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Two Phase 3 Studies on Ophthalmologic Effects of Roxadustat Versus Darbepoetin

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Introduction: Roxadustat is an orally administered hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor that represents a novel therapeutic option for patients with anemia of chronic kidney disease (CKD).

Methods: Conducted in Japan, CL-0307 (NCT02952092) and CL-310 (NCT02988973) were phase 3, darbepoetin alfa (DA)-controlled studies conducted in dialysis-dependent (DD) and non–DD (NDD) patients with CKD, respectively, where patients were randomized to receive roxadustat or DA. Ophthalmic imaging and assessments of visual acuity were performed up to week 24 or at study discontinuation. Ophthalmic imaging was centrally evaluated by independent readers masked to the study treatment.

Results: In CL-0307, 302 patients (roxadustat, $n = 150$; DA, $n = 152$) received ≥1 dose of the study drug and were included in this analysis. In CL-0310, 262 patients (roxadustat, $n = 131$; DA, $n = 131$) received ≥1 dose of the study drug and were included in this analysis. Proportions of DD patients with new or worsening retinal hemorrhages (RHs) in the roxadustat group and DA group were 32.4% (46 of 142) and 36.6% (53 of 145), respectively. Proportions of NDD patients with CKD with new or worsening RH in the roxadustat and DA groups were 31.4% (38 of 121) and 39.8% (51 of 128), respectively. Similar trends were apparent in subgroup analyses: patients with/without RH at baseline and with/without diabetes mellitus at baseline. In both studies, there were no differences in retinal thickness, visual acuity, presence of hard exudates or cotton wool spots, or presence of intra- and subretinal fluid between groups, at any given time point.

Conclusion: In these studies, roxadustat, compared with DA, was not associated with an increased risk of adverse ophthalmologic events in these cohorts.

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Anemia is a complication of CKD resulting from decreased oxygen sensing by the kidneys, resulting in diminished synthesis of erythropoietin by the impaired kidneys and an altered iron metabolism.[1] Erythropoiesis-stimulating agents (ESAs) are currently available for the treatment of anemia of CKD. Nevertheless, data suggest that, under certain conditions, ESAs may increase the risk of adverse cardiovascular events in some patients[2,3] and the safety concerns associated with higher ESA doses and hemoglobin (Hb) goals in patients with CKD have resulted in a responsive decrease in the doses of ESAs used globally.[4,5] Furthermore, ESAs are administered parenterally, which may present a barrier to treatment in some patients.[6] The efficacy of ESAs may be limited in some patients,[7,8] particularly in those with inflammation.[9] As such, alternative therapeutic options for anemia of CKD are currently being investigated.

Roxadustat is an orally administered HIF prolyl hydroxylase inhibitor that represents a new therapeutic option for patients with anemia of CKD. It is currently approved for the treatment of anemia of CKD in numerous countries and regions for patients who are DD and NDD. HIF is a transcription factor that responds to tissue oxygen tension and, in hypoxic conditions, induces erythropoietin expression, iron absorption, and recycling of iron from macrophages.[10,11] In the presence of normal oxygen tension, HIF-α is targeted for degradation by HIF prolyl

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hydroxylase, whereas during hypoxic conditions, this enzyme is temporarily inhibited, allowing for the transient stabilization of HIF-α and its subsequent dimerization with HIF-β, which stimulates erythropoiesis and increases iron absorption and mobilization.[12,13] Therefore, inhibition of HIF prolyl hydroxylase by roxadustat promotes a coordinated erythropoietic response that increases Hb levels by activating the body's natural response to hypoxia, even in the presence of normal oxygen levels.

During hypoxia, up-regulation of the vascular endothelial growth factor (VEGF) by the HIF-1α pathway may increase retinal angiogenesis; data suggest that retinal angiogenesis may be associated with an increased risk of certain retinal pathologies.[14–18] To date, preclinical data suggest that roxadustat does not meaningfully influence VEGF levels, even in the presence of increased erythropoiesis.[19] Nevertheless, it is important to ascertain whether roxadustat, by acting on the HIF pathway, may be associated with an increased risk of adverse ophthalmologic events.

In phase 3 studies, roxadustat has been found to have efficacy and safety in achieving and maintaining Hb target levels in DD[20–23] and NDD[24–26] patients with CKD with anemia. Specifically, 2 Japanese phase 3 studies have revealed the efficacy of roxadustat in maintaining Hb within 10.0 to 12.0 g/dl in DD (study 1517-CL-0307)[20] and NDD[26] patients with CKD with anemia whose Hb levels were previously maintained with ESAs; in both studies, roxadustat was found to be noninferior to DA.

In this article, we report the results of a prespecified analysis that focused on centrally evaluated ophthalmologic/retinal-related events in the 2 aforementioned studies. In addition to evaluating these events in roxadustat-treated patients, both studies also evaluated ophthalmologic/retinal-related events in ESA-controlled patients, as ESAs are the current standard of care for many patients with CKD with anemia and are not suspected of contributing to increased risk of adverse ophthalmologic events. The results of *post hoc* analyses comparing roxadustat and DA on the ophthalmologic/retinal-related parameters are also reported as a reference for comparability.

METHODS

Study Design

Study 1517-CL-0307[20] was a multicenter, randomized, DA-controlled, double-masked study conducted in Japan from November 2016 to March 2018 (ClinicalTrials.gov: NCT02952092). In this study, DD patients with CKD were randomized (1:1) to receive roxadustat 3 times weekly or DA once weekly for a maximum of 24 weeks (Figure 1a).

