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# Factors Affecting Doses of Roxadustat Versus Darbepoetin Alfa for Anemia in Nondialysis Patients

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**Keywords**
Anemia · Chronic kidney disease · Erythropoiesis-stimulating agent · Hemoglobin · Roxadustat

**Abstract**

***Introduction:*** Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor for treating anemia of chronic kidney disease (CKD). This post hoc analysis of a Japanese, open-label, partially randomized, phase 3 study in nondialysis-dependent (NDD) CKD patients treated with traditional erythropoiesis-stimulating agents (ESAs) evaluated dosing trends of roxadustat and darbepoetin alfa (DA) required to maintain target hemoglobin concentrations in patients with risk factors associated with ESA hyporesponsiveness. ***Methods:*** Patients enrolled in the 1517-CL-0310 study (NCT02988973) that demonstrated noninferiority of roxadustat to DA for change in average hemoglobin levels of week 18–24 from baseline who had used human recombinant erythropoietin or DA before conversion and who were randomized to either roxadustat or DA were included. The endpoints were the average allocated dose of roxadustat and DA per administration in the last 6 weeks (AAD/6W), assessed by subgroups known to be associated with ESA hyporesponsiveness. The analysis of variance was performed by the treatment group to test the influence of subgroup factors on the AAD/6W of study drug. The ratios between the mean AAD/6W in each subgroup category and the within-arm mean AAD/6W were calculated. ***Results:*** Two hundred and sixty-two patients were randomized to either the roxadustat or DA comparative group and received treatment (roxadustat, $n = 131$; DA, $n = 131$). Higher mean (standard deviation) doses of both roxadustat (63.15 [24.84] mg) and DA (47.33 [29.79] μg) were required in the highest ESA resistance index (≥6.8) quartile ($p = 0.003$ and $p < 0.001$, respectively). Patients with adequate iron repletion had the lowest doses for both roxadustat (45.54 [18.01] mg) and DA (28.13 [20.98] μg). High-sensitivity C-reactive protein ≥28.57 nmol/L and the estimated glomerular filtration rate <15 mL/min/1.73 $m^2$ were associated with requiring higher DA but not roxadustat doses. ***Discussion/Conclusion:*** The roxadustat dose required to maintain target hemoglobin in NDD patients in Japan with anemia of CKD relative to DA dose may not be impacted by low-grade inflammation. Roxadustat may be beneficial for ESA-hyporesponsive NDD CKD patients.



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## Introduction

Anemia prevalence increases with the severity of chronic kidney disease (CKD), peaking at approximately 60% in Japanese patients with stage 5 CKD [1]. However, treatment for anemia of CKD in the majority of nondialysis-dependent (NDD) patients is delayed or not provided due to late nephrology referral [1]. In Japan, erythropoiesis-stimulating agents (ESAs) are used minimally in patients with anemia of stage 4 and 5 CKD, with utilization rates of approximately 7.9% and 22.4%, respectively [1]. Anemia of CKD has been associated with increased rates of red blood cell transfusion, hospitalization, and death, especially in patients with cancer, cardiovascular conditions, and diabetes [2–5].

The development of anemia in patients with CKD does not solely originate from endogenous erythropoietin deficiency but may also result from multiple other factors, including elevated hepcidin concentrations and disease states that increase inflammation (e.g., diabetes and progressed CKD) [6–10]. Similarly, ESA dosing in patients with anemia of CKD may be affected by a variety of clinical and patient-specific factors such as gender, the estimated glomerular filtration rate (eGFR), hemoglobin concentration, and high-sensitivity C-reactive protein (hs-CRP) [10]. Patients who require excessively high or progressively increasing ESA doses to maintain hemoglobin concentrations within a target range or are unable to achieve that target range may have ESA hyporesponsiveness or resistance [11, 12]. ESA hyporesponsiveness has been associated with elevated risks of mortality and end-stage kidney disease development [9, 13]. In Japan, ESA hyporesponsiveness occurs in approximately 10% of patients and is associated with increased risk of cardiovascular events and death [10].

Roxadustat (ASP1517, FG-4592, and AZD9941) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor approved in multiple countries for anemia of CKD in patients with dialysis-dependent (DD) and NDD CKD. In the phase 3, multicenter, partially randomized, open-label study (1517-CL-0310), patients with NDD CKD receiving recombinant human erythropoietin (rHuEPO), darbepoetin alfa (DA), or epoetin beta pegol were randomized/allocated to DA or roxadustat [14]. Roxadustat maintained hemoglobin within the target range of 10–12 g/dL and was noninferior to DA. The safety profiles were comparable to previous studies in NDD CKD [15–18]. Because high-dose epoetin alfa and DA have been linked to increased risks of cardiovascular events and death, identifying patients who respond preferentially to roxadustat is imperative [19–24]. A post hoc subgroup analysis of the 1517-CL-0310 study was conducted to evaluate dosing trends of roxadustat and DA required to maintain target hemoglobin concentrations in patients with risk factors associated with ESA hyporesponsiveness in prior studies.

