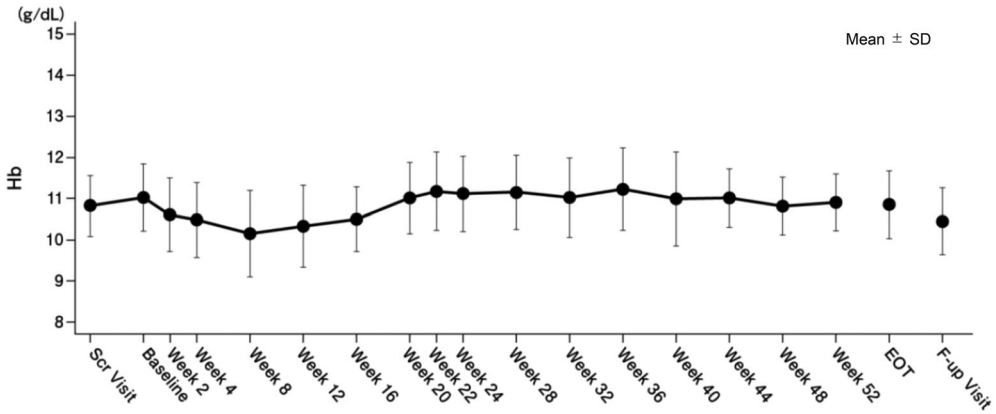

FIGURE 5 Time course of Hb levels over time (full analysis set). Each point indicates the mean Hb level in enarodustat, and bars indicate the standard deviation. Hb, hemoglobin; SD, standard deviation; Scr visit, screening visit; EOT, end of treatment; F-up Visit; follow-up visit

4.2 | Iron parameters

The time courses of changes in iron-related parameters from week 0 and the median value of iron-related parameters at weeks 0 and 24 after switching from existing ESA therapy in Phase III comparative studies (SYMPHONY ND and HD studies) are shown in Figure 6 and Table 2, respectively. In both studies, hepcidin was decreased, and the total iron-binding capacity was increased in the enarodustat arm compared with the DA arm. Transferrin saturation and ferritin remained at >20% and ~100 ng/ml, respectively, in the enarodustat arm.[36, 38]

4.3 | Safety

4.3.1 | Overall safety assessment

Enarodustat is well tolerated for up to 52 weeks of treatment. Phase III comparative studies (SYMPHONY ND and HD studies) reported no apparent safety concerns of enarodustat compared with DA (Table 3).[36, 38] Long-term Phase III studies (SYMPHONY ND-Long and HD-Long studies) confirmed that the incidence of any AEs did not increase over time.[37] No clinically significant changes in laboratory tests including VEGF, total and low-density lipoprotein cholesterol, and albumin, vital signs, standard 12-lead electrocardiogram, chest X-ray, and fundoscopy were observed.[34–38] In addition, the thorough QT/QTc study with healthy subjects in the United States indicated no clinically significant effects on cardiac depolarization and no new clinically relevant morphological changes.[39]

4.3.2 | AEs of interest

In this section, the potential concerns regarding HIF-PH inhibitors are summarized. "Retinal disorders," "malignant or unspecified tumors," "hypertension," and "embolic and thrombotic events" (categorized with reference to the Standardized Med-DRA Queries) were listed in Table 4 using the safety data from Phase III comparative studies (SYMPHONY ND and HD studies). In the SYMPHONY ND study, no "malignant or unspecified tumors" and no "embolic and thrombotic events" were reported in the enarodustat arm. The occurrence of "hypertension" was not different between the treatment arms. The occurrence of "retinal disorders" was numerically higher in the enarodustat arm (3.7% [4/107]) than that in the DA arm (0.9% [1/109]), but no moderate or

