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Factors affecting the doses of roxadustat vs darbepoetin alfa for anemia treatment in hemodialysis patients

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Abstract

Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor for the treatment of anemia in chronic kidney disease (CKD). Emerging evidence suggests that roxadustat may be beneficial for patients who inadequately respond to erythropoiesis-stimulating agents (ESAs). This post-hoc analysis of a Japanese, double-blind, randomized, phase 3 study in hemodialysis-dependent CKD patients treated with traditional ESAs assessed the impact of factors associated with ESA hyporesponsiveness on roxadustat and darbepoetin alfa (DA) doses required to maintain target hemoglobin. Endpoints included mean of average doses of roxadustat and DA per administration in the last 6 weeks (AAD/6W) by prior ESA-resistance index (ERI), iron repletion (transferrin saturation; ferritin), and high-sensitivity C-reactive protein (hs-CRP). Of 415 enrolled patients, 303 were randomized (roxadustat, n = 151; DA, n = 152). Weight-adjusted AAD/6W increased with increasing ERI for roxadustat (ERI <3.3, 0.89 mg/kg; ERI ≥8.4, 1.51 mg/kg) and DA (ERI <3.3, 0.26 μg/kg; ERI ≥8.4, 0.91 μg/kg); the weight-adjusted AAD/6W relative to within-arm mean AAD/6W showed a trend toward increased DA doses for the ERI ≥8.4 category ($P = .089$). AAD/6W remained stable for roxadustat but increased for DA with decreasing baseline iron repletion markers. The relationship between roxadustat doses and end of treatment (EoT) hs-CRP was not significant (estimated slope, −0.494; $P = .814$); a trend toward increased DA doses was observed with increasing EoT hs-CRP (estimated slope, 2.973; $P = .075$). Roxadustat doses required to maintain target hemoglobin appear to be less affected by factors that underlie ESA hyporesponsiveness, relative to DA; roxadustat may be beneficial for patients hyporesponsive to ESAs.

KEYWORDS

anemia, chronic kidney disease, darbepoetin alfa, inflammation, roxadustat

1 | INTRODUCTION

Anemia is a complication of chronic kidney disease (CKD) caused by dysregulation in oxygen sensing from the failing kidneys, reduced erythropoiesis, shortened red blood cell survival, inflammation, and impaired iron metabolism.[1] Traditional erythropoiesis-stimulating agents (ESAs) are effective in treating CKD anemia;

however, their doses have decreased globally due to dose-related safety concerns in patients with cancer, diabetes, and cardiovascular disease.[2,3] Furthermore, 5% to 10% of patients do not respond adequately[4] to ESAs and ESA hyporesponsiveness has been associated with increased risk of death or cardiovascular events.[5,6] Inflammation has been reported to cause ESA hyporesponsiveness, and elevated C-reactive protein levels—a marker of inflammation—occur in 30% to 50% of non-dialysis-dependent (NDD) and dialysis-dependent (DD) patients. Other causes of ESA hyporesponsiveness include absolute or functional iron deficiency and altered nutritional status.[4] Therefore, alternative therapies for patients with CKD anemia who are hyporesponsive to traditional ESAs are needed.

Hypoxia-inducible factor prolyl hydroxylase inhibitors have been developed as an alternative to ESAs for the treatment of CKD anemia. These agents mimic the body's natural response to hypoxia regardless of the oxygen levels and activate the transcription of several genes, including erythropoietin (EPO), leading to increased erythropoiesis, transferrin receptor expression, and iron absorption.[7]

Roxadustat (ASP1517, FG-4592, AZD9941) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor approved in China for DD and NDD CKD anemia, and in Japan for DD CKD anemia. Phase 3 studies have demonstrated the efficacy and safety of roxadustat in maintaining hemoglobin (Hb) levels in DD[8–11] and NDD[12] patients. A phase 3 Japanese study (1517-CL-0307[9]) demonstrated that titrated roxadustat maintained Hb within the target range of 10.0 to12.0 g/dL in hemodialysis (HD) CKD patients whose Hb levels were previously maintained with recombinant human erythropoietin (rHuEPO) or darbepoetin alfa (DA), and its efficacy was non-inferior to DA. A post-hoc subgroup analysis of the 1517-CL-0307 study[9] was conducted to determine whether roxadustat may be effective in patients with ESA hyporesponsiveness and to examine the dosing trends of roxadustat and DA required to maintain Hb in patients with known risk factors associated with ESA hyporesponsiveness.

2 | PATIENTS AND METHODS

2.1 | Study design

The 1517-CL-0307 study[9] (NCT02952092) was a Japanese, phase 3, multicenter, randomized, double-blind study with DA as an active comparator conducted from 30 November 2016 to 15 March 2018. Patients were randomized (1:1) to titrated oral roxadustat three times weekly (TIW) or DA injections once weekly for up to 24 weeks. Patients were assigned to an initial dose of roxadustat (70 mg or 100 mg) or DA (10-60 μg) based on the average weekly dose of rHuEPO or DA before randomization. Dose adjustments were conducted throughout the study to maintain Hb within 10 to 12 g/dL. Additional details are reported in the Appendix.

2.2 | Study population

Patients were aged ≥20 years with CKD anemia, on stable HD for >12 weeks TIW, had been receiving IV short-acting rHuEPO or DA for >8 weeks, and had Hb levels within 10.0 to 12.0 g/dL and transferrin saturation (TSAT) ≥20% or serum ferritin ≥100 ng/mL.