## Materials and Methods

*Study Design*

Patients enrolled in the open-label 1517-CL-0310 study (NCT02988973) who had used rHuEPO or DA before conversion were randomized to either the roxadustat (initial dose 70 mg or 100 mg 3 times weekly) or the DA (initial dose 10–60 μg every 2 weeks) treatment arm [14]. Patients who had used epoetin beta pegol before conversion were allocated to the roxadustat treatment arm (reference arm) but were not included in this post hoc analysis. Initial conversion doses were based on the prescribed ESA dose immediately prior to registration and dose adjustments were regulated according to prespecified criteria. Dose adjustments were conducted throughout the study to maintain hemoglobin within 10–12 g/dL. For patients who received roxadustat, treatment was continued until week 52 to evaluate long-term efficacy and safety. Treatment was ended at week 24 for patients who were randomized to the DA treatment arm. Data through week 24 were used for this post hoc analysis to allow for comparable drug exposure.

*Study Population*

Eligible patients were aged ≥20 years, had been diagnosed with CKD (eGFR ≤89 mL/min/1.73 $m^2$), and were not receiving dialysis. Patients had anemia of CKD and had been receiving subcutaneous ESA, within the doses approved in Japan, for ≥8 weeks before prescreening assessments, and were considered to have stable hemoglobin levels, defined as 10–12 g/dL on the 2 most recent assessments. The full analysis set for this post hoc analysis included patients converted from rHuEPO or DA and not those in the reference arm who were allocated to roxadustat, which totaled 262 patients receiving roxadustat ($n$ = 131) or DA ($n$ = 131).

*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 the subgroup using the following factors chosen by expert opinion that have previously been associated with ESA hyporesponsiveness: the ESA resistance index (ERI) at baseline (quartile); iron repletion (ferritin <100 ng/mL and transferrin saturation [TSAT] <20%; ferritin <100 ng/mL and TSAT ≥20%; ferritin ≥100 ng/mL and TSAT <20%; ferritin ≥100 ng/mL and TSAT ≥20%) in the last 6 weeks; hs-CRP (nmol/L; <28.57, ≥28.57); presence of diabetes mellitus (DM) at baseline (with, without); eGFR (mL/min/1.73 $m^2$; ≥15, <15); CKD etiology (chronic glomerular nephritis [CGN], diabetic nephropathy [DN], nephrosclerosis [NS], and other); concomitant angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) use (yes, no); the geriatric nutritional risk index (GNRI) at baseline (quintile); and the prognostic nutritional index (PNI) at baseline (quartile) [25, 26]. Established cutoff values for select factors that denote increased risk for a diagnosis or harm or the upper limit of normal were used [27–31].

**Table 1.** Patient demographics and baseline characteristics (FAS)

| Parameter | DA (comparative) (*n* = 131) | Roxadustat (comparative) (*n* = 131) |
|---|---|---|
| Sex, *n* (%) | | |
| Male | 75 (57.3) | 83 (63.4) |
| Female | 56 (42.7) | 48 (36.6) |
| Age, years | | |
| Mean (SD) | 70.9 (10.2) | 68.9 (11.6) |
| BMI, kg/m$^2$ (prescreening) | | |
| Mean (SD) | 23.95 (3.57) | 23.58 (4.59) |
| Duration of anemia associated with CKD, months | | |
| Mean (SD) | 33.95 (45.94) | 28.39 (31.42) |
| Baseline Hb, g/dL | | |
| Mean (SD) | 10.96 (0.52) | 10.98 (0.57) |
| ERI, *n* (%) | | |
| <1.9 | 26 (19.8) | 32 (24.6) |
| ≥1.9–<3.5 | 40 (30.5) | 32 (24.6) |
| ≥3.5–<6.8 | 35 (26.7) | 30 (23.1) |
| ≥6.8 | 30 (22.9) | 36 (27.7) |
| Iron, μmol/L | | |
| Mean (SD) | 15.0 (5.0) | 16.0 (5.3) |
| Iron repletion, *n* (%) | | |
| Ferritin ≥100 ng/mL and TSAT ≥20% | 66 (50.4) | 69 (52.7) |
| Ferritin <100 ng/mL and TSAT ≥20% | 52 (39.7) | 51 (38.9) |
| Ferritin ≥100 ng/mL and TSAT <20% | 9 (6.9) | 6 (4.6) |
| Ferritin <100 ng/mL and TSAT <20% | 4 (3.1) | 5 (3.8) |
| Iron groups by repletion status, *n* (%) | | |
| Ferritin ≥100 ng/mL and TSAT ≥20% | 66 (50.4) | 69 (52.7) |
| Ferritin <100 ng/mL or TSAT <20% | 65 (49.6) | 62 (47.3) |
| Hs-CRP, nmol/L, *n* (%) | | |
| <28.57 | 106 (80.9) | 108 (82.4) |
| ≥28.57 | 25 (19.1) | 23 (17.6) |
| DM, *n* (%) | | |
| Present | 68 (51.9) | 68 (51.9) |
| Absent | 63 (48.1) | 63 (48.1) |
| eGFR, mL/min/1.73m$^2$ (prescreening) | | |
| Mean (SD) | 18.2 (8.8) | 17.9 (8.2) |
| eGFR by mL/min/1.73m$^2$ cutoff, *n* (%) | | |
| <15 | 62 (47.3) | 57 (43.5) |
| ≥15 | 69 (52.7) | 74 (56.5) |
| Primary disease of CKD, *n* (%) | | |
| CGN | 20 (15.3) | 33 (25.2) |
| DN | 52 (39.7) | 52 (39.7) |
| NS | 45 (34.4) | 36 (27.5) |
| Other | 14 (10.7) | 10 (7.6) |
| Concomitant ACEi/ARB use, *n* (%) | | |
| Yes | 109 (83.2) | 108 (82.4) |
| No | 22 (16.8) | 23 (17.6) |
| GNRI category, *n* (%) | | |
| <95.1 | 21 (16.0) | 31 (23.7) |
| ≥95.1–<98.3 | 25 (19.1) | 20 (15.3) |
| ≥98.3–<101.3 | 27 (20.6) | 18 (13.7) |
| ≥101.3–<104.2 | 24 (18.3) | 30 (22.9) |
| ≥104.2 | 34 (26.0) | 32 (24.4) |
| PNI category, *n* (%) | | |
| <43.6 | 30 (22.9) | 34 (26.0) |
| ≥43.6–<46.8 | 36 (27.5) | 29 (22.1) |
| ≥46.8–<49.7 | 37 (28.2) | 30 (22.9) |
| ≥49.7 | 28 (21.4) | 38 (29.0) |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ERI, erythropoiesis-stimulating agent resistance index; FAS, full analysis set; GNRI, geriatric nutritional risk index; Hb, hemoglobin; PNI, prognostic nutritional index; SD, standard deviation; TSAT, transferrin saturation; DA, darbepoetin alfa; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; CGN, chronic glomerular nephritis; DN, diabetic nephropathy; NS, nephrosclerosis.