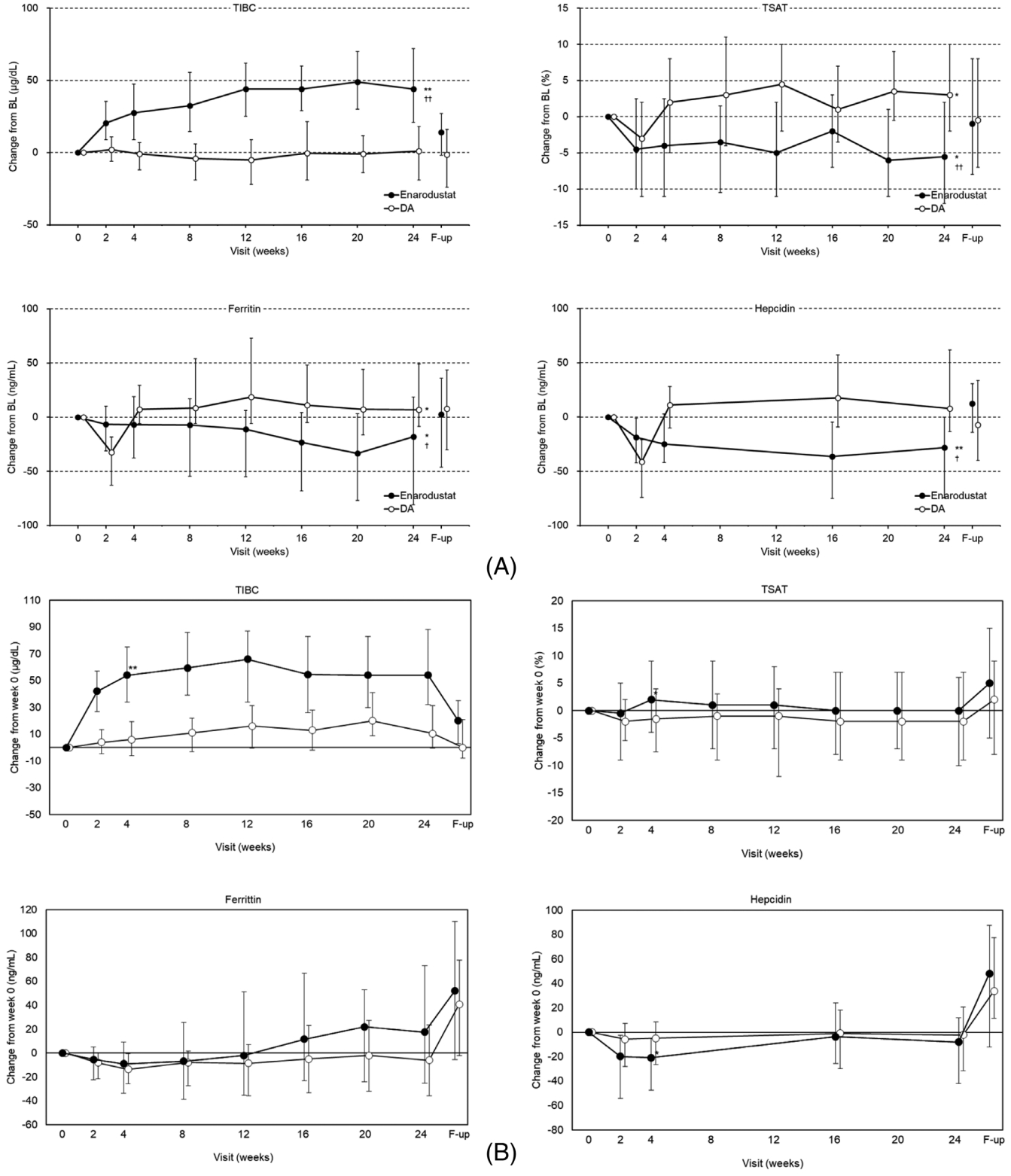

FIGURE 6 Changes in iron-related parameters after switching from existing ESA therapy (full analysis set). (A) Nondialysis CKD subjects. Each point indicates the median value in each treatment arm, and bars indicate Q1 and Q3. Post hoc analysis was performed for changes at week 24, which were compared with week 0 using the Wilcoxon signed-rank test and between both arms using the Wilcoxon rank-sum test (significance level: 5%, two-sided). Adjustment for multiplicity was not performed. *$p < 0.05$ and **$p < 0.0001$ for comparisons with week 0, †$p < 0.05$ and ††$p < 0.0001$ for comparisons between both arms. (B) Hemodialysis subjects. Each point indicates the median value in each arm (closed circles: enarodustat arm; open circles: DA arm), and bars indicate the interquartile range. Intergroup comparisons of changes at week 4 between arms were performed for the post hoc analysis using the Wilcoxon rank-sum test (significance level: 5%, two-sided). *$p < 0.05$; **$p < 0.0001$. fig. 4a adapted from fig. 2b in Akizawa et al.[36] fig. 4b adapted from fig. 2b–e in Akizawa et al.[38] BL, baseline; DA, darbepoetin alfa; TIBC, total iron-binding capacity; TSAT, transferrin saturation; F-up, follow-up; ESA, erythropoiesis-stimulating agent; CKD; chronic kidney disease

TABLE 2 Iron-related parameters after switching from existing ESA therapy at week 0 and week 24 (full analysis set)