2.3 | Endpoints

The endpoints of this post-hoc analysis were the average allocated dose of roxadustat and DA per administration in the last 6 weeks (AAD/6W) assessed by subgroup using the following factors: ESA resistance index (ERI, quartile); high-sensitivity C-reactive protein (hs-CRP, mg/L; <3.000, ≥3.000); geriatric nutritional risk index (GNRI, quintile); iron repletion (ferritin <100 ng/mL, TSAT <20%; ferritin <100 ng/mL, TSAT ≥20%; ferritin ≥100 ng/mL, TSAT <20%; ferritin ≥100 ng/mL, TSAT ≥20%) at baseline and by average in the last 6 weeks; presence of diabetes mellitus (DM, presence, [DM+]; absence, [DM−]); Kt/V (a measure of dialysis adequacy, <1.4, ≥1.4)[13]; and normalized protein catabolic rate (nPCR, <0.84, ≥0.84). The hs-CRP threshold of 3.000 mg/L represents the upper limit of the normal hs-CRP range. The cutoff value of 1.4 for Kt/V was based on the Japanese Society for Dialysis Therapy recommendation of a target dialysis dose of Kt/V >1.4.[14] The GNRI cutoff value of 91.2 is associated with an increased nutritional risk.[15] The ERI subgroup analysis was conducted using the weight-adjusted AAD/6W. Additional details are reported in the Appendix.

2.4 | Statistical analysis

All statistical analyses were conducted using the full analysis set (FAS) including all patients who received ≥1 dose of study drug and had ≥1 efficacy measurement. Analysis of variance was conducted by treatment group to test the effect of the aforementioned factors on AAD/6W. For all factors, the ratios between the mean AAD/6W in each category and the within-arm mean AAD/6W of study drug were calculated and *t*-tests were performed to compare the two treatment groups. Scatter plots and linear regression analyses of the last allocated doses of study drug per administration against hs-CRP (mg/L) at Week 0 and at the end of treatment (EoT) were performed for each treatment group. Demographic and

TABLE 1 Patient demographics and baseline characteristics (FAS)

Parameter	Roxadustat (n = 150)	Darbepoetin alfa (n = 151)
Sex, n (%)		
Male	101 (67)	107 (71)
Female	49 (33)	44 (29)
Age, years		
Mean (SD)	65 (12)	65 (10)
Median	66	66
Min-max	24 to 89	37 to 85
Weight (after hemodialysis), kg		
Mean (SD)	58 (12)	59 (13)
Median	57	58
Min-max	37 to 100	36 to 107
Hemodialysis vintage, months		
Mean (SD)	93 (90)	100 (102)
Median	60	54
Min-max	3 to 489	4 to 422
Previous ESA medication, n (%)		
rHuEPO	43 (29)	46 (30)
DA	107 (71)	105 (70)
Previous rHuEPO dose, IU/week		
Mean (SD)	4692 (2436)	4777 (2246)
Median	4500	4500
Min-max	1500 to 9000	1500 to 9000
Previous DA dose, μg/week		
Mean (SD)	18 (15)	19 (16)
Median	15	15
Min-max	3 to 120	1 to 120
Hemoglobin, g/dL		
Mean (SD)	11.0 (0.6)	11.0 (0.6)
Median	11.0	11.0
Min-max	9.7 to 12.1	10.0 to 12.2
hs-CRP, mg/L		
Mean (SD)	1.3246 (2.4124)	1.4622 (2.2948)
Median	0.5650	0.5640
Min-max	0.050 to 19.000	0.050 to 13.400
hs-CRP group, mg/L, n (%)		
<3.000	136 (91)	129 (85)
≥3.000	14 (9)	22 (15)
ERI		
Mean (SD)	6.4 (4.6)	6.7 (5.2)
Median	5.1	5.5
Min-max	0.7 to 35.0	0.3 to 42.9
GNRI		
Mean (SD)	95.5 (5.4)	95.4 (5.0)

(Continues)

TABLE 1 (Continued)

Parameter	Roxadustat (n = 150)	Darbepoetin alfa (n = 151)
Median	95.9	96.7
Min-max	81.0 to 108.7	76.9 to 108.7
Iron (μmol/L)		
Mean (SD)	12.1 (5.1)	12.6 (4.5)
Median	11.0	11.0
Min-max	5 to 46	4 to 27
Ferritin, ng/mL		
Mean (SD)	102.3 (83.4)	96.3 (75.1)
Median	83.1	84.3
Min-max	6.9 to 521.0	9.0 to 477.0
TSAT, %		
Mean (SD)	28.3 (11.7)	29.0 (10.2)
Median	25.2	26.9
Min-max	12.7 to 93.4	14.1 to 66.5
Iron repletion, n (%)		
Ferritin <100 ng/mL and TSAT <20%	28 (19)	12 (8)
Ferritin <100 ng/mL and TSAT ≥20%	68 (45)	81 (54)
Ferritin ≥100 ng/mL and TSAT <20%	10 (7)	10 (7)
Ferritin ≥100 ng/mL and TSAT ≥20%	44 (29)	48 (32)
Transferrin, g/L		
Mean (SD)	1.8 (0.3)	1.8 (0.3)
Median	1.8	1.8
Min-max	1.2 to 3.0	1.1 to 2.5
Reticulocyte Hb, pg		
Mean (SD)	34.7 (2.0)	35.1 (2.3)
Median	34.8	35.3
Min-max	29.1 to 41.4	23.4 to 40.0
Previous or concurrent retinal vascular disorder, n (%)		
Absent	88 (59)	94 (62)
Present	62 (41)	57 (38)
Kt/V		
Mean (SD)	1.6 (0.3)	1.5 (0.3)
Median	1.5	1.5
Min-max	0.9 to 2.7	0.9 to 2.8
nPCR		
Mean (SD)	0.8 (0.2)	0.9 (0.1)
Median	0.8	0.8
Min-max	0.5 to 1.4	0.4 to 1.2