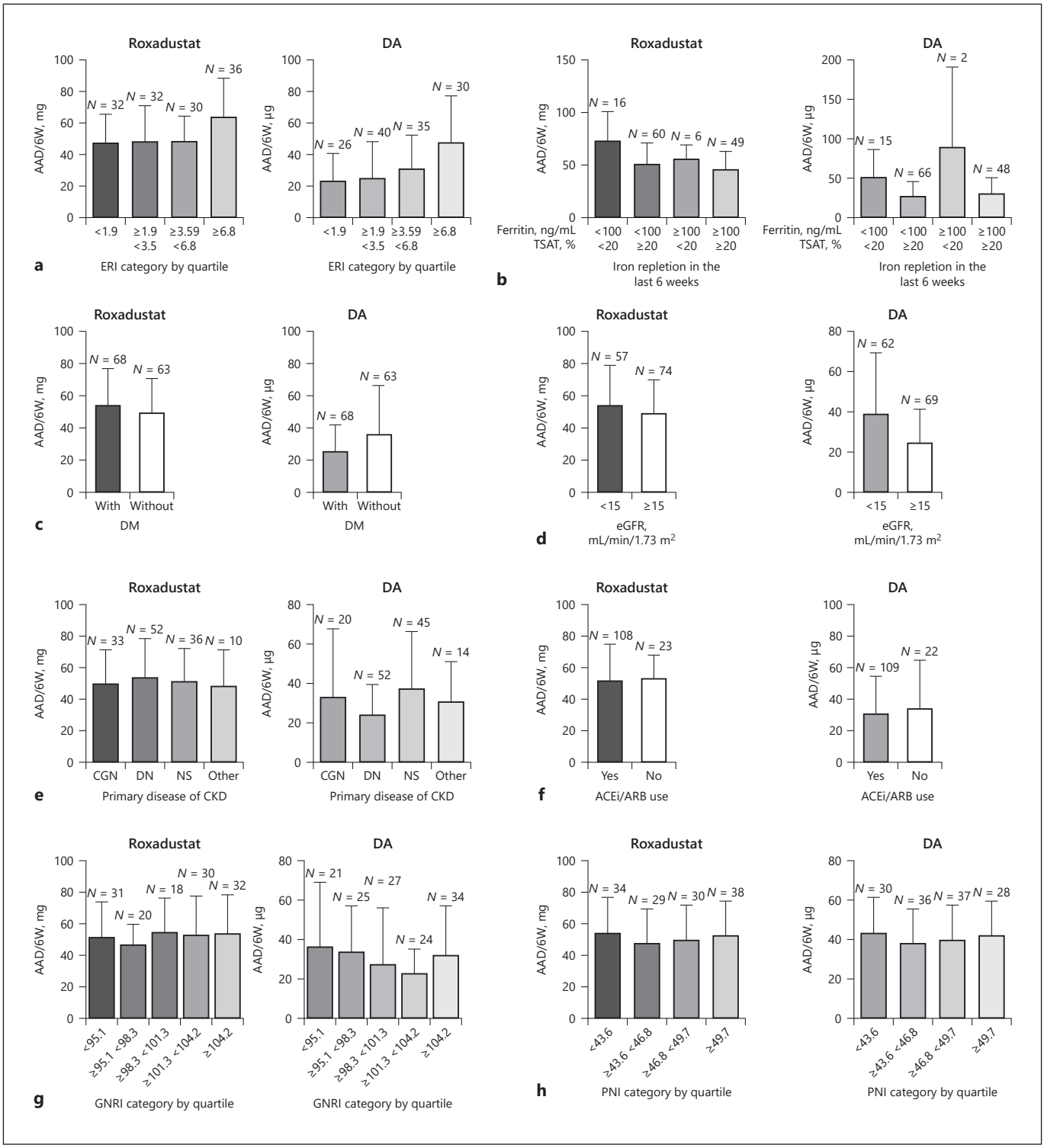


**Fig. 1.** Allocated dose (mean, SD) of study drug per intake in the last 6 weeks (AAD/6W). Subgroup factors presented are ERI category by quartile (**a**), iron repletion category (**b**), DM status (**c**), eGFR (**d**), primary disease of CKD (**e**), concomitant ACEi/ARB use (**f**), GNRI quintile (**g**), and PNI quartile (**h**). CKD, chronic kidney disease; ERI, erythropoiesis-stimulating agent resistance index; SD, standard deviation; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; AAD/6W, average allocated dose of roxadustat or darbepoetin alfa per administration in the last 6 weeks.