	SYMPHONY-ND				SYMPHONY-HD			
	Enarodustat arm ($n = 57$)		DA arm ($n = 55$)		Enarodustat arm ($n = 86$)		DA arm ($n = 86$)	
Median (Q1, Q3)	Week 0	Week 24	Week 0	Week24	Week 0	Week 24	Week 0	Week24
TIBC (μg/dl)	282.0 (245.0, 298.0)	320.0 (289.0, 342.0)	271.0 (247.0, 285.0)	267.5 (239.0, 296.0)	233.0 (213.0, 256.0)	289.5 (259.0, 331.0)	243.0 (212.0, 271.0)	251.0 (221.5, 285.0)
TSAT (%)	31.0 (24.0, 38.0)	25.5 (22.0, 28.0)	33.0 (25.0, 38.0)	33.5 (27.0, 43.0)	27.0 (22.5, 35.0)	26.0 (20.0, 33.0)	27.0 (21.0, 34.0)	24.5 (20.0, 34.0)
Ferritin (ng/ml)	117.0 (64.1, 219.0)	93.2 (55.7, 149.0)	114.0 (68.8, 181.0)	147.5 (84.3, 200.0)	90.9 (49.6, 161.0)	102.0 (57.2, 184.0)	90.3 (45.2, 141.0)	84.4 (38.3, 160.0)
Hepcidin (ng/ml)	72.5 (43.4, 118.0)	42.1 (30.7, 63.9)	87.9 (58.3, 115.0)	106.0 (68.5, 137.0)	70.5 (27.7, 123.0)	49.2 (15.7, 89.5)	51.5 (25.3, 97.6)	47.3 (21.8, 92.3)

Abbreviations: DA, darbepoetin alfa; ESA, erythropoiesis-stimulating agent; TIBC, total iron-binding capacity; TSAT, transferrin saturation.
Note: Table modified from tab. S3 in Akizawa et al.[36] and tab. 5S in Akizawa et al.[38]

severe AEs were reported, and no AEs resulted in treatment discontinuation.[36] In the SYMPHONY HD study, the occurrence of "malignant or unspecified tumors" and "embolic and thrombotic events" was not different between the treatment arms. Hypertension was reported at a low frequency (<5%) in the enarodustat arm, and no apparent difference in frequency was noted between the arms. The occurrence of "retinal disorders" was higher in the enarodustat arm (6.9% [6/87]) than in the DA arm (3.5% [3/86]). Events observed in >1 subject among this category included retinal hemorrhage, and its occurrence was similar in each arm (3.4% [3/87] in the enarodustat arm and 3.5% [3/86] in the DA arm).[38] Regarding other concerns indicated in the recommendation on the appropriate use of HIF-PH inhibitors,[14, 18] no apparent concerns for enarodustat compared with DA were observed.[36, 38]

4.4 | Others

4.4.1 | eGFR based on serum creatinine (eGFRcreat)

eGFRcreat values at weeks 0 and 24 in SYMPHONY ND and ND-Long studies were listed in Table 5. In the SYMPHONY ND study, the eGFRcreat at week 24 was not decreased compared with week 0, which was slower than that in the DA arm. Urine protein at week 24 was increased in both arms.[36] In the SYMPHONY ND-Long study, the eGFRcreat gradually decreased over the treatment period, which appeared to be within the natural course of CKD progression.[37, 40]

4.4.2 | Fibroblast growth factor (FGF) 23

No obvious changes in the median C-terminal FGF 23 and intact FGF 23 values were observed during enarodustat treatment in SYMPHONY ND-Long and HD-Long studies (Figure 7).[37]

5 | DISCUSSION

Several clinical studies demonstrated that enarodustat corrected and maintained Hb levels in anemic patients with CKD not on dialysis, on hemodialysis, and on peritoneal dialysis. Phase III comparative studies also confirmed that the efficacy of enarodustat in controlling mean Hb levels was noninferior to that of DA. In contrast to ESAs, enarodustat promoted erythropoiesis without excessive EPO production and improved iron utilization.

TABLE 3 Adverse events reported in 5% or more subjects in phase III comparative studies (safety analysis population)

	SYMPHONY-ND		SYMPHONY-HD	
	Enarodustat ($n = 107$)	**DA ($n = 109$)**	**Enarodustat ($n = 87$)**	**DA ($n = 86$)**
AEs (≥5% subjects)				
Any AEs	70 (65.4)	90 (82.6)	76 (87.4)	72 (83.7)
Viral upper respiratory tract infection	19 (17.8)	25 (22.9)	28 (32.2)	33 (38.4)
Diarrhea	3 (2.8)	9 (8.3)	0 (0)	0 (0)
Upper respiratory tract inflammation	2 (1.9)	7 (6.4)	5 (5.7)	6 (7.0)
Contusion	1 (0.9)	6 (5.5)	5 (5.7)	3 (3.5)
Vomiting	0 (0)	0 (0)	9 (10.3)	2 (2.3)
Influenza	0 (0)	0 (0)	8 (9.2)	5 (5.8)
Back pain	0 (0)	0 (0)	6 (6.9)	3 (3.5)
Gastroenteritis	0 (0)	0 (0)	5 (5.7)	0 (0)
Shunt stenosis	0 (0)	0 (0)	5 (5.7)	9 (10.5)

Note: Table modified from tab. 2 in Akizawa et al.[36] and tab. 2 in Akizawa et al.[38] Values shown are *n* (%).
Abbreviations: AEs, adverse events; DA, darbepoetin alfa.