Study 1517-CL-0310[26] was a multicenter, partially randomized (nonrandomized reference group is described subsequently), DA-controlled, open-label study conducted in Japan from January 2017 to March 2020 (ClinicalTrials.gov: NCT02988973). In this study, NDD patients with CKD previously treated with recombinant human erythropoietin or DA were

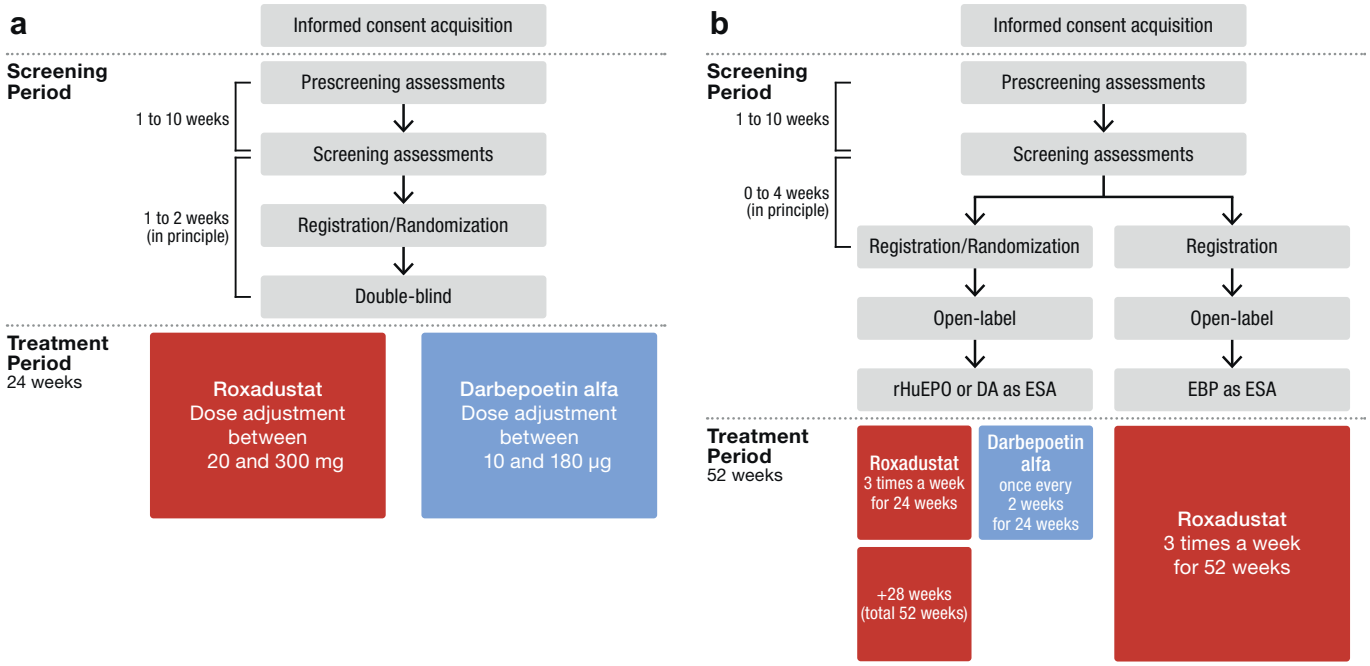

Figure 1. Study flowchart for (a) study 1517-CL-0307 and (b) study 1517-CL-0310. DA, darbepoetin alfa; EBP, epoetin beta pegol; ESA, erythropoiesis-stimulating agent; rHuEPO, recombinant human erythropoietin.

randomized to initially receive roxadustat 3 times weekly for 52 weeks or DA once every 2 weeks for 24 weeks, whereas NDD patients with CKD who had previously used epoetin beta pegol were assigned to receive roxadustat 3 times weekly for 52 weeks (reference group); the reference group was not included in this ophthalmologic analysis (Figure 1b).

In both studies, the initial doses of roxadustat (70 mg or 100 mg) and DA (10–60 μg) were based on the average weekly dose of recombinant human erythropoietin or DA received during the 4 weeks before registration (Supplementary Tables S1 and S2), and dose adjustments for both roxadustat and DA were conducted in accordance with dose-adjusting rules to maintain Hb within 10 to 12 g/dl (Supplementary Tables S3, S4, and S5). In both studies, dose adjustments were conducted every 2 weeks, starting from week 4. For both roxadustat and DA, administration of i.v. iron was permitted only when transferrin saturation was <20% or serum ferritin was <100 ng/ml, whereas oral iron was permitted without restrictions.

Study Population

In both studies, patients were aged ≥20 years with anemia of CKD; must have had a mean of the 2 most recent Hb levels (measured ≥1 week apart) of 10 to 12 g/dl during the screening period; were iron replete as determined by transferrin saturation ≥ 20% or serum ferritin ≥ 100 ng/ml during the screening period; and had been receiving i.v. (study CL-0307) or s.c. (study CL-0310) recombinant human erythropoietin or DA for ≥8 weeks before prescreening assessments. Patients eligible for study CL-0307 had to be on stable chronic maintenance hemodialysis 3 times a week for ≥12 weeks before prescreening, whereas patients eligible for study CL-0310 were not on dialysis. In both studies, patients were excluded if they had untreated retinal neovascular lesion (including proliferative diabetic retinopathy, exudative age-related macular degeneration, and retinal vein occlusion), untreated macular edema, or uncontrolled hypertension.

Study Assessments

Ophthalmic imaging (color fundus photography [4 wide-field or wide-angle color fundus photographs] and optical coherence tomography to capture images of the macula and its surrounding area) and assessments of visual acuity were performed at baseline, week 12, and week 24 or at study discontinuation; standardized collection of ophthalmic images was conducted according to the Ophthalmic Image Acquisition Guidelines. Central evaluation of ophthalmologic examination results was conducted in accordance with the Safety Independent Ophthalmology Review Charter by 2 independent readers at the Ocular Imaging Research and Reading Center (Sunnyvale, CA) who were masked to the study treatment. In case of disagreement between the reviewers, adjudication was performed by a masked, independent grader who did not participate in the primary review of the patient data.