*Statistical Analysis*

Demographic and baseline characteristics were summarized by descriptive statistics and frequency tabulation by treatment groups (roxadustat and DA). The analysis of variance was performed by the treatment group to test the influence of subgroup factors on AAD/6W of study drug (roxadustat and DA). The ratios between the mean AAD/6W in each subgroup category and the within-arm mean AAD/6W were calculated, and student *t* tests were performed to compare the 2 treatment groups. When considering subgroups by iron repletion, the ratios between the mean AAD/6W in each category and that in the baseline category (ferritin ≥100 ng/mL and TSAT ≥20%) were calculated. A scatter plot was used to graphically represent the AAD/6W against log hs-CRP at baseline and at the end of week 24. A linear regression analysis was performed using the AAD/6W as the outcome variable and log hs-CRP at baseline and at the end of week 24 as the explanatory variable. All analyses were conducted by the treatment group. All data processing, summarization, and analyses were performed using SAS® v9.4.

## Results

*Patient Disposition and Baseline Characteristics*

Of the 431 patients who provided informed consent, 262 patients in the comparative groups were randomized and received treatment (roxadustat, $n = 131$; DA, $n = 131$) [14]. The 24-week treatment was completed by 230 patients (87.8%): roxadustat ($n = 109$, 83.2%) and DA ($n = 121$, 92.4%). In the full analysis set, patient demographics and baseline characteristics were similar between the comparative treatment groups (Table 1). The mean (standard deviation [SD]) baseline hemoglobin was 10.98 (0.57) g/dL in the roxadustat group and 10.96 (0.52) g/dL in the DA group. The proportion of iron replete patients (ferritin ≥100 ng/mL and TSAT ≥20%) was 52.7% in the roxadustat group and 50.4% in the DA group.

*Subgroup Analyses*

The mean (SD) AAD/6W by subgroups is presented in Figure 1, and the ratio to the within-arm average of the mean of AAD/6W by subgroups is presented in Table 2 and Figure 2.

*Erythropoiesis-Stimulating Agent Resistance Index*

Both roxadustat and DA had significant differences in the mean (SD) AAD/6W between ERI categories, defined by the sample quartile (roxadustat [mg]: <1.9, 46.56 [18.93]; ≥1.9–<3.5, 47.51 [23.28]; ≥3.5–<6.8, 47.78 [16.17]; ≥6.8, 63.15 [24.84]; $p = 0.003$; and DA [μg]: <1.9, 22.69 [17.68]; ≥1.9–<3.5, 24.38 [22.96]; ≥3.5–<6.8, 29.71 [22.19]; ≥6.8, 47.33 [29.79]; $p < 0.001$, respectively). Whereas AAD/6W rose incrementally as the ERI increased for DA, the AAD/6W remained similar for roxadustat in the 3 lowest ERI categories. A considerable, nonsignificant mean difference in the ratio to within-arm AAD/6W favoring roxadustat was observed in the highest ERI category (−0.322, 1.219 vs. 1.541, $p = 0.085$).

*Iron Repletion Status*

Iron repletion status in the last 6 weeks of treatment affected the AAD/6W for both roxadustat and DA ($p < 0.001$ for both). The mean (SD) AAD/6W was highest in roxadustat patients with ferritin <100 ng/mL and TSAT <20% (72.71 [28.63] mg) and lowest for both roxadustat and DA in those who were iron replete (i.e., ferritin ≥100 ng/mL and TSAT ≥20%) (45.54 [18.01] mg and 28.13 [20.98] μg). There were no differences in the ratio to the mean AAD/6W for the category TSAT ≥20% and ferritin ≥100 ng/mL for each iron repletion category between roxadustat and DA though the ferritin ≥100 ng/mL and TSAT <20% category showed a numerically greater ratio for DA (3.111) than roxadustat (1.238) (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000519043; online suppl. Fig. 1).

*High-Sensitivity C-Reactive Protein*

Greater hs-CRP values at baseline and at the end of week 24 were not associated with increased AAD/6W for roxadustat (baseline: estimated slope 0.114, $p = 0.935$; end of week 24: estimated slope 1.314, $p = 0.214$) but were both associated with increased AAD/6W for DA (baseline: estimated slope 4.169, $p = 0.005$; end of week 24: estimated slope 5.756, $p < 0.001$, online suppl. Fig. 2). The ratio to within-arm mean AAD/6W in DA was numerically higher in the subgroup with hs-CRP ≥28.57 (1.230), while the ratio in roxadustat was close to 1 even in the subgroup with hs-CRP ≥28.57 (1.066).

*Diabetes Mellitus*

The mean (SD) AAD/6W of roxadustat was not affected by DM status (without, 49.71 [20.67] mg; with, 53.75 [23.50] mg; $p = 0.299$); however, patients with DM required a lower DA AAD/6W (without, 36.11 [31.32] μg; with, 25.74 [16.44] μg; $p = 0.018$) and had a lower ratio to within-arm AAD/6W compared with roxadustat (mean difference, 0.200; 1.038 vs. 0.838, $p = 0.020$).