TABLE 1 (Continued)

Parameter	Roxadustat (n = 150)	Darbepoetin alfa (n = 151)
Diabetes mellitus, n (%)		
Absent	96 (64)	97 (64)
Present	54 (36)	54 (36)

Abbreviations: DA, darbepoetin alfa; ERI, ESA resistance index; ESA, erythropoiesis-stimulating agent; FAS, full analysis set; GNRI, geriatric nutritional risk index; hs-CRP, high-sensitivity C-reactive protein; nPCR, normalized protein catabolic rate; rHuEPO, recombinant human erythropoietin; TSAT, transferrin saturation.

baseline characteristics were summarized using descriptive statistics. Additional details are reported in the Appendix. All data processing, summarization, and analyses were performed using SAS Version 9.4 (eg, PROC MIXED for analysis of variance, PROC TTEST for *t*-test, and PROC REG for linear regression analysis) and R software version 3.5.1 (eg, glmnet package for multivariable analysis by lasso regression).

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Of 415 patients who provided informed consent, 112 discontinued before randomization and 303 were randomized to roxadustat (n = 151) or DA (n = 152), and 301 were included in the FAS (roxadustat, n = 150 [99.3%]; DA, n = 151 [99.3%]); 250 (82.5%) patients (roxadustat, n = 119 [78.8%]; DA, n = 131 [86.2%]) completed the study and 53 discontinued (roxadustat, n = 32 [21.2%]; DA, n = 21 [13.8%]). Demographics and baseline characteristics were similar between the groups. In the FAS, the proportion of patients with ferritin <100 ng/mL and TSAT <20% was higher in the roxadustat (19%) group than in the DA (8%) group (Table 1).

The mean Hb levels for both groups remained stable throughout the study. The primary analysis showed that during weeks 18 to 24, the 95% confidence interval of the average Hb levels was within the target range of 10.0 to 12.0 g/dL confirming the efficacy of roxadustat and the non-inferiority of roxadustat to DA.

3.2 | Results of the subgroup analyses

3.2.1 | Previous ESA use and Hb response: ERI

For roxadustat, the mean (SD) weight-adjusted AAD/6W values and ratios to the within-arm mean dose for each ERI category were: ERI <3.3, 0.89 (0.51) mg/kg and 0.722; ERI ≥3.3 to <5.2, 1.20 (0.69) mg/kg and 0.968; ERI ≥5.2 to <8.4, 1.35 (0.63) mg/kg and 1.095; ERI ≥8.4, 1.51 (0.69) mg/kg and 1.224. For DA, the mean (SD) weight-adjusted AAD/6W values and ratios were: ERI <3.3, 0.26 (0.31) μg/kg and 0.478; ERI ≥3.3 to <5.2, 0.36 (0.30) μg/kg and 0.653; ERI ≥5.2 to <8.4, 0.62 (0.71) μg/kg and 1.146; ERI ≥8.4, 0.91 (0.81) μg/kg and 1.675. A significant increase in mean weight-adjusted AAD/6W was observed for both roxadustat ($P < .001$) and DA ($P < .001$) with increasing ERI, defined by the sample quartile (Figure 1). Furthermore, a non-significant, but meaningful, difference (−0.452; $P = .089$) was observed between roxadustat and DA for the mean weight-adjusted AAD/6W in the ERI ≥8.4 category relative to the within-arm mean, suggesting that the dose change with increasing ERI values was more pronounced for DA than for roxadustat (Figure 1). Similar results were obtained without weight adjustments. In both treatment groups, the average Hb levels of weeks 18 to 24 were maintained within 10 to 12 g/dL regardless of ERI values (Table S4).

3.2.2 | Iron repletion

For roxadustat, the mean (SD) AAD/6W values and the ratios to the mean dose for the category TSAT ≥20% and ferritin ≥100 ng/mL at baseline for each iron repletion category were: TSAT <20% and ferritin <100 ng/mL, 73.25 (42.40) mg and 1.247; TSAT ≥20% and ferritin <100 ng/mL, 72.76 (42.82) mg and 1.239; TSAT <20% and ferritin ≥100 ng/mL, 75.33 (15.01) mg and 1.282; TSAT ≥20% and ferritin ≥100 ng/mL, 58.74 (27.49) mg and 1. For DA, the mean (SD) AAD/6W values and ratios were: TSAT <20% and ferritin <100 ng/mL, 40.28 (28.83) μg and 2.688; TSAT ≥20% and ferritin <100 ng/mL, 39.55 (41.29) μg and 2.639; TSAT <20% and ferritin ≥100 ng/mL, 14.51 (3.93) μg and 0.968; TSAT ≥20% and ferritin ≥100 ng/mL, 14.99 (7.79) μg and 1. With roxadustat, mean AAD/6W remained stable regardless of baseline markers of iron repletion ($P = .208$), whereas with DA, a significant increase in mean AAD/6W was observed with decreasing ferritin ($P < .001$; Figure 2). For roxadustat, the mean (SD) AAD/6W values and the ratios to the