These findings supported the notion that HIF-PH inhibitors provide a physiologic approach to the treatment of anemia by mimicking the hypoxia response, which is expected to improve poor prognoses associated with high ESA doses and be effective in patients with ESA hyporesponsiveness due to defective iron utilization or other factors.[12, 14]

HIF activation has the potential to protect against kidney disease through the optimization of cellular adaptive responses to hypoxic conditions, which is supported by the results of preclinical studies with enarodustat.[24–29] In clinical settings, the SYMPHONY ND study reported that the decrease in the eGFRcreat in the enarodustat arm was numerically slower than that in the DA arm. The SYMPHONY ND-Long study reported that the eGFRcreat gradually decreased during enarodustat treatment, which appeared to be within the natural course of CKD progression. Taken together, the effect of enarodustat on preventing CKD progression has not been clearly confirmed in clinical studies, and further studies evaluating the effect of enarodustat on the prevention of CKD progression as a primary endpoint are required.

Regarding safety, enarodustat is well tolerated. One potential concern with HIF-PH inhibitors is the occurrence of VEGF-related AEs. VEGF is a HIF-target gene associated with pathological neovascularization in the retina and choroid[15, 16] and poor tumor prognosis.[17] As a result, HIF-PH inhibitors may increase these risks through their effects on VEGF expression. Therefore, a large difference between the clinical dose that increases Hb levels and the dose that increases VEGF is critical to minimize these potential risks. A preclinical study suggested that plasma VEGF concentrations are increased by enarodustat at a >10-fold higher dosage than that required for endogenous EPO-mediated erythropoiesis. In addition, no increases in retinal VEGF levels, effects on vascular permeability, or effects on tumor growth were observed, even at high doses that increased plasma VEGF concentrations. For AEs of interest, in Phase III comparative studies, although the occurrence of "retinal disorders" was numerically higher in the enarodustat arm than that in the DA arm, no obvious changes in fundoscopy were observed. The occurrences of "malignant or unspecified tumors" were not different between the treatment arms. Therefore, enarodustat is unlikely to increase these events via the expression of VEGF. However, because patients at high risk for these diseases (e.g., patients with malignancy or retinopathy requiring intervention) were excluded from the clinical studies, these potential risks of enarodustat should be continuously assessed. For other concerns related to HIF-PH inhibitors, such as "hypertension" and "embolic and thrombotic events," no apparent difference in frequency was noted between the arms in Phase III comparative studies. It was also reported that no obvious changes in FGF 23, a known risk factor of mortality and cardiovascular events in patients with CKD,[41] were observed in Phase III long-term studies with enarodustat. Although it was reported that exogenous EPO administration or endogenous EPO production through the HIF pathway was associated with increased FGF 23 levels in rodents,[42, 43] the results of Phase III studies indicated that enarodustat is unlikely to increase the safety risk associated with elevated FGF

TABLE 4 Adverse events of interest in phase III comparative studies (safety analysis population)

	SYMPHONY-ND		SYMPHONY-HD	
	Enarodustat ($n = 107$)	DA ($n = 109$)	Enarodustat ($n = 87$)	DA ($n = 86$)
AEs of interest				
Retinal disorders	4 (3.7)	1 (0.9)	6 (6.9)	3 (3.5)
Retinal hemorrhage	2 (1.9)	0 (0)	3 (3.4)[a]	3 (3.5)[b]
Retinal tear	1 (0.9)	0 (0)	0 (0)	0 (0)
Retinal detachment	1 (0.9)[c]	0 (0)	0 (0)	0 (0)
Macular edema	1 (0.9)[c]	0 (0)	1 (1.1)[d]	0 (0)
Chorioretinopathy	0 (0)	0 (0)	1 (1.1)	0 (0)
Diabetic retinopathy	0 (0)	0 (0)	1 (1.1)	0 (0)
Vitreous hemorrhage	0 (0)	0 (0)	1 (1.1)[d]	0 (0)
Diabetic retinal edema	0 (0)	1 (0.9)	0 (0)	0 (0)
Malignant or unspecified tumors	0 (0)	3 (2.8)	2 (2.3)	1 (1.2)
Neoplasm skin	0 (0)	0 (0)	1 (1.1)	0 (0)
Renal cancer	0 (0)	0 (0)	1 (1.1)	0 (0)
Malignant neoplasm of renal pelvis	0 (0)	1 (0.9)	0 (0)	1 (1.2)
Gastric cancer	0 (0)	1 (0.9)	0 (0)	0 (0)
Soft tissue neoplasm	0 (0)	1 (0.9)	0 (0)	0 (0)
Hypertension	5 (4.7)	5 (4.6)	4 (4.6)	2 (2.3)
Blood pressure increased	4 (3.7)	2 (1.8)	1 (3.4)	0 (0)
Hypertension	1 (0.9)	3 (2.8)	3 (1.1)	2 (2.3)
Embolic and thrombotic events	0 (0)	0 (0)	6 (6.9)	5 (5.8)
Shunt occlusion	0 (0)	0 (0)	4 (4.6)[e]	4 (4.7)
Acute myocardial infarction	0 (0)	0 (0)	1 (1.1)	0 (0)
Lacunar infarction	0 (0)	0 (0)	1 (1.1)	0 (0)
Pulmonary embolism	0 (0)	0 (0)	1 (1.1)[e]	0 (0)
Arterial occlusive disease	0 (0)	0 (0)	0 (0)	1 (1.2)