The total number of RHs and its change from baseline, including the proportion of patients with new or worsening RHs, were reported for each treatment group, per patient, for both eyes. New or worsening RHs were also summarized by treatment arm (roxadustat or DA) for the 2 subgroups: RHs at baseline (present or absent) and diabetes mellitus (present or absent). The proportion of patients with hard exudates and cotton wool spots or with the presence of intraretinal fluid and subretinal fluid were reported for each treatment group, per patient, for both eyes. Retinal thickness and visual acuity, and their changes from baseline, were evaluated in each eye for both treatment groups. Grading results and visual acuity were analyzed descriptively. Ophthalmologic/retinal-related findings were also analyzed descriptively. Assessments were conducted using the safety analysis set, which included patients who received ≥1 dose of the study drug.

Outcomes

RHs were defined as abnormal bleeding of the blood vessels in the retina. If RHs were present, the grader identified them as one or more of the following types: flame hemorrhage, dot-blot hemorrhage, or other. If present, the grader counted the number of RHs in each of the following quadrants (or indicated if RHs could not be graded in a quadrant): superior, nasal, inferior, or temporal. The occurrence of new or worsening RHs during treatment was determined by the color fundus photography grading form and defined by the variables related to RHs in the right or left eye: any evidence of RH from "No" at baseline to "Yes" and/or an increase from baseline in the total number of RHs.

Central subfield retinal thickness (μm) was defined as the average retinal thickness in the central 1000-μm diameter of the Early Treatment Diabetic Retinopathy Study grid.[27] Retinal thickness is the distance between the inner boundary of the internal limiting membrane and the outer boundary of the retinal pigment epithelium-basement membrane complex. The grader measured and provided the central subfield retinal thickness for the applicable eye or indicated "Cannot Grade" if central subfield retinal thickness could not be determined. The central subfield retinal thickness measurement was based on optical coherence tomography.

Table 1. Demographics and baseline characteristics (safety analysis set)

	Dialysis dependent		Non-dialysis dependent	
Parameters	**Roxadustat ($n = 150$)**	**DA ($n = 152$)**	**Roxadustat ($n = 131$)**	**DA ($n = 131$)**
Sex, *n* (%)				
Male	101 (67.3)	108 (71.1)	83 (63.4)	75 (57.3)
Female	49 (32.7)	44 (28.9)	48 (36.6)	56 (42.7)
Age, yr				
Mean (SD)	64.6 (11.7)	64.9 (10.2)	68.9 (11.6)	70.9 (10.2)
Median	65.5	66.0	71.0	72.0
Min, max	24, 89	37, 85	25, 92	42, 90
Weight, kg				
Mean (SD)	57.85 (11.94)	58.86 (12.92)	59.97 (13.36)	60.98 (11.24)
Median	56.85	58.05	59.80	59.50
Min, max	36.5, 99.6	36.4, 109.2	33.1, 109.6	37.2, 95.3
Duration of CKD anemia, mo				
Mean (SD)	91.27 (73.71)	95.17 (80.93)	28.39 (31.42)	33.95 (45.94)
Median	68.37	58.71	15.47	22.08
Min, max	7.2, 365.7	4.7, 349.4	2.1, 173.5	2.0, 430.3
Hemodialysis vintage, mo			NA	NA
Mean (SD) Median Min, max	92.77 (89.78) 59.45 3.4, 488.7	101.01 (102.64) 56.13 4.3, 422.4		
Previous or concurrent retinal vascular disorder[a], *n* (%)				
Absent	88 (58.7)	95 (62.5)	66 (50.8)	68 (51.9)
Present	62 (41.3)	57 (37.5)	64 (49.2)	63 (48.1)
Missing	0	0	1	0
Diabetes mellitus, *n* (%)				
Absent	96 (64.0)	98 (64.5)	63 (48.1)	63 (48.1)
Present	54 (36.0)	54 (35.5)	68 (51.9)	68 (51.9)
Hemoglobin A1c (fraction)				
Mean (SD)	0.0564 (0.0079)	0.0564 (0.0074)	0.0606 (0.0083)	0.0613 (0.0088)
Median	0.0545	0.0540	0.0590	0.0590
Min, max	0.043, 0.088	0.045, 0.086	0.048, 0.100	0.048, 0.101
History of hypertension, *n* (%)	138 (92.0)	142 (93.4)	124 (94.7)	129 (98.5)
Systolic blood pressure (mm Hg)				
Mean (SD)	150.9 (22.6)	150.3 (20.0)	137.4 (18.8)	138.9 (18.5)
Median	150.0	150.5	136.0	139.0
Min, max	78, 224	86, 207	92, 191	88, 196
Diastolic blood pressure (mm Hg)				
Mean (SD)	79.9 (11.2)	79.1 (11.8)	72.2 (11.1)	73.2 (11.3)
Median	80.0	78.5	72.0	72.0
Min, max	46, 110	46, 110	45, 102	40, 98
History of diabetes mellitus and retinal vascular disease[a], *n* (%)	49 (32.7)	42 (27.6)	53 (40.8)	56 (42.7)

CKD, chronic kidney disease; DA, darbepoetin alfa; Max, maximum; Min, minimum; NA, not applicable.
[a]Refers to retinal hemorrhage, vitreous hemorrhage, nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, macular edema, retinal vein occlusion, and retinal artery occlusion.

The occurrence of new hard exudates during treatment was determined by the color fundus photography grading form and defined by the variables related to hard exudates in the right or left eye: any evidence of hard exudates from "No" at baseline to "Yes."

Cotton wool spots are small yellowish-white superficial lesions that obscure underlying blood vessels, clinically evident only in the postequatorial retina where the nerve fiber layer is of sufficient thickness to render them visible. If cotton wool spots were present, the grader identified which of the following sections displayed cotton wool spots (or indicated if they could not be graded): superior, nasal, inferior, temporal, and central subfield.