*Estimated Glomerular Filtration Rate*

The eGFR did not affect the mean (SD) AAD/6W of roxadustat (<15 mL/min/1.73 $m^2$, 54.30 [24.15] mg vs. ≥15 mL/min/1.73 $m^2$, 49.89 [20.52] mg; $p = 0.261$), whereas patients with eGFR <15 mL/min/1.73 $m^2$ required

**Table 2.** Ratio between the mean AAD/6W in each subgroup category and the within-arm mean AAD/6W (FAS)

| Parameter | DA (comparative) | Roxadustat (comparative) | Difference | *p* value |
|---|---|---|---|---|
| ERI | | | | |
| <1.9 | 0.739 | 0.899 | 0.160 | 0.203 |
| ≥1.9–<3.5 | 0.793 | 0.917 | 0.124 | 0.413 |
| ≥3.5–<6.8 | 0.967 | 0.922 | −0.045 | 0.753 |
| ≥6.8 | 1.541 | 1.219 | −0.322 | 0.085 |
| Hs-CRP by nmol/L cutoff | | | | |
| <28.57 | 0.946 | 0.986 | 0.040 | 0.628 |
| ≥28.57 | 1.230 | 1.066 | −0.164 | 0.493 |
| DM | | | | |
| With | 0.838 | 1.038 | 0.200 | 0.020 |
| Without | 1.175 | 0.959 | −0.216 | 0.120 |
| eGFR by mL/min/1.73m$^2$ cutoff | | | | |
| <15 | 1.239 | 1.048 | −0.191 | 0.192 |
| ≥15 | 0.785 | 0.963 | 0.178 | 0.025 |
| Primary disease of CKD | | | | |
| CGN | 1.058 | 0.955 | −0.103 | 0.640 |
| DN | 0.789 | 1.049 | 0.260 | 0.007 |
| NS | 1.219 | 0.989 | −0.229 | 0.179 |
| Other | 1.000 | 0.933 | −0.067 | 0.786 |
| Concomitant ACEi/ARB use | | | | |
| Yes | 0.984 | 0.995 | 0.011 | 0.896 |
| No | 1.080 | 1.023 | −0.057 | 0.796 |
| GNRI category | | | | |
| <95.1 | 1.217 | 0.986 | −0.231 | 0.274 |
| ≥95.1–<98.3 | 1.100 | 0.898 | −0.202 | 0.263 |
| ≥98.3–<101.3 | 0.898 | 1.044 | 0.146 | 0.540 |
| ≥101.3–<104.2 | 0.746 | 1.014 | 0.269 | 0.034 |
| ≥104.2 | 1.053 | 1.039 | −0.014 | 0.935 |
| PNI category | | | | |
| <43.6 | 1.199 | 1.054 | −0.145 | 0.415 |
| ≥43.6–<46.8 | 1.071 | 0.941 | −0.131 | 0.486 |
| ≥46.8–<49.7 | 0.946 | 0.974 | 0.028 | 0.858 |
| ≥49.7 | 0.767 | 1.018 | 0.250 | 0.048 |

AAD/6W, average allocated dose of roxadustat or DA per administration in the last 6 weeks; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ERI, erythropoiesis-stimulating agent resistance index; FAS, full analysis set; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; TSAT, transferrin saturation; DA, darbepoetin alfa; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; CGN, chronic glomerular nephritis; DN, diabetic nephropathy; NS, nephrosclerosis.



greater AAD/6W of DA (<15 mL/min/1.73 m$^2$, 38.06 [30.76] μg vs. ≥15 mL/min/1.73 m$^2$, 24.13 [16.45] μg; $p$ = 0.001). This difference in AAD/6W for DA allowed DA to have a lower within-arm AAD/6W compared with roxadustat in the ≥15 mL/min/1.73 m$^2$ group (mean difference, 0.178; 0.963 vs. 0.785; $p$ = 0.025). The ratio in DA was numerically higher in the subgroup with eGFR <15 mL/min/1.73 m$^2$ (1.239), while the ratio in roxadustat was close to 1 even in the subgroup with eGFR <15 mL/min/1.73 m$^2$ (1.048).

*CKD Etiology*

CKD etiology did not impact the mean (SD) AAD/6W of roxadustat (CGN, 49.49 [21.73] mg; DN, 54.33 [23.85] mg; NS, 51.25 [20.43] mg; and other, 48.34 [22.79] mg; $p$ = 0.734) but did have a considerable but not statistically significant association with the mean (SD) AAD/6W of DA (CGN, 32.50 [34.85] μg; DN, 24.23 [15.35] μg; NS, 37.44 [29.24] μg; and other, 30.71 [20.46] μg; $p$ = 0.078). Only patients with DN as the CKD etiology had a different ratio to within-arm AAD/6W favoring DA (mean difference, 0.260; 1.049 vs. 0.789, $p$ = 0.007).