Note: Table modified from tab. 2 in Akizawa et al.[36] and tab. 2 in Akizawa et al.[38] Values shown are *n* (%).
Abbreviations: AEs, adverse events; DA, darbepoetin alfa.
[a]One of the events was judged to be related to enarodustat.
[b]Two of the events were judged to be related to DA.
[c]AEs occurred in the same subject.
[d]One subject experienced two AEs.
[e]One subject experienced two AEs.

23. In summary, on the basis of the results of preclinical and clinical studies, no new safety concerns for enarodustat compared with ESAs were identified.

Among HIF-PH inhibitors approved or under development, several apparent differences were observed. The occurrence of drug–drug interactions (DDI) is one of the main differentiating factors among HIF-PH inhibitors. Unlike other HIF-PH inhibitors, enarodustat has only one DDI concerns that exposure to enarodustat decreases when it is co-administrated with phosphate binders (PBs), including sevelamer carbonate, although the Phase I study showed that staggered administration substantially reduced this effect of sevelamer carbonate on enarodustat exposure. In Phase IIb and Phase III studies with no restrictions for the timing of PB administration (ferric citrate hydrate, sucroferric oxyhydroxide, sevelamer hydrochloride, bixalomer, lanthanum carbonate hydrate, precipitated calcium carbonate, and calcium lactate hydrate), the efficacy of enarodustat was almost the same, even if these drugs were concomitantly used with enarodustat (data not shown). For these reasons, the DDI between enarodustat and PBs is not clinically relevant. Another difference is the cholesterol-lowering effect, which has been reported for roxadustat[44, 45] and

TABLE 5 Estimated glomerular filtration rate based on serum creatinine in the SYMPHONY ND and ND-long studies (safety analysis population)

	SYMPHONY-ND				SYMPHONY-ND-Long		
	Enarodustat arm ($n = 107$)		DA arm ($n = 109$)		Enarodustat ($n = 132$)		
Parameter	**Week 0**	**Week 24**	**Week 0**	**Week 24**	**Week 0**	**Week 24**	**Week 52**
eGFRcreat ml/min/1.73 m^2, mean (SD)	18.35 (10.22)	18.21 (11.40)	17.10 (7.83)	15.61 (8.30)	18.11 (8.60)	16.58 (8.59)	16.87 (9.18)
Change from Week 0 ml/min/1.73 m^2, mean (SD)	—	−0.28 (3.93)	—	−1.57 (2.89)	—	−1.39 (2.79)	−2.21 (3.83)
Intragroup difference[a]		$p = 0.0550$		$p < 0.0001$		NT	NT
Intergroup difference[b]		$p = 0.0044$		—		—	—

Note: Table modified from tab. S4 in Akizawa et al.[36] and tab. 4 in Akizawa et al.[37]
Abbreviations: DA, darbepoetin alfa; eGFR, estimated glomerular filtration rate; NT, not tested; SD, standard deviation.
[a]Wilcoxon signed-rank test.
[b]Wilcoxon rank-sum test.