Intraretinal fluid was defined as the accumulation of clear or serous fluid within the neurosensory retinal layers. The grader examined the optical coherence tomography images and indicated whether there was presence of intraretinal fluid in the applicable eye. Subretinal fluid corresponded to the accumulation of clear or serous fluid in the space between the neurosensory retina and the underlying retinal pigment epithelium, in the absence of retinal breaks, tears, or

Table 2. Total number of retinal hemorrhages (per patient, both eyes) (safety analysis set)

	Result			Change from baseline		
Population and end point	*n*	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)
Dialysis dependent						
Roxadustat						
Week 0	148	4.8 (13.8)	0.0 (0, 85)	—	—	—
End of treatment	144	5.1 (13.5)	0.0 (0, 76)	142	0.2 (7.7)	0.0 (−64, 21)
Darbepoetin alfa						
Week 0	148	4.1 (13.4)	0.0 (0, 104)	—	—	—
End of treatment	149	4.3 (12.9)	0.0 (0, 106)	145	0.3 (3.7)	0.0 (−15, 22)
Non-dialysis dependent						
Roxadustat						
Week 0	125	13.1 (33.2)	0.0 (0, 197)	—	—	—
End of week 24	126	11.3 (28.5)	0.0 (0, 166)	121	−1.6 (13.8)	0.0 (−79, 67)
Darbepoetin alfa						
Week 0	129	11.4 (26.2)	0.0 (0, 180)	—	—	—
End of week 24	130	9.8 (23.8)	0.0 (0, 190)	128	−1.6 (7.7)	0.0 (−45, 22)

max, maximum; min, minimum.

traction. The grader examined the optical coherence tomography images and indicated whether there was presence of subretinal fluid in the applicable eye.

Statistical Analysis

Demographics, baseline characteristics, and ophthalmologic findings were summarized descriptively.

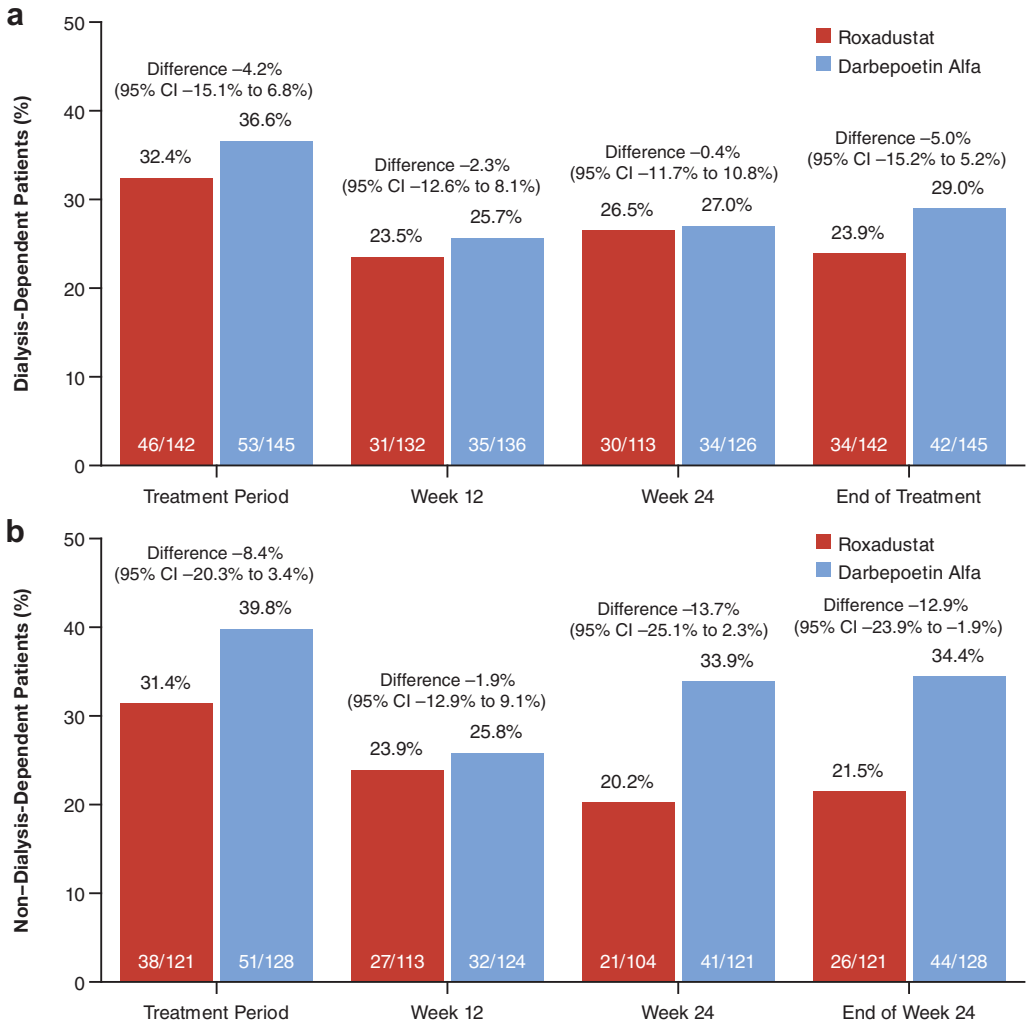

Figure 2. Proportion of (a) dialysis-dependent and (b) non–dialysis-dependent patients with new or worsening retinal hemorrhages compared with baseline (safety analysis set). Treatment period, detected throughout the entire 24-week treatment.