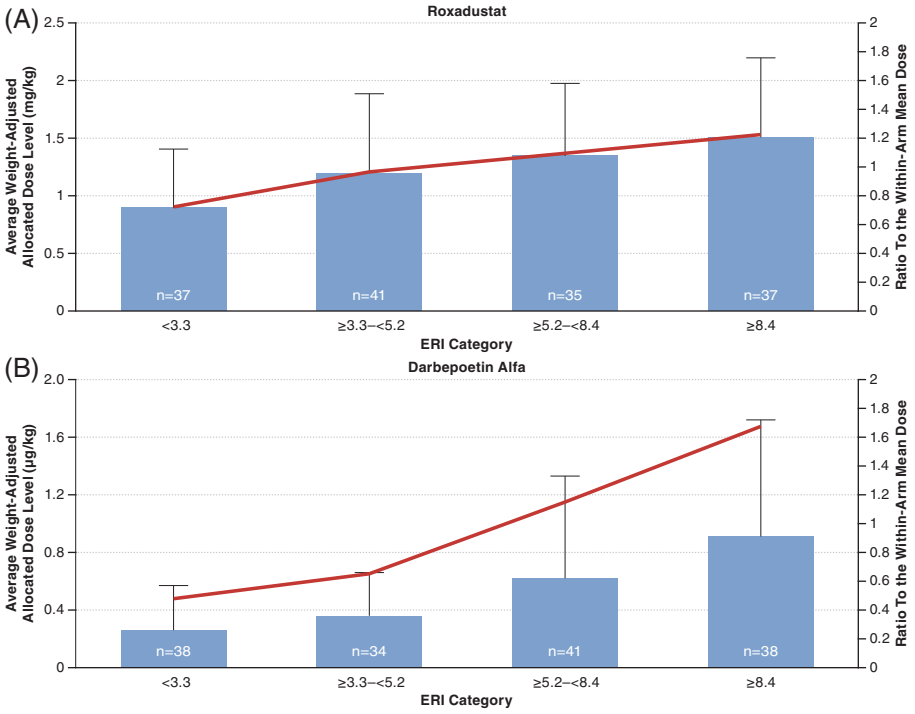

FIGURE 1 Average weight-adjusted allocated dose of study drug per intake in the last 6 weeks stratified by ERI (FAS). DA, darbepoetin alfa; ERI, ESA resistance index; ESA, erythropoiesis-stimulating agent; FAS, full analysis set. Bar plot: mean of average weight-adjusted allocated dose with SD. Line plot: ratio to the within-arm mean dose [Color figure can be viewed at wileyonlinelibrary.com]

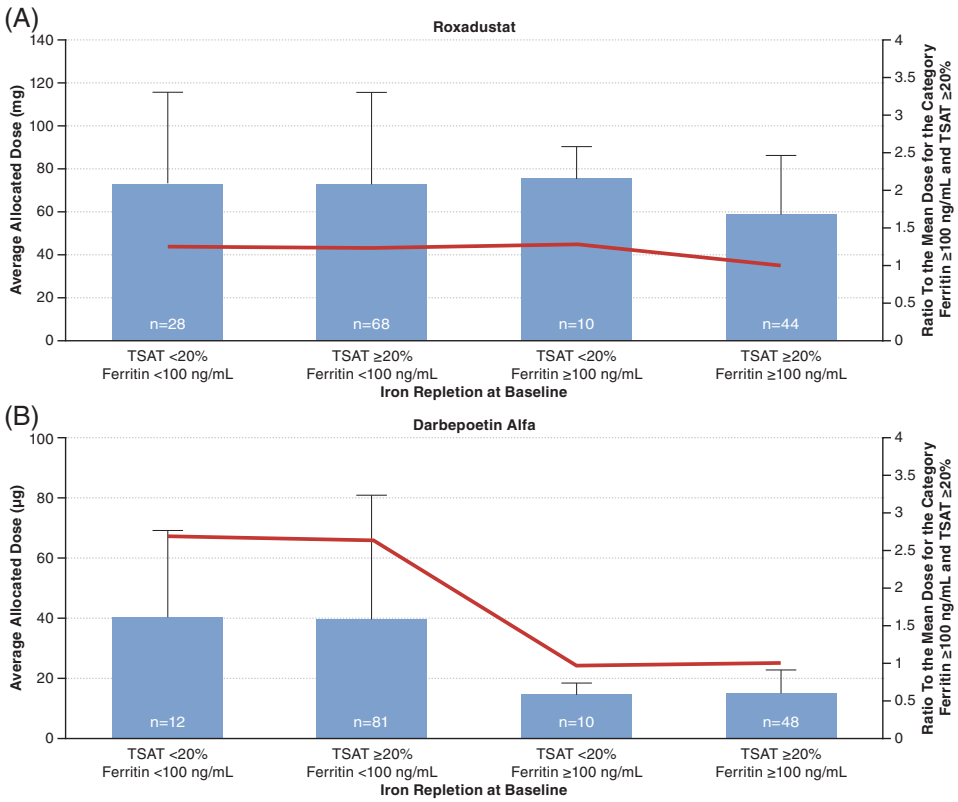

FIGURE 2 Average allocated dose of study drug per intake in the last 6 weeks stratified by baseline levels of ferritin and TSAT (FAS). DA, darbepoetin alfa; FAS, full analysis set; TSAT, transferrin saturation. Bar plot: average allocated dose with SD. Line plot: ratio to the mean dose [Color figure can be viewed at wileyonlinelibrary.com]

mean dose for the category TSAT ≥20% and ferritin ≥100 ng/mL by average in the last 6 weeks for each iron repletion category were: TSAT <20% and ferritin <100 ng/mL, 95.20 (45.60) mg and 1.550; TSAT ≥20% and ferritin <100 ng/mL, 57.08 (29.42) mg and 0.929; TSAT <20% and ferritin ≥100 ng/mL, 68.33 (65.66) mg and 1.112; TSAT ≥20% and ferritin ≥100 ng/mL, 61.43 (25.38) mg and 1. For DA, the mean (SD) AAD/6W values and ratios were: TSAT <20% and ferritin <100 ng/mL, 46.18 (42.31) μg and 3.164; TSAT ≥20% and ferritin <100 ng/mL, 29.98 (34.44) μg and 2.054; TSAT <20% and ferritin ≥100 ng/mL, 29.18 (9.85) μg and 1.999; TSAT