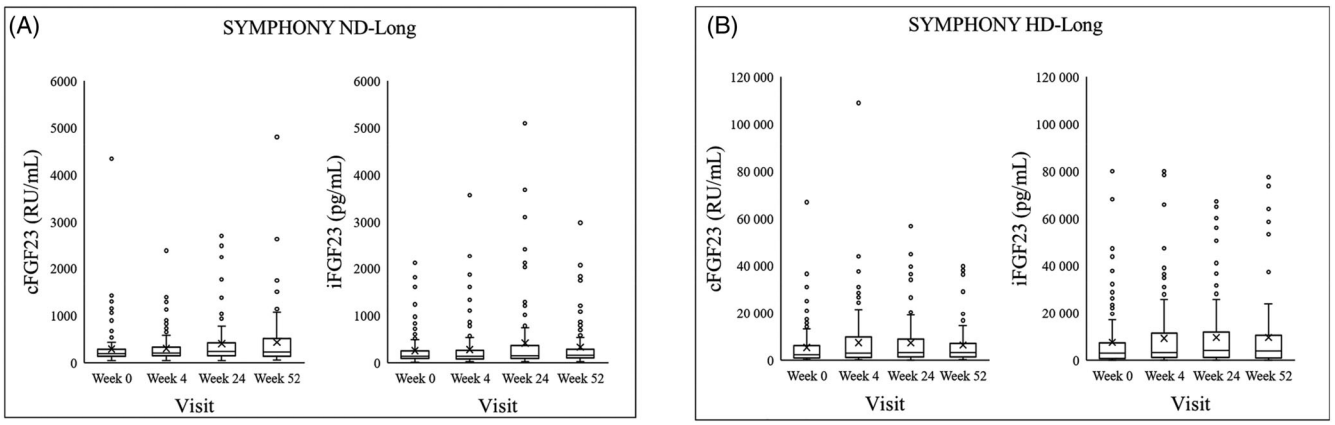

FIGURE 7 Box plot of C-terminal fibroblast growth factor 23 and intact fibroblast growth factor 23 in the (a) SYMPHONY ND-long study and (b) SYMPHONY HD-long study (safety analysis population). Figure adapted from fig. 2 in Akizawa et al.[37] FGF, Fibroblast growth factor

daprodustat[46] but not enarodustat. The dosing schedule and starting dose in the clinical setting are other differentiating factors. The dosing schedules were set as three times weekly for roxadustat and once-daily for the other HIF-PH inhibitors. The starting dose of some HIF-PH inhibitors, including roxadustat and daprodustat, needs to be selected based on prior ESA use and/or ESA doses, body weight, and Hb levels at baseline,[14, 47, 48] but other HIF-PH inhibitors, including enarodustat, can be used regardless of these factors.[30] Additionally, the initial response to each drug appears to be different because of the clinical setting of the starting dose. Thus, it is preferred to select an appropriate HIF-PH inhibitor according to the patient's condition.

In conclusion, the newly approved HIF-PH inhibitor enarodustat is an effective and safe agent to correct and maintain Hb levels in anemic patients with CKD. However, further data, including its long-term safety and protective effect on the kidney and other organs, are needed to confirm its potential safety concerns and other possible benefits. Enarodustat is expected to be developed and used worldwide as the preferred treatment for anemia associated with CKD.

ACKNOWLEDGMENTS

This review article were funded by Torii Pharmaceutical Co., Ltd. We acknowledge the editorial support of ASCA Corporation (http://www.asca-co.com/english_site/) for proofreading a draft of this manuscript funded by Torii Pharmaceutical Co., Ltd.

CONFLICT OF INTEREST

Ryo Fujikawa and Masaki Fujioka are employees of Torii Pharmaceutical Co., Ltd. Yuji Nagao is an employee of

Japan Tobacco Inc. Tadao Akizawa has received consulting fees from Japan Tobacco Inc., Torii Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Astellas Pharma Inc., Bayer Yakuhin, Ltd., Ono Pharmaceutical Co., Ltd., and Sanwa Chemical Co., Ltd.; lecture fees from Torii Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., Kissei Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and Mitsubishi-Tanabe Pharmaceutical Co., Ltd; and manuscript fees from Astellas Pharma Inc.