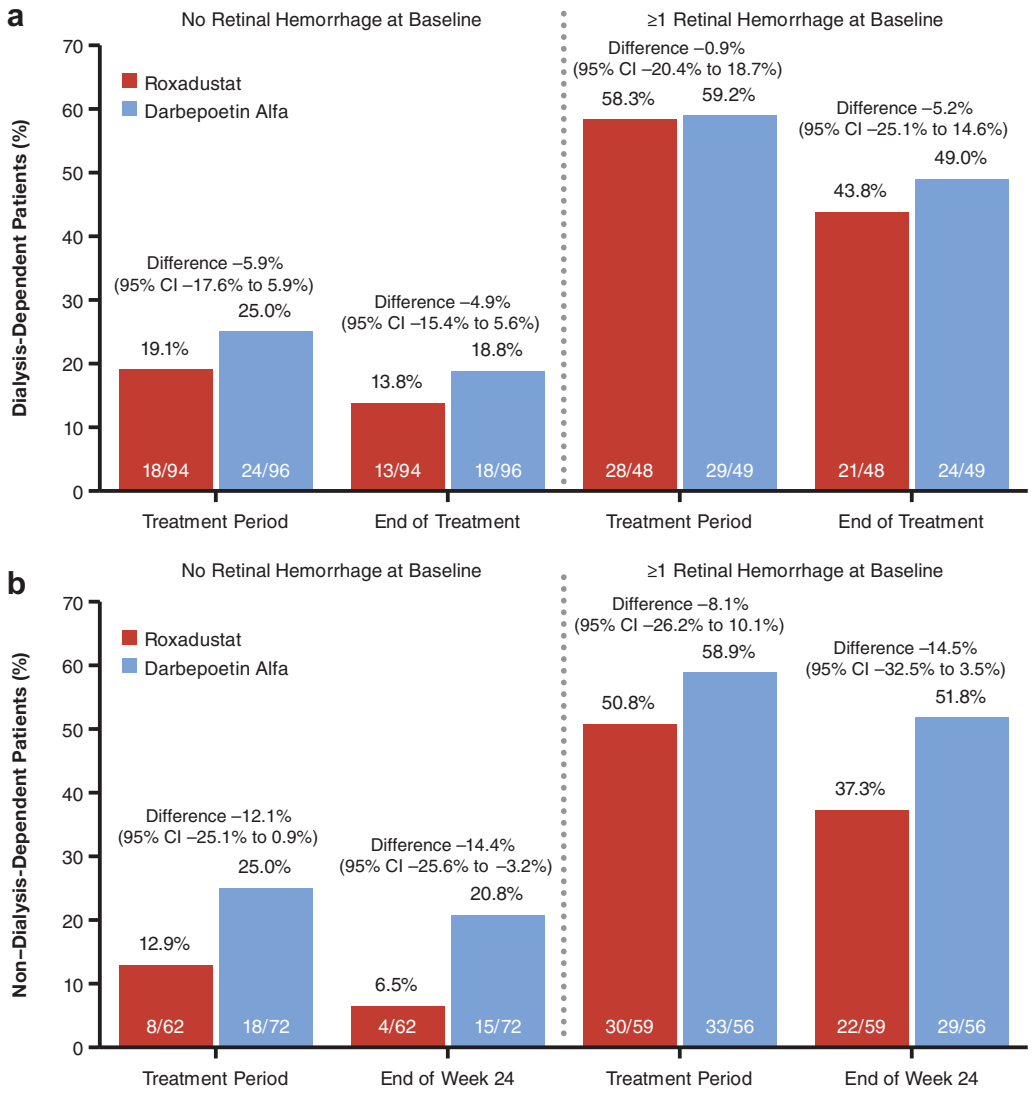

Figure 3. Proportion of (a) dialysis-dependent and (b) non–dialysis-dependent patients with new or worsening retinal hemorrhages by the presence or absence of retinal hemorrhages at baseline (safety analysis set). Treatment period, detected throughout the entire 24-week treatment.

As *post hoc* analyses, the differences of the proportions of patients with new or worsening RHs between the treatment groups, during the entire 24-week treatment period, at week 12, at week 24, and at end of treatment or week 24, were calculated along with 95% CIs by the normal approximation and were tested by the Wald method. The analyses of the difference on the occurrence of new or worsening RHs were repeated by the following subgroups: RHs at baseline (no or ≥1) and history of diabetes mellitus (absent or present). Generalized pairwise comparison was performed to estimate the net benefit statistics of the change from baseline in the total number of RHs at week 12, week 24, and at end of treatment or week 24, which were interpreted as the difference between treatment groups.[28] The 95% CIs and *P* values of the net benefit statistics were obtained using a nonparametric bootstrap method. The differences of the change from baseline in retinal thickness and visual acuity between treatment groups at week 12, at week 24, and at end of treatment or week 24 were calculated along with 95% CIs and were tested by *t* test. In addition, the differences of proportions of patients with evidence of hard exudates, evidence of cotton wool spots, presence of subretinal fluid, and presence of intraretinal fluid between treatment groups, at week 12, week 24, and at end of treatment or week 24, were calculated along with 95% CIs by the normal approximation and were tested by the Wald method. If the number of patients with events were 0 in either treatment group, a continuity correction was applied.

RESULTS

Patient Disposition and Baseline Characteristics

In study CL-0307, 303 DD patients were randomized to roxadustat ($n = 151$) or DA ($n = 152$); 250 (roxadustat, $n = 119$ [78.8%]; DA, $n = 131$ [86.2%]) patients completed the 24-week treatment and 53 (roxadustat,