≥20% and ferritin ≥100 ng/mL, 14.59 (6.82) μg and 1. In both groups, mean AAD/6W increased significantly with decreasing markers of iron repletion measured during the last 6 weeks (roxadustat, $P < .001$; DA, $P = .001$) (Figure S1). However, the ratios between mean AAD/6W for each iron repletion category in the last 6 weeks and mean dose for the category TSAT ≥20% and ferritin ≥100 ng/mL were less affected by iron repletion status in the roxadustat group compared with the DA group (TSAT <20% and ferritin <100 ng/mL, $P = .001$; TSAT ≥20% and ferritin <100 ng/mL, $P < .001$; TSAT <20% and ferritin ≥100 ng/mL, $P = .210$) (Figure S1), suggesting that the dose of roxadustat required to maintain Hb remains stable regardless of iron repletion status. The average Hb levels during weeks 18 to 24 were maintained within 10.0 to 12.0 g/dL across all iron repletion categories (Table S4).

3.2.3 | Inflammation: hs-CRP

A regression analysis failed to demonstrate a relationship between the last allocated doses of roxadustat and hs-CRP levels at baseline (estimated slope, −1.926; $P = .461$) and EoT (estimated slope, −0.494; $P = .814$). The relationship between the last allocated DA doses and hs-CRP levels at baseline (estimated slope, 2.363; $P = .270$) was not significant, whereas a non-significant, but meaningful, trend toward an increase in DA dose was observed with increasing hs-CRP levels at EoT (estimated slope, 2.973; $P = .075$) (Figure 3). This finding provides preliminary evidence suggesting that higher DA doses may be required to maintain Hb in the presence of inflammation. Similar results were obtained with a regression analysis conducted using the AAD/6W and hs-CRP levels (Figure S2). Mean hs-CRP levels remained stable with both roxadustat and DA (Table S5). The average Hb levels of weeks 18 to 24 were maintained within 10.0 to 12.0 g/dL across all hs-CRP categories in both groups (Table S4).

3.2.4 | Diabetes mellitus

When analyzed by history of DM, a surrogate for an inflammatory state,[16] no significant difference was

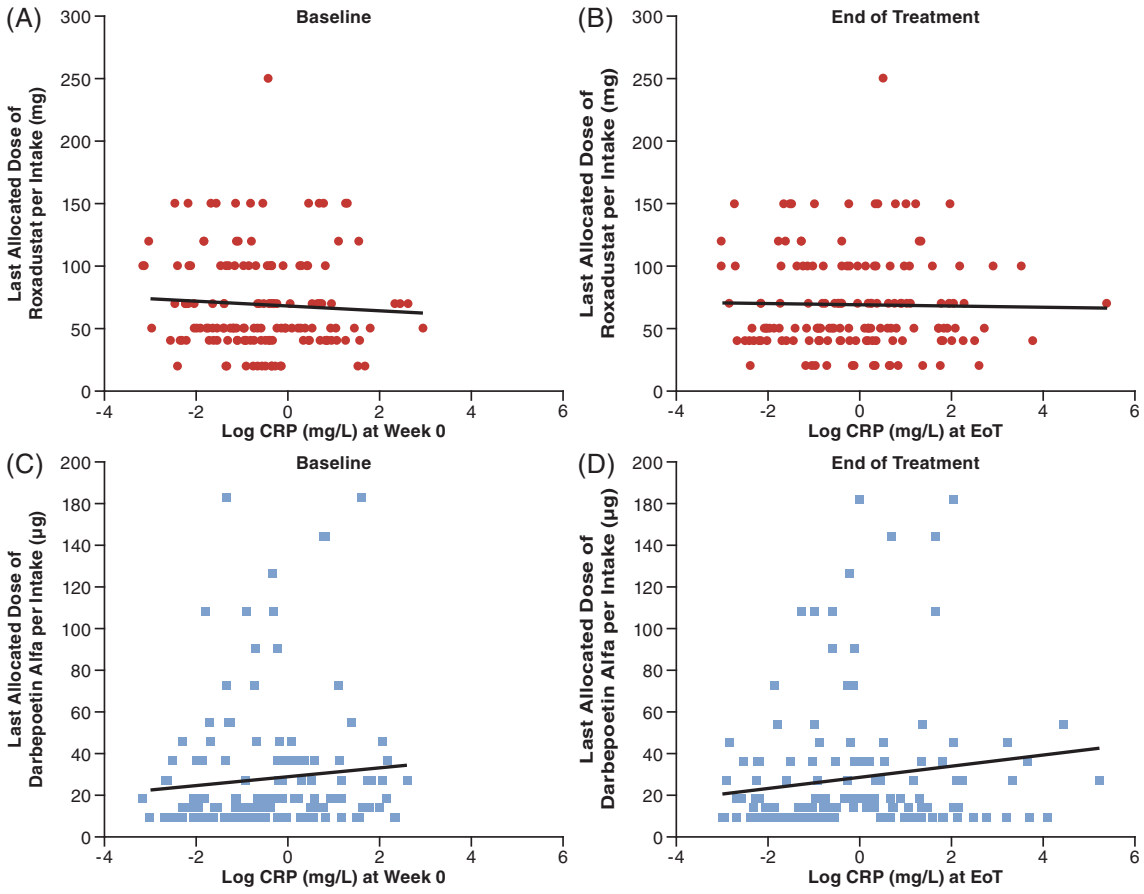

FIGURE 3 Scatter plot of the last allocated dose of roxadustat, A,B, and DA, C,D, against hs-CRP at baseline and EoT (FAS). CRP, C-reactive protein; DA, darbepoetin alfa; EoT, end of treatment; FAS, full analysis set; hs-CRP, high-sensitivity C-reactive protein [Color figure can be viewed at wileyonlinelibrary.com]