ORCID

Tadao Akizawa https://orcid.org/0000-0002-6150-9201

REFERENCES

1. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the third National Health and nutrition examination survey (1988–1994). Arch Intern Med. 2002;162(12):1401–8.
2. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23(10):1631–4.
3. Scrutinio D, Passantino A, Santoro D, Catanzaro R. The cardio-renal anaemia syndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival. Eur J Heart Fail. 2011;13(1):61–7.
4. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol. 2000;35(7):1737–44.
5. Silverberg D, Wexler D, Blum M, Wollman Y, Iaina A. The cardio-renal anemia syndrome: does it exist? Nephrol Dial Transplant. 2003;18(Suppl 8):viii7–12.
6. Kanbay M, Perazella MA, Kasapoglu B, Koroglu M, Covic A. Erythropoiesis stimulatory agent-resistant anemia in dialysis patients: review of causes and management. Blood Purif. 2010;29(1):1–12.
7. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355(20):2085–98.
8. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339(9):584–90.
9. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Tonelli M, Garg AX, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. Ann Intern Med. 2010;153(1):23–33.
10. Minamishima YA, Kaelin WG Jr. Reactivation of hepatic EPO synthesis in mice after PHD loss. Science. 2010;329(5990):407.
11. Nangaku M, Eckardt KU. Hypoxia and the HIF system in kidney disease. J Mol Med. 2007;85(12):1325–30.
12. Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol. 2015;11(7):394–410.
13. Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. Kidney Int. 2017;92(2):306–12.
14. Yap DYH, McMahon LP, Hao CM, Hu N, Okada H, Suzuki Y, et al. Recommendations by the Asian Pacific Society of Nephrology (APSN) on the appropriate use of HIF-PH inhibitors. Nephrology (Carlton). 2021;26(2):105–18.
15. Krzystolik MG, Afshari MA, Adamis AP, Gaudreault J, Gragoudas ES, Michaud NA, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol. 2002;120(3):338–46.
16. Aiello LP, Pierce EA, Foley ED, Takagi H, Chen H, Riddle L, et al. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. Proc Natl Acad Sci USA. 1995;92(23):10457–61.
17. Amini A, Moghaddam SM, Morris DL, Pourgholami MH. The critical role of vascular endothelial growth factor in tumor angiogenesis. Curr Cancer Drug Targets. 2012;12(1):23–43.
18. Uchida K, Nangaku M, Abe M, Okada K, Takeda N, Hanabusa N, et al. Recommendation on use of HIF-PH inhibitors. Jpn J Nephrol. 2020;62(7):711–6. (In Japanese).
19. Ogoshi Y, Matsui T, Mitani I, Yokota M, Terashita M, Motoda D, et al. Discovery of JTZ-951: a HIF prolyl hydroxylase inhibitor for the treatment of renal anemia. ACS Med Chem Lett. 2017;8(12):1320–5.
20. Fukui K, Tanaka T, Nangaku M. Enarodustat to treat anemia in chronic kidney disease. Drugs Today (Barc). 2021;57(8):491–7.
21. A multicenter, randomized, double-blind, placebo-controlled phase III clinical study of SAL-0951 tablets in the treatment of renal anemia in non-dialysis chronic kidney disease. Chinese clinical trial registry. 2020 Nov 28. Updated 2021 Feb 22. http://www.chictr.org.cn/showprojen.aspx?proj=64965. Accessed 2 Nov 2021.
22. Fukui K, Shinozaki Y, Kobayashi H, Deai K, Yoshiuchi H, Matsui T, et al. JTZ-951 (enarodustat), a hypoxia-inducible factor prolyl hydroxylase inhibitor, stabilizes HIF-α protein and induces erythropoiesis without effects on the function of vascular endothelial growth factor. Eur J Pharmacol. 2019;859:172532.
23. Shinozaki Y, Fukui K, Kobayashi H, Yoshiuchi H, Matsuo A, Matsushita M. JTZ-951 (enarodustat), a hypoxia-inducible factor prolyl hydroxylase inhibitor, improves iron utilization and anemia of inflammation: comparative study against recombinant erythropoietin in rat. Eur J Pharmacol. 2021;898:173990.
24. Ito M, Tanaka T, Ishii T, Wakashima T, Fukui K, Nangaku M. Prolyl hydroxylase inhibition protects the kidneys from ischemia via upregulation of glycogen storage. Kidney Int. 2020;97(4):687–701.
25. Sugahara M, Tanaka S, Tanaka T, Saito H, Ishimoto Y, Wakashima T, et al. Prolyl hydroxylase domain inhibitor protects against metabolic disorders and associated kidney disease in obese type 2 diabetic mice. J Am Soc Nephrol. 2020;31(3):560–77.
26. Hasegawa S, Tanaka T, Saito T, Fukui K, Wakashima T, Susaki EA, et al. The oral hypoxia-inducible factor prolyl hydroxylase inhibitor enarodustat counteracts alterations in