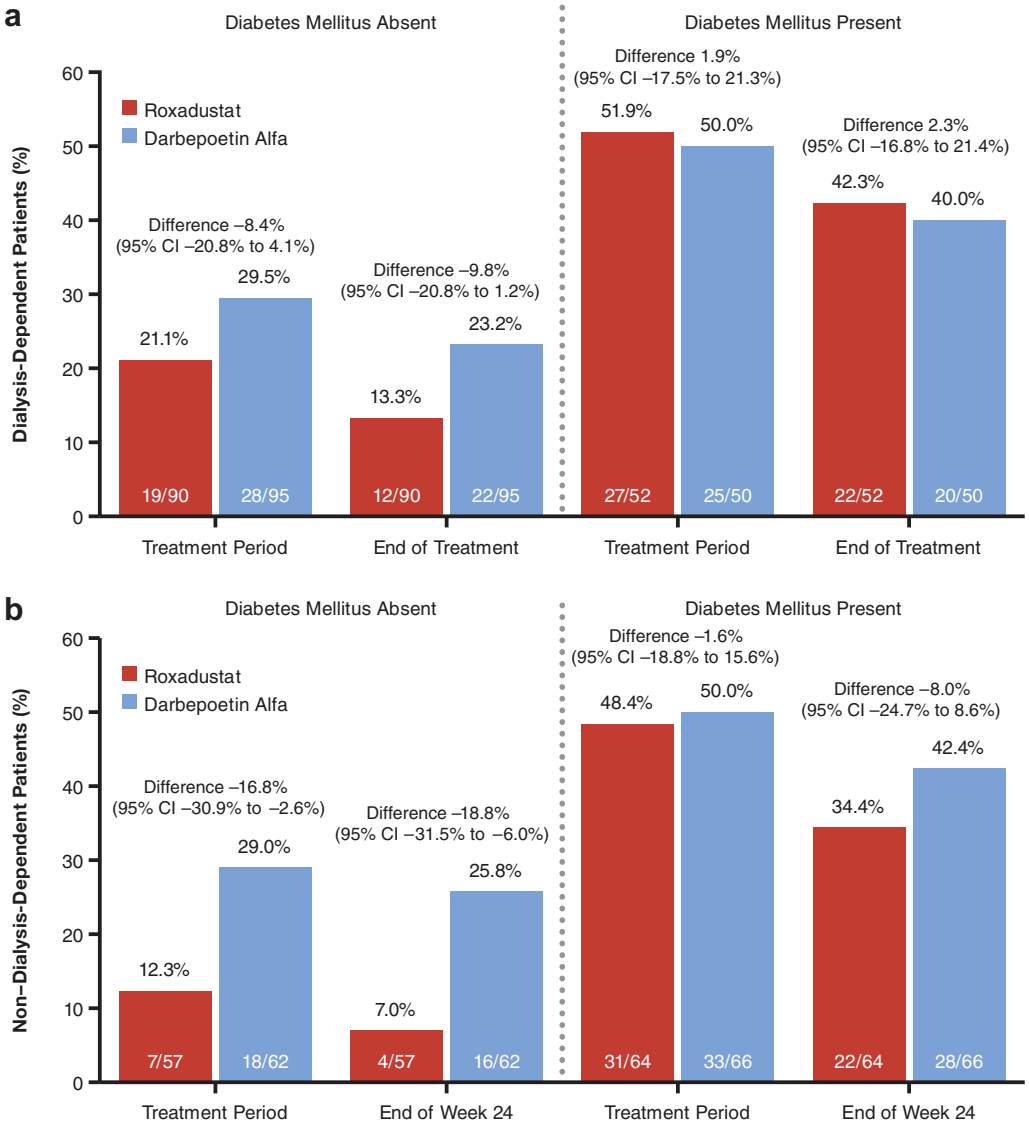

Figure 4. Proportion of (a) dialysis-dependent and (b) non–dialysis-dependent patients with new or worsening retinal hemorrhages by the presence or absence of diabetes mellitus at baseline (safety analysis set). Treatment period, detected throughout the entire 24-week treatment.

$n = 32$ [21.2%]; DA, $n = 21$ [13.8%]) discontinued the study treatment; 302 (roxadustat, $n = 150$ [99.3%]; DA, $n = 152$ [100.0%]) patients received ≥1 dose of the study drug and were included in the safety analysis set.

In study CL-0310, 263 NDD patients with CKD were randomized to roxadustat ($n = 132$) or DA ($n = 131$); 230 (roxadustat, $n = 109$ [82.6%]; DA, $n = 121$ [92.4%]) patients completed the 24-week treatment and 33 (roxadustat, $n = 23$ [17.4%]; DA, $n = 10$ [7.6%]) discontinued the study treatment; 262 (roxadustat, $n = 131$ [99.2%]; DA, $n = 131$ [100.0%]) patients received ≥1 dose of the study drug and were included in the safety analysis set.

Demographics and baseline characteristics were similar in the roxadustat and DA groups in each study (Table 1).

Ophthalmologic Findings

In both the roxadustat and DA groups, RHs were present at baseline in approximately 25% (right eye: 74 of 293, 25.3%; left eye: 78 of 295, 26.4%) of patients with DD CKD and 40% (right eye: 105 of 251, 41.8%; left eye: 97 of 252, 38.5%) of patients with NDD CKD. The total number of RHs was similar at baseline and at the end of treatment or week 24 in the roxadustat and the DA groups in patients with DD or NDD CKD (Table 2).

The proportions of patients with DD or NDD CKD with new or worsening RHs (compared with baseline) in the roxadustat and DA groups and subgroups are presented in Supplementary Table S6. There were no differences in the proportions of new or worsening RHs in patients with DD in the roxadustat and DA groups, which were 32.4% (46 of 142 patients) and 36.6% (53 of 145 patients), respectively, during the entire

Table 3. Retinal thickness (safety analysis set)

	Retinal thickness, μm			Change from baseline		
Population and end point	*n*	Mean (SD)	Median (min, max)	*n*	Mean (SD)	Median (min, max)
Dialysis dependent						
Roxadustat						
Week 0						
Right eye	148	253.35 (42.58)	249.95 (142.3, 460.7)	—	—	—
Left eye	147	255.44 (43.39)	252.30 (115.0, 483.1)	—	—	—
End of treatment						
Right eye	145	247.80 (40.81)	246.60 (145.7, 385.6)	143	−4.93 (26.08)	−0.90 (−230.7, 106.8)
Left eye	143	253.45 (40.77)	250.90 (118.0, 417.4)	141	−1.93 (32.72)	−2.00 (−249.6, 147.4)
Darbepoetin alfa						
Week 0						
Right eye	147	252.08 (74.08)	243.20 (137.8, 1057.5)	—	—	—
Left eye	149	249.95 (36.02)	244.20 (146.1, 376.5)	—	—	—
End of treatment						
Right eye	145	253.07 (91.03)	244.10 (125.8, 1282.1)	142	1.64 (23.49)	0.65 (−95.0, 224.6)
Left eye	147	250.43 (34.97)	246.70 (134.3, 384.5)	145	0.07 (9.80)	0.20 (−38.5, 55.5)
Non-dialysis dependent						
Roxadustat						
Week 0						
Right eye	124	258.94 (51.56)	250.09 (159.1, 597.8)	—	—	—
Left eye	121	264.07 (59.62)	252.50 (184.9, 676.2)	—	—	—
End of week 24						
Right eye	124	257.40 (43.73)	250.77 (151.6, 442.2)	119	−2.74 (30.13)	−0.82 (−209.0, 127.2)
Left eye	125	263.74 (58.04)	253.12 (177.5, 634.7)	118	−0.37 (23.63)	−0.52 (−89.2, 116.3)
Darbepoetin alfa						
Week 0						
Right eye	125	262.56 (46.43)	256.99 (160.4, 478.7)	—	—	—
Left eye	127	259.50 (43.99)	251.69 (155.4, 450.3)	—	—	—
End of week 24						
Right eye	124	263.31 (47.26)	257.27 (141.1, 474.0)	121	−0.73 (13.11)	−1.65 (−66.1, 57.8)
Left eye	128	262.16 (52.52)	254.35 (150.8, 524.1)	125	2.62 (27.11)	−0.04 (−59.5, 212.2)