observed with roxadustat in mean (SD) AAD/6W between DM− (70.55 [35.40] mg) and DM+ (65.99 [41.80] mg; $P = .480$). Similarly, with DA, there was no significant difference in mean (SD) AAD/6W between DM− (32.74 [38.52] μg) and DM+ (25.46 [22.19] μg; $P = .204$). In both groups, average Hb levels during weeks 18 to 24 were maintained within 10.0 to 12.0 g/dL in both the DM− and DM+ groups (Table S4).

3.2.5 | Nutritional status: GNRI

For roxadustat, the mean (SD) AAD/6W values and the ratios to the within-arm mean dose for each GNRI category were: GNRI <91.2, 73.22 (37.35) mg and 1.063; GNRI ≥91.2 to <95.3, 66.34 (27.19) mg and 0.963; GNRI ≥95.3 to <96.9, 58.73 (31.92) mg and 0.852; GNRI ≥96.9 to <99.8, 73.05 (35.30) mg and 1.060; GNRI ≥99.8, 74.01 (50.07) mg and 1.074. For DA, the mean (SD) AAD/6W values and ratios were: GNRI <91.2, 43.71 (43.93) μg and 1.450; GNRI ≥91.2 to <95.3, 30.31 (37.89) μg and 1.006; GNRI ≥95.3 to <96.9, 31.43 (32.07) μg and 1.043; GNRI ≥96.9 to <99.8, 22.07 (19.08) μg and 0.732; GNRI ≥99.8, 21.17 (24.46) μg and 0.702. A subgroup analysis of mean AAD/6W and GNRI levels, defined by sample quintile, showed that roxadustat doses were not associated with GNRI levels ($P = .431$), whereas a trend toward an increase in allocated DA doses with decreasing GNRI levels was observed ($P = .069$; Figure 4). In both groups, the average Hb levels during weeks 18 to 24 were maintained within 10.0 to 12.0 g/dL across GNRI categories (Table S4).

3.2.6 | Kt/V

With roxadustat, the mean (SD) AAD/6W was lower for patients with Kt/V ≥1.4 (63.98 [30.86] mg) than for those with Kt/V <1.4 (80.06 [48.54] mg; $P = .016$). In contrast, with DA, there was no significant difference in mean (SD) AAD/6W between patients with Kt/V ≥1.4 (31.92 [35.68] μg) and those with Kt/V <1.4 (26.86 [29.76] μg; $P = .380$). However, a multivariate analysis of AAD/6W by lasso regression suggested that Kt/V did not