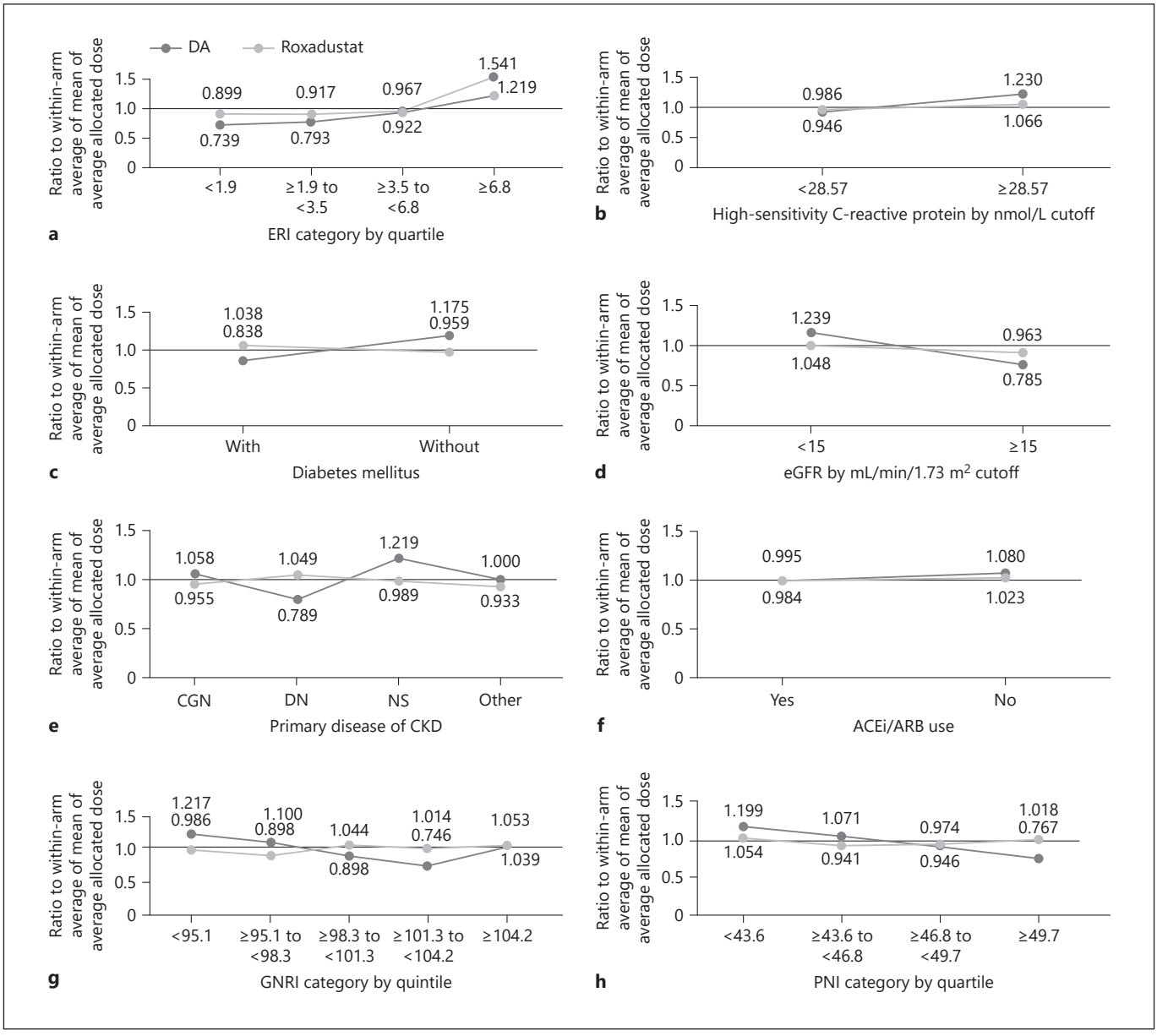


**Fig. 2.** Ratio between the mean AAD/6W in each subgroup category and the within-arm mean AAD/6W. Subgroup factors presented are ERI category by quartile (**a**), hs-CRP (**b**), DM status (**c**), eGFR (**d**), primary disease of CKD – CGN (**e**), DN, NS, and other, concomitant ACEi/ARB use (**f**), GNRI quintile (**g**), and PNI quartile (**h**). CKD, chronic kidney disease; ERI, erythropoiesis-stimulating agent resistance index; DA, darbepoetin alfa; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; CGN, chronic glomerular nephritis; DN, diabetic nephropathy; NS, nephrosclerosis; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; AAD/6W, average allocated dose of roxadustat or darbepoetin alfa per administration in the last 6 weeks.

*Concomitant ACEi/ARB Use*

The concomitant use of ACEi or ARB was not associated with the mean (SD) AAD/6W for roxadustat (no use, 52.98 [14.56] mg; use, 51.56 [23.55] mg; $p = 0.782$) or DA (no use, 33.18 [31.38] μg; use, 30.23 [23.89] μg; $p = 0.618$).