max, maximum; min, minimum.

treatment period with a difference of −4.2% (95% CI: −15.1% to 6.8%, $P = 0.459$) and were similar between treatment groups at week 12 with a difference of −2.3% (95% CI: −12.6% to 8.1%, $P = 0.669$) and week 24 with a difference of −0.4% (95% CI: −11.7% to 10.8%, $P = 0.939$) (Figure 2a). The proportion of patients with NDD CKD with new or worsening RHs were similar at 31.4% (38 of 121 patients) and 39.8% (51 of 128 patients) in the roxadustat and DA groups, respectively, during the entire 24-week treatment period, with a difference of −8.4% (95% CI: −20.3% to 3.4%, $P = 0.165$). The proportion of patients with NDD CKD with new or worsening RHs (compared with baseline) was lower in the roxadustat (20.2%) versus the DA (33.9%) group at week 24 with a difference of −13.7% (95% CI: −25.1% to −2.3%, $P = 0.022$) (Figure 2b).

In the entire 24-week treatment period, among patients with no RHs at baseline, there were no differences in proportions between those with new RHs; the roxadustat and DA groups were 19.1% and 25.0% with a difference of −5.9% (95% CI: −17.6% to 5.9%, $P = 0.331$) (Figure 3a), respectively, in patients with DD CKD and 12.9% and 25.0% with a difference of −12.1% (95% CI: −25.1% to 0.9%, $P = 0.077$), respectively, in patients with NDD CKD (Figure 3b). Among patients with ≥1 RH at baseline, those with new or worsening RHs were similar: 58.3% and 59.2% with a difference of −0.9% (95% CI: −20.4% to 18.7%, $P = 0.932$) (Figure 3a), respectively, in patients with DD CKD, and 50.8% and 58.9% with a difference of −8.1% (95% CI: −26.2% to 10.1%, $P = 0.384$), respectively, in patients with NDD CKD (Figure 3b).

In the entire 24-week treatment period, among patients without diabetes mellitus, those with new or worsening RHs in the roxadustat and DA groups were similar (21.1% and 29.5% with a difference of −8.4% [95% CI: −20.8% to 4.1%, $P = 0.192$], respectively) (Figure 4a), in patients with DD CKD, and lower in the roxadustat group in patients with NDD CKD: 12.3% and 29.0% with a difference of −16.8% (95% CI: −30.9% to −2.6%, $P = 0.025$) (Figure 4b), respectively. Among patients with diabetes mellitus, proportions were similar among those with new or worsening RHs: 51.9% and

Table 4. Visual acuity (safety analysis set)

	Laterality			Change from baseline		
Population and end point	*n*	Mean (SD)	Median (min, max)	*n*	Mean (SD)	Median (min, max)
Dialysis dependent						
Roxadustat						
Week 0						
Right eye	150	0.79 (0.40)	0.90 (0.0, 2.0)	—	—	—
Left eye	150	0.79 (0.41)	0.80 (0.0, 2.0)	—	—	—
End of treatment						
Right eye	145	0.79 (0.40)	0.90 (0.1, 2.0)	145	0.00 (0.17)	0.00 (−0.5, 0.5)
Left eye	145	0.79 (0.41)	0.80 (0.0, 2.0)	145	0.00 (0.17)	0.00 (−0.6, 0.5)
Darbepoetin alfa						
Week 0						
Right eye	149	0.85 (0.40)	1.00 (0.0, 2.0)	—	—	—
Left eye	151	0.86 (0.39)	0.90 (0.0, 2.0)	—	—	—
End of treatment						
Right eye	147	0.88 (0.39)	1.00 (0.0, 1.5)	146	0.02 (0.18)	0.00 (−0.5, 1.0)
Left eye	149	0.87 (0.38)	0.90 (0.1, 2.0)	148	1.1 (0.17)	0.00 (−0.4, 0.6)
Non-dialysis dependent						
Roxadustat						
Week 0						
Right eye	126	0.73 (0.43)	0.75 (0.0, 1.5)	—	—	—
Left eye	126	0.77 (0.40)	0.80 (0.0, 1.5)	—	—	—
End of week 24						
Right eye	127	0.70 (0.41)	0.70 (0.0, 1.5)	123	−0.02 (0.21)	0.00 (−1.4, 0.7)
Left eye	127	0.76 (0.41)	0.80 (0.0, 1.5)	123	−0.00 (0.21)	0.00 (−1.4, 0.6)
Darbepoetin alfa						
Week 0						
Right eye	129	0.82 (0.39)	0.90 (0.0, 2.0)	—	—	—
Left eye	130	0.80 (0.38)	0.90 (0.0, 1.5)	—	—	—
End of week 24						
Right eye	129	0.79 (0.40)	0.80 (0.0, 1.5)	128	−0.03 (0.20)	0.00 (−0.8, 0.5)
Left eye	130	0.81 (0.37)	0.90 (0.0, 1.5)	129	0.01 (0.19)	0.00 (−0.5, 0.5)

max, maximum; min, minimum.

50.0% with a difference of 1.9% (95% CI: −17.5% to 21.3%, $P = 0.846$) (Figure 4a), respectively, in patients with DD CKD, and 48.4% and 50.0% with a difference of −1.6% (95% CI: −18.8% to 15.6%, $P = 0.859$), respectively, in patients with NDD CKD (Figure 4b).

In patients with DD or NDD CKD, retinal thickness (Table 3 and Supplementary Table S7), visual acuity (Table 4 and Supplementary Table S8), and total number of RHs (Supplementary Table S9) were stable from week 0 to the end of treatment or week 24 in both treatment groups.

Among patients with DD and NDD CKD, at any given time point, there generally were no differences in the relative change in proportion of patients with hard exudates and cotton wool spots or with the presence of intraretinal fluid and subretinal fluid between treatment groups at any given time point (Table 5 and Supplementary Tables S10–S13).

DISCUSSION

This report summarizes the ophthalmologic findings from 2 phase 3 studies comparing roxadustat versus DA in patients with DD or NDD CKD. Both studies were multicenter, randomized, DA-controlled studies conducted in Japanese patients, in which the central evaluation of ophthalmologic examination results was conducted in a masked manner. Data from this analysis suggest that treatment with roxadustat, compared with treatment with DA, is not associated with increased risk of new or worsening RHs, retinal thickness, visual acuity, hard exudates, cotton wool spots, intraretinal fluid, or subretinal fluid; these findings were also the case, regardless of whether or not patients are receiving dialysis and whether or not patients have diabetes mellitus.

There are data to suggest that increased angiogenesis may underlie certain retinal pathologies; the role of angiogenesis-driven retinal pathologies is particularly pertinent in diabetic retinopathy and neovascular age-related macular degeneration.[14–18] Specifically, data suggest that increases in HIF-1α are associated with VEGF up-regulation[14]; VEGF up-regulation may lead to increased vessel permeability and induction of a fenestrated phenotype in the retina, 2 features of VEGF bioactivity that are responsible for RHs.[29] Considering

Table 5. Hard exudates, cotton wool spots, intraretinal fluid, and subretinal fluid (safety analysis set)

	Roxadustat	Darbepoetin alfa	Roxadustat	Darbepoetin alfa
Population and end point	Right eye		Left eye	
Dialysis dependent				
Hard exudates, *n* (%)				
Week 0	7/148 (4.7)	7/145 (4.8)	8/148 (5.4)	5/147 (3.4)
End of treatment	8/144 (5.6)	13/147 (8.8)	5/141 (3.5)	10/148 (6.8)
Cotton wool spots, *n* (%)				
Week 0	7/148 (4.7)	2/145 (1.4)	7/148 (4.7)	2/147 (1.4)
End of treatment	5/144 (3.5)	1/147 (0.7)	4/141 (2.8)	1/148 (0.7)
Subretinal fluid, *n* (%)				
Week 0	2/148 (1.4)	1/146 (0.7)	0/147 (0.0)	2/149 (1.3)
End of treatment	2/145 (1.4)	1/145 (0.7)	2/143 (1.4)	1/147 (0.7)
Intraretinal fluid, *n* (%)				
Week 0	21/148 (14.2)	11/147 (7.5)	15/147 (10.2)	12/149 (8.1)
End of treatment	18/145 (12.4)	10/146 (6.8)	16/143 (11.2)	11/147 (7.5)
Non-dialysis dependent				
Hard exudates, *n* (%)				
Week 0	12/123 (9.8)	11/128 (8.6)	14/124 (11.3)	10/128 (7.8)
End of week 24	13/123 (10.6)	6/128 (4.7)	14/122 (11.5)	6/128 (4.7)
Cotton wool spots, *n* (%)				
Week 0	3/123 (2.4)	1/128 (0.8)	1/124 (0.8)	2/128 (1.6)
End of week 24	1/123 (0.8)	2/128 (1.6)	2/122 (1.6)	0/128 (0.0)
Subretinal fluid, *n* (%)				
Week 0	4/125 (3.2)	4/127 (3.1)	6/123 (4.9)	7/128 (5.5)
End of week 24	2/126 (1.6)	2/123 (1.6)	8/125 (6.4)	4/128 (3.1)
Intraretinal fluid, *n* (%)				
Week 0	24/124 (19.4)	26/127 (20.5)	26/123 (21.1)	24/128 (18.8)
End of week 24	19/126 (15.1)	25/124 (20.2)	24/125 (19.2)	25/128 (19.5)

the possibility that HIF prolyl hydroxylase inhibitors may induce angiogenesis by VEGF expression and that a considerable number of patients with CKD are older and/or have diabetes, it is prudent to clinically characterize the retinal safety profile of HIF prolyl hydroxylase inhibitors in patients with CKD. Interestingly, there is also preclinical evidence to suggest that stabilization of HIF-1α may actually have a protective effect.[30] Hoppe *et al.*[31,32] found that stabilization of extraretinal HIF-1 in the liver, in the case of dimethyloxalylglycine, or hepatic and retinal HIF-1 pathways, in the case of roxadustat, induced retinovascular protection in mice. In addition, in 2019, Hoppe *et al.*[33] reported that roxadustat did not induce expression of HIF-2–dependent genes critical to pathologic angiogenesis based on data collected in mice. As such, the effects of HIF-1α stabilization in all settings, including in patients with CKD, warrant further investigation.

Preliminary evidence provided by both the current clinical studies suggests that treatment with roxadustat does not result in increased risk of ophthalmologic abnormalities compared with DA. In both patients with DD and NDD CKD, there were no differences in the total number of RHs in either treatment group at any given time point. Furthermore, in both DD and NDD patients with CKD, the proportion of patients with new or worsening RHs was not higher in the roxadustat group versus the DA group; similar results were observed in the subgroups of patients with no RHs at baseline or with ≥1 RH at baseline, and in the subgroups of patients with or without diabetes mellitus. The proportions were