renal energy metabolism in the early stages of diabetic kidney disease. Kidney Int. 2020;97(5):934–50.
27. Saito H, Tanaka T, Sugahara M, Tanaka S, Fukui K, Wakashima T, et al. Inhibition of prolyl hydroxylase domain (PHD) by JTZ-951 reduces obesity-related diseases in the liver, white adipose tissue, and kidney in mice with a high-fat diet. Lab Investig. 2019;99(8):1217–32.
28. Uchida L, Tanaka T, Saito H, Sugahara M, Wakashima T, Fukui K, et al. Effects of a prolyl hydroxylase inhibitor on kidney and cardiovascular complications in a rat model of chronic kidney disease. Am J Physiol Renal Physiol. 2020;318(2): F388–401.
29. Wakashima T, Tanaka T, Fukui K, Komoda Y, Shinozaki Y, Kobayashi H, et al. JTZ-951, an HIF prolyl hydroxylase inhibitor, suppresses renal interstitial fibroblast transformation and expression of fibrosis-related factors. Am J Physiol Renal Physiol. 2020;318(1):F14–24.
30. Enaroy (Enarodustat). Prescribing information. Japan Tobacco Inc. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/530614_3999052F1029_1_03 (2021). Accessed 9 Nov 2021.
31. Pai SM, Yamada H. Hemodialysis clearance of enarodustat (JTZ-951), an oral erythropoiesis stimulating agent, in patients with end-stage renal disease. Clin Pharmacol Drug Dev. 2021; 10(5):463–70.
32. Pai SM, Connaire J, Yamada H, Enya S, Gerhardt B, Maekawa M, et al. A mass balance study of 14 C-labeled JTZ-951 (enarodustat), a novel orally available erythropoiesis-stimulating agent, in patients with end-stage renal disease on hemodialysis. Clin Pharmacol Drug Dev. 2020;9(6):728–41.
33. Pai S, Koretomo R, Tamaki S, Berg J, Marbury T, Galloway C, et al. JTZ-951, a novel HIF-PHD inhibitor, demonstrates increases in hemoglobin, iron mobilization, reproducible pharmacokinetics, and safety following once daily administration for 15 days in patients with anemia receiving hemodialysis. Nephrol Dial Transplant. 2015;30(Suppl 3): iii293–4.
34. Akizawa T, Nangaku M, Yamaguchi T, Arai M, Koretomo R, Matsui A, et al. A placebo-controlled, randomized trial of enarodustat in patients with chronic kidney disease followed by long-term trial. Am J Nephrol. 2019;49(2):165–74.
35. Akizawa T, Nangaku M, Yamaguchi T, Arai M, Koretomo R, Maeda K, et al. Enarodustat, conversion and maintenance therapy for anemia in hemodialysis patients: a randomized, placebo-controlled phase 2b trial followed by long-term trial. Nephron. 2019;143(2):77–85.
36. Akizawa T, Nangaku M, Yamaguchi T, Koretomo R, Maeda K, Miyazawa Y, et al. A phase 3 study of enarodustat in anemic patients with CKD not requiring dialysis: the SYMPHONY ND study. Kidney Int Rep. 2021;6(7):1840–9.
37. Akizawa T, Nangaku M, Yamaguchi T, Koretomo R, Maeda K, Yamada O, et al. Two long-term phase 3 studies of enarodustat (JTZ-951) in Japanese anemic patients with chronic kidney disease not on dialysis or on maintenance hemodialysis: SYMPHONY ND-long and HD-long studies. Ther Apher Dial. 2022;26(2):345–356. https://doi.org/10.1111/1744-9987.13724.
38. Akizawa T, Nangaku M, Yamaguchi T, Koretomo R, Maeda K, Miyazawa Y, et al. A phase 3 study of enarodustat (JTZ-951) in Japanese hemodialysis patients for treatment of anemia in chronic kidney disease: SYMPHONY HD study. Kidney Dis. 2021;7(6):494–502.
39. Pai SM, Yamada H, Kleiman RB, Zhuo R, Huang QM, Koretomo R. Thorough QT/QTc evaluation of the cardiac safety of enarodustat (JTZ-951), an oral erythropoiesis-stimulating agent, in healthy adults. Clin Pharmacol Drug Dev. 2021;10(8):884–98.
40. Inaguma D, Imai E, Takeuchi A, Ohashi Y, Watanabe T, Nitta K, et al. Risk factors for CKD progression in Japanese patients: findings from the chronic kidney disease Japan cohort (CKD-JAC) study. Clin Exp Nephrol. 2017;21(3):446–56.
41. Kovesdy CP, Quarles LD. The role of fibroblast growth factor-23 in cardiorenal syndrome. Nephron Clin Pract. 2013;123(3–4):194–201.
42. Hanudel MR, Eisenga MF, Rappaport M, Chua K, Qiao B, Jung G, et al. Effects of erythropoietin on fibroblast growth factor 23 in mice and humans. Nephrol Dial Transplant. 2019; 34(12):2057–65.
43. Flamme I, Ellinghaus P, Urrego D, Krüger T. FGF23 expression in rodents is directly induced via erythropoietin after inhibition of hypoxia inducible factor proline hydroxylase. PLoS One. 2017;12(10):e0186979.
44. Chen N, Hao C, Peng X, Lin H, Yin A, Hao L, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. N Engl J Med. 2019;381(11):1001–10.
45. Chen N, Hao C, Liu BC, Lin H, Wang C, Xing C, et al. Roxadustat treatment for anemia in patients undergoing long-term dialysis. N Engl J Med. 2019;381(11):1011–22.
46. Tsubakihara Y, Akizawa T, Nangaku M, Onoue T, Yonekawa T, Matsushita H, et al. A 24-week anemia correction study of daprodustat in Japanese dialysis patients. Ther Apher Dial. 2020;24(2):108–14.
47. Evrenzo (Roxadustat). Prescribing information. Astellas Pharma Inc. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/800126_3999047F1028_1_05 (2021). Accessed 9 Nov 2021.
48. Duvroq (Daprodustat). Prescribing information. GlaxoSmithKline K.K. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/340278_3999049F1027_1_03 (2021). Accessed 9 Nov 2021.

How to cite this article: Fujikawa R, Nagao Y, Fujioka M, Akizawa T. Treatment of anemia associated with chronic kidney disease with the HIF prolyl hydroxylase inhibitor enarodustat: A review of the evidence. Ther Apher Dial. 2022;26: 679–93. https://doi.org/10.1111/1744-9987.13820