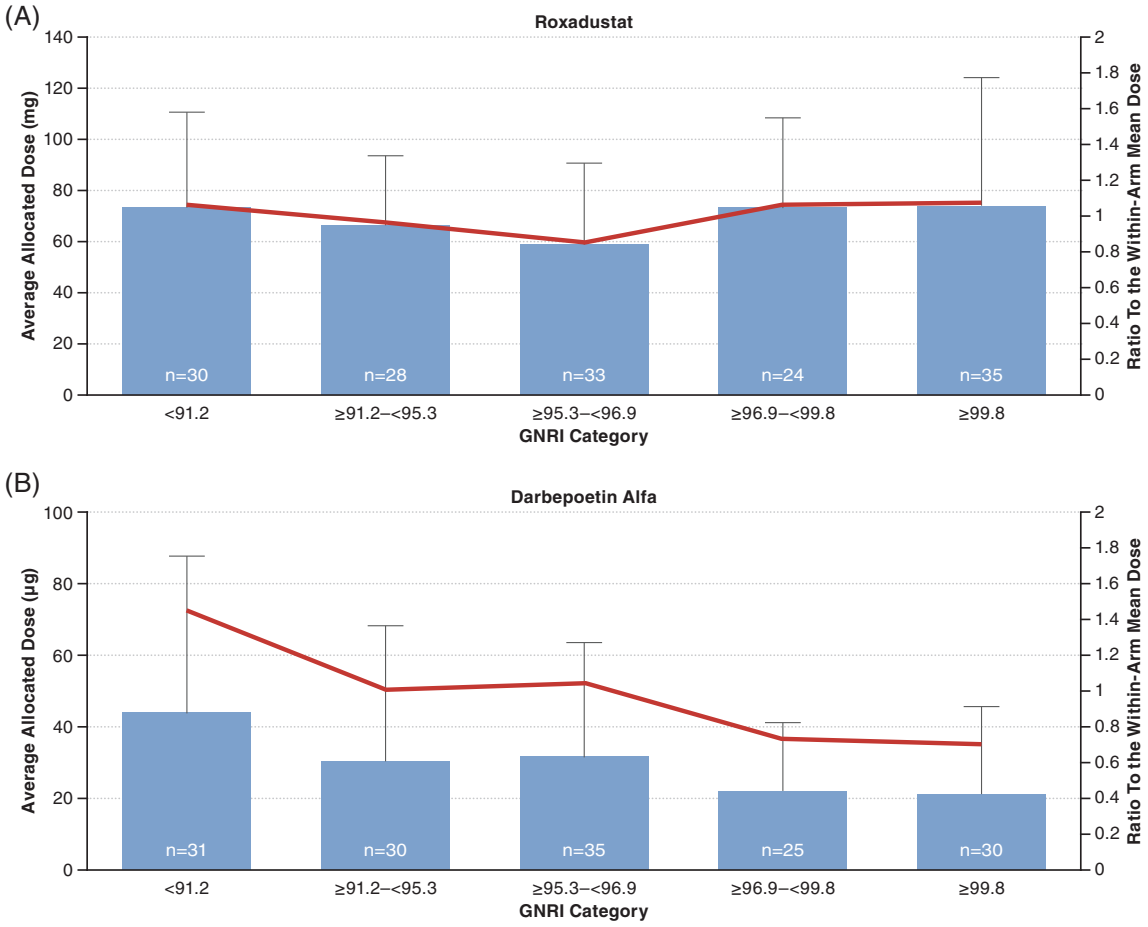

FIGURE 4 Average allocated dose of study drug per intake in the last 6 weeks stratified by GNRI (FAS). DA, darbepoetin alfa; FAS, full analysis set; GNRI, geriatric nutritional risk index. Bar plot: average allocated dose with SD. Line plot: ratio to the mean dose [Color figure can be viewed at wileyonlinelibrary.com]

substantially affect the AAD/6W for both roxadustat and DA groups (Table S6). In both groups, the average Hb levels during weeks 18 to 24 were maintained within 10.0 to 12.0 g/dL regardless of Kt/V values (Table S4).

3.2.7 | nPCR

With roxadustat, patients with nPCR <0.84 required a lower mean (SD) AAD/6W (61.87 [30.94] mg) than those with nPCR ≥0.84 (74.90 [41.98] mg; $P = .035$), whereas no association was observed with DA for mean (SD) AAD/6W between patients with nPCR <0.84 (28.61 [27.87] μg) and those with nPCR ≥0.84 (31.57 [38.50] μg; $P = .591$). However, a multivariate analysis did not confirm this finding (Table S6). In both groups, the average Hb levels of weeks 18 to 24 were maintained within 10.0 to 12.0 g/dL in both nPCR categories (Table S4).

4 | DISCUSSION

This post-hoc analysis of the 1517-CL-0307 study[9] investigated the impact of factors associated with traditional ESA hyporesponsiveness on the doses of roxadustat and DA necessary to maintain Hb in HD CKD patients.

While, in both groups, increasing ERI values was associated with significant increases in mean weight-adjusted AAD/6W to maintain target Hb, a non-significant, but meaningful, difference was observed between roxadustat and DA with increasing ERI relative to the within-arm mean, thereby providing preliminary evidence that roxadustat may be more effective than DA for the treatment of CKD anemia in ESA hyporesponsive patients. When analyzed by baseline iron repletion status, AAD/6W of DA was higher in the low ferritin category, whereas AAD/6W of roxadustat remained stable regardless of iron repletion status. When analyzed using ferritin and TSAT levels in the last 6 weeks, AAD/6W increased for both DA and roxadustat. However, the AAD/6W in each iron status category relative to the AAD/6W for the category TSAT ≥20% and ferritin ≥100 ng/mL remained stable for roxadustat but was higher in the low ferritin and low TSAT categories for DA. Overall, these data suggest that while the dose of DA required to maintain Hb levels may vary with iron status, the dose of roxadustat is not affected.

The association between roxadustat AAD/6W and baseline or EoT hs-CRP levels was not significant, whereas a trend toward a significant increase in DA AAD/6W with hs-CRP levels at EoT was observed. This finding provided preliminary evidence that the presence of inflammation may impact the dose of DA, but not the dose of roxadustat, that is required to maintain Hb (in accordance with the post-hoc subgroup analysis of the 1517-CL-0307 study[9]). Previous studies have shown a reduction in serum hepcidin levels during roxadustat treatment resulting in iron mobilization.[8,17,18] Since inflammation increases hepcidin levels with consequent reduction in iron availability, the efficacy of roxadustat in the presence of inflammation is in line with the proposed mechanism of action. The correlation between CRP levels and ESA hyporesponsiveness has been previously shown in DD patients.[4,11] A study of HD patients showed that the incidence of ESA hyporesponsiveness assessed at 4 months was higher among those with higher vs lower baseline CRP levels, and remained higher after 12 months of follow-up.[19] In another study of roxadustat in HD patients with stable Hb maintained with epoetin alfa, baseline CRP levels were positively correlated with the pre-enrollment maintenance doses of epoetin alfa, whereas the same association between CRP and roxadustat maintenance doses was not observed during the last 7 weeks of roxadustat treatment.[18] Additional studies will be required to draw any firm conclusions regarding the effect of inflammation on the doses of roxadustat required to maintain Hb levels.

To further examine the effect of inflammation on the doses required to maintain target Hb, another subgroup analysis was conducted with DM as a factor. Like high hs-CRP levels, the presence of DM is an indicator of inflammation, although not as sensitive as hs-CRP. No significant difference in DA or roxadustat AAD/6W was observed between DM+ and DM− patients. This is in contrast with previous reports[20,21] showing a correlation between DM and ESA hyporesponsiveness and may be due to several factors, including the small population analyzed.

While a trend toward an increase in DA doses required to maintain Hb was observed with decreasing GNRI, no association was observed between GNRI and roxadustat AAD/6W, indicating that the dose of roxadustat required to maintain Hb remains stable regardless of nutritional status.