*Nutritional Status*

Nutritional status did not affect the mean (SD) AAD/6W for roxadustat (GNRI: <95.1, 51.08 [22.91] mg; ≥95.1–<98.3, 46.51 [12.30] mg; ≥98.3–<101.3, 54.07 [21.47] mg; ≥101.3–<104.2, 52.56 [25.08] mg; ≥104.2,

53.85 [24.43] mg; $p = 0.802$; PNI: <43.6, 54.61 [23.01] mg; ≥43.6–<46.8, 48.74 [21.25] mg; ≥46.8–<49.7, 50.44 [22.58] mg; ≥49.7, 52.72 [22.35] mg; $p = 0.739$) or DA (GNRI: <95.1, 37.38 [31.77] μg; ≥95.1–<98.3, 33.80 [23.60] μg; ≥98.3–<101.3, 27.59 [28.80] μg; ≥101.3–<104.2, 22.92 [12.42] μg; ≥104.2, 32.35 [25.11] μg; $p = 0.321$; PNI: <43.6, 36.83 [28.08] μg; ≥43.6–<46.8, 32.92 [28.67] μg; ≥46.8–<49.7, 29.05 [23.21] μg; ≥49.7, 23.57 [17.84] μg; $p = 0.217$). Differences were not found in within-arm AAD/6W between roxadustat and DA in most PNI quartiles or GNRI quintiles though in the lowest categories (GNRI<95.1 and PNI <43.6), the ratios to within-arm AAD/6W were numerically higher than the other categories for DA (1.217 and 1.199), while the ratios to within-arm AAD/6W in roxadustat were close to 1 (0.986 and 1.054).

## Discussion

This is the first study to evaluate dosing trends of roxadustat and DA required to maintain target hemoglobin concentrations in NDD patients with risk factors associated with ESA hyporesponsiveness. In this post hoc analysis of NDD patients with anemia of CKD enrolled in a phase 3 study [14], higher doses of both roxadustat and DA were required in the highest ERI quartile to achieve target hemoglobin. Consequently, risk factors for ESA hyporesponsiveness were evaluated for the potential impact on roxadustat and DA dosing trends. Patients with adequate iron repletion had the lowest doses for both roxadustat and DA. Additionally, inflammation (i.e., hs-CRP ≥28.57 nmol/L) and eGFR ≤15 mL/min/1.73 $m^2$ (i.e., stage 5 CKD) were associated with a requirement for higher doses of DA but did not affect roxadustat dosing. Conversely, DM diagnosis did not affect roxadustat dosing but was associated with lower DA doses.

Roxadustat dosing was similar in the 3 lower ERI quartiles, while DA dosing progressively increased as ERI increased, suggesting that ESA hyporesponsiveness may affect DA more than roxadustat. Increased risks of cardiovascular events and death have been associated with high-dose ESAs likely resulting from off-target effects from supraphysiologic concentrations of erythropoietin [19–24, 32]. Identifying patients in whom an alternative agent, such as roxadustat, may be used could decrease the likelihood of these complications by targeting near-normal erythropoietin concentrations. Roxadustat, as compared to epoetin alfa treatment, previously resulted in approximately 5 times lower plasma erythropoietin concentrations, exposing patients to modest levels of endogenous erythropoietin within or near the physiologic range compared with epoetin alfa, which can increase levels to greater than 30 fold above normal [8, 32]. Because a similar trend toward increased DA doses compared with roxadustat doses in patients in the highest ERI quartile has also been observed in DD CKD patients, the consequences of these higher doses on clinical outcomes remain a research focus [25].

Roxadustat and DA doses were lowest in patients who were iron replete. Roxadustat doses were higher in those with lower TSAT, whereas DA had an inadequate number of patients in this state to assess. The higher AAD/6W required when iron stores were not replete is supported by prior data that the most common causes of ESA hyporesponsiveness are primarily absolute and secondarily functional iron deficiency [33]. Additionally, in a population of DD patients with anemia of CKD, the dose of roxadustat required to maintain hemoglobin remained stable regardless of iron repletion status; however, a significant increase in the mean AAD/6W was observed with decreasing ferritin in patients who received DA [25]. The mechanisms of action of epoetin alfa and DA are limited to stimulation of the erythropoietin receptor, whereas roxadustat also induces expression of proteins that promote iron absorption and recycling from the macrophage iron storage system [34, 35]. Targeting higher serum ferritin concentrations (e.g., 200–500 mg/L) and TSAT (e.g., 30–50%) with iron, especially when parenterally administered, can restore ESA responsiveness; however, parenteral iron was only allowed in select cases [14, 36–39]. Previous phase 2 and 3 studies have found that roxadustat corrected anemia and maintained hemoglobin without parenteral iron administration despite baseline iron depletion in approximately two-thirds of patients, suggesting that additional evaluation on the impact of iron repletion on roxadustat efficacy and dosing is needed [8, 25, 39].

Roxadustat dosing was unaffected by inflammation, whereas DA AAD/6W was significantly higher in patients with elevated hs-CRP, suggesting higher doses of DA but not roxadustat may be required to maintain target hemoglobin concentrations in the presence of inflammation. Several studies have clearly demonstrated an inverse association between inflammatory indices or cytokines and ESA responsiveness [40–44]. These inflammatory cytokines may directly inhibit erythropoiesis and promote apoptosis of erythroid precursors [45, 46]. Resistance to ESAs also appears to be partially mediated by elevated hepcidin levels, which are increased in inflammation, limiting iron availability [47, 48].

Prior evaluations in DD patients have suggested that ESA responsiveness continues to worsen as time progresses in patients with high hs-CRP [8, 25]. NDD CKD patients with elevated inflammatory markers may be more responsive to roxadustat than DA though the extent of this improved responsiveness and its effects on clinical outcomes requires quantification.