Several limitations should be considered when evaluating these results. Importantly, the results of this study are based on a post-hoc analysis of the 1517-CL-307 study[9] that was designed to address a different scientific question. Moreover, the subgroups of the post-hoc analysis are not necessarily exclusive, therefore multiple factors associated with ESA hyporesponsiveness may be present in each patient and the interactions between factors were not studied. The statistical power of this study was limited by the small sample size, and since the study population was exclusively Japanese, larger studies should be conducted in different countries to extend the

findings to other ethnicities. This study enrolled only HD patients previously treated with ESAs and with stable Hb levels within the target range, which introduces the possibility of a selection bias that favors good ESA responders. Furthermore, since peritoneal dialysis and NDD patients were not included, the findings cannot be generalized to those patients.

5 | CONCLUSIONS

The results of this post-hoc analysis suggest that the roxadustat doses required to maintain target Hb may not be as heavily impacted by factors contributing to ESA-hyporesponsiveness, including hs-CRP, GNRI, and iron parameters. Moreover, roxadustat doses required to maintain target Hb are affected by ERI to a lesser extent than DA. Overall, these results provide preliminary evidence that roxadustat may be beneficial to ESA hyporesponsive patients.

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DISCLOSURE OF INTERESTS

Tadao Akizawa reports personal fees from Astellas, Bayer Yakuhin Ltd., GlaxoSmithKline, JT Pharmaceuticals, Kissei Pharmaceutical Co. Ltd., Kyowa Hakko Kirin, and Chugai Pharmaceutical Co. Ltd during the conduct of the study, and reports personal fees from Ono Pharmaceutical Co. Ltd., Fuso Pharmaceutical Industries, Ltd., Nipro Corporation, Sanwa Chemical, Otsuka, and Torii Pharmaceutical Co. Ltd. outside of the submitted work. Michael Reusch is an employee of Astellas Pharma Europe B.V. Yoshikatsu Majikawa and Yusuke Yamaguchi are employees of Astellas Pharma, Inc.

DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

REFERENCES

1. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23(10):1631–1634.
2. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019–2032.
3. Del Vecchio L, Locatelli F. An overview on safety issues related to erythropoiesis-stimulating agents for the treatment of anaemia in patients with chronic kidney disease. Expert Opin Drug Saf. 2016;15(8):1021–1030.
4. Johnson DW, Pollock CA, Macdougall IC. Erythropoiesis-stimulating agent hyporesponsiveness. Nephrology (Carlton, Vic). 2007;12(4):321–330.
5. Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010;363(12):1146–1155.
6. Luo J, Jensen DE, Maroni BJ, Spectrum BSM. Burden of erythropoiesis-stimulating agent Hyporesponsiveness among contemporary Hemodialysis patients. Am J Kidney Dis. 2016;68(5):763–771.
7. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. Am J Kidney Dis. 2017;69(6):815–826.
8. Akizawa T, Otsuka T, Reusch M, Ueno M. Intermittent oral dosing of roxadustat in peritoneal dialysis chronic kidney disease patients with anemia: A randomized, phase 3, multicenter, open-label study. Ther Apher Dial. 2019;24(2):115–125.
9. Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M. Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan. J Am Soc Nephrol. 2020;31:1628–1639.
10. Akizawa T, Ueno M, Shiga T, Reusch M. Oral roxadustat three times weekly in ESA-naive and ESA-converted patients with anemia of chronic kidney disease on hemodialysis: Results from two phase 3 studies. Ther Apher Dial. 2020;24(6):628–641.
11. Chen N, Hao C, Liu BC, et al. Roxadustat treatment for anemia in patients undergoing long-term dialysis. N Engl J Med. 2019;381(11):1011–1022.
12. Chen N, Hao C, Peng X, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. N Engl J Med. 2019;381(11):1001–1010.
13. Tsubakihara Y, Nishi S, Akiba T, et al. 2008 Japanese Society for Dialysis Therapy: Guidelines for renal anemia in chronic kidney disease. Ther Apher Dial. 2010;14(3):240–275.
14. Watanabe Y, Kawanishi H, Suzuki K, et al. Japanese society for dialysis therapy clinical guideline for "maintenance hemodialysis: Hemodialysis prescriptions". Ther Apher Dial. 2015;19(Suppl 1):67–92.
15. Yamada K, Furuya R, Takita T, et al. Simplified nutritional screening tools for patients on maintenance hemodialysis. Am J Clin Nutr. 2008;87(1):106–113.
16. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011;11(2):98–107.
17. Chen N, Qian J, Chen J, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. Nephrol Dial Transplant. 2017;32(8):1373–1386.
18. Provenzano R, Besarab A, Wright S, et al. Roxadustat (FG-4592) versus Epoetin alfa for anemia in patients receiving maintenance hemodialysis: A phase 2, randomized, 6- to 19-week, open-label,

active-comparator, dose-ranging, safety and exploratory efficacy study. Am J Kidney Dis. 2016;67(6):912–924.
19. Kimachi M, Fukuma S, Yamazaki S, et al. Minor elevation in C-reactive protein levels predicts incidence of erythropoiesis-stimulating agent hyporesponsiveness among hemodialysis patients. Nephron. 2015;131(2):123–130.
20. Eriguchi R, Taniguchi M, Ninomiya T, et al. Hyporesponsiveness to erythropoiesis-stimulating agent as a prognostic factor in Japanese hemodialysis patients: The Q-cohort study. J Nephrol. 2015;28(2):217–225.
21. Kuwahara M, Arai Y, Takehara E, et al. Early response to erythropoiesis-stimulating agents in non-dialysis chronic kidney disease patients. Clin Exp Nephrol. 2016;20(4):585–594.

SUPPORTING INFORMATION

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

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