Patients with DM required lower DA doses, while roxadustat doses were unaffected. The ratio to within-arm average of the mean AAD/6W was numerically lower for roxadustat in patients without DM. In DD patients with anemia of CKD, DM did not affect roxadustat or DA dosing [25]. This difference between DD and NDD CKD patients may suggest the finding in this study occurred by chance, could have been affected by medication use (e.g., statins), or could suggest that NDD CKD patients with DM are more responsive to DA, with this responsiveness abating as CKD progresses [25, 49]. Other potential factors in patients with DM that have previously been identified to affect ESA hyporesponsiveness that may have influenced this finding include gender, hypoglycemic agent use, eGFR, baseline hemoglobin, baseline N-terminal pro-B-natriuretic protein, and iron supplementation [50]. Because any potential difference in roxadustat and DA dosing is likely multifactorial in nature, the effect of DM on roxadustat and DA dosing, particularly in CKD patients beginning dialysis, must be studied to better inform ESA recommendations.

Patients in stage 5 CKD required higher DA dosing, whereas CKD stage did not affect roxadustat dosing in NDD CKD patients. The prevalence of anemia increases with the severity of CKD [51]. Additionally, in a cohort of Japanese patients, ESA doses and cardiovascular complications as well as all-cause death increased as CKD progressed [52]. Some of these outcomes could have resulted from an increase in hepcidin concentrations as CKD progresses, leading to impaired iron metabolism and decreased ESA efficacy [53]. Roxadustat has been shown to decrease hepcidin concentrations, which may mitigate the effect of worsening CKD [8]. Hepcidin concentrations warrant further investigation in patients with stage 5 CKD receiving roxadustat. The cause for these worse outcomes also could have been the necessity for higher doses of epoetin alfa and DA, in addition to more advanced disease [19–24]. Although a prior pharmacokinetic analysis did not find that eGFR affected roxadustat pharmacokinetics, most patients had stage 4 or 5 CKD [54]. Studies evaluating long-term outcomes from roxadustat in patients with NDD CKD who progress in their disease and require dialysis are ongoing [39, 55–57].

Subgroup factors that did not affect roxadustat or DA dosing were CKD etiology, treatment with an ACEi or ARB, and nutritional status. While a numerical difference existed for DA in CKD etiology, none existed for roxadustat, suggesting roxadustat may be considered in patients regardless of CKD etiology. ACEi or ARB use has previously been identified as protective for ESA hyporesponsiveness development; however, that result was not confirmed for either roxadustat or DA in this study [26]. Further investigation is needed, as clinical phenotypes may exist for which these or other agents may be protective. Although the importance of nutritional status is emphasized in CKD management, few data are reported for the nutritional evaluation before dialysis. In this study, there were no statistically significant differences among PNI categories within roxadustat and DA treatment arms. However, the dose of DA tended to increase in the lower PNI categories, whereas the dose of roxadustat remained fairly consistent across PNI categories. Because the nutritional status of patients not undergoing dialysis is frequently adequate compared to those receiving dialysis who often experience protein wasting and malnutrition, further investigation into nutritional status in CKD is needed [58, 59].

Because the results of this study were based on a post hoc analysis of the 1517-CL-0310 study, which was designed to address a different scientific question, these findings should be considered hypothesis generating [14]. Nevertheless, many observations align with previous findings for ESA hyporesponsiveness for DA and have biological plausibility [25]. Subgroups of the post hoc analysis are not necessarily exclusive; therefore, patients may possess multiple factors associated with ESA hyporesponsiveness. The interactions between these factors were not studied because of the small number of patients who had features of ESA hyporesponsiveness. Additionally, sample sizes for some subgroups were inadequate to draw confident conclusions, suggesting that larger studies that evaluate ERI-related factors together should be performed. The Japanese population may affect generalizability to other populations, particularly those with different baseline characteristics and those who are managed within health-care systems that treat NDD CKD differently than in Japan. In particular, parenteral iron use was restricted, which may not represent real-world practice for many NDD CKD patients [60]. Other patient-specific factors have been evaluated for effects on roxadustat pharmacokinetics, including weight, sex, age, and serum albumin, which were not investigated in this study but may be considered for future assessment [54].

## Conclusion

The roxadustat dose required to maintain target hemoglobin in NDD patients in Japan with anemia of CKD compared to the DA dose may not be impacted by some factors contributing to ESA hyporesponsiveness, such as the presence of low-grade inflammation. Roxadustat may be beneficial for ESA-hyporesponsive NDD CKD patients.


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## Statement of Ethics

All study protocols were approved by relevant institutional review boards and/or Ethics Committees and were conducted in accordance with the tenets of the Declaration of Helsinki, the International Council for Harmonization guidelines for Good Clinical Practice, and any other applicable local health and regulatory requirements. All patients provided written informed consent before enrollment.

## Conflict of Interest Statement

K.T.A., T.O., and Y.Y. are employees of Astellas Pharma, Inc. T.A. reports personal fees from Astellas, Kyowa Kirin, Bayer Yakuhin Ltd., GlaxoSmithKline, JT Pharmaceuticals, Kissei Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd, Ono Pharmaceutical Co. Ltd., Fuso Pharmaceutical Industries Ltd., Torii Pharmaceutical Co. Ltd., Nipro Corporation, Otsuka, Sanwa Chemical, and Tanabe-Mitsubishi Co. Ltd.


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## Author Contributions

T.A., K.T., and T.O. contributed to the conception and design. K.T. and T.O. contributed to acquisition of data. T.A., K.T., T.O., and Y.Y contributed to analysis and interpretation of the data. T.A., K.T., T.O., and Y.Y. contributed to drafting and critical revision of the article for important intellectual content.

## 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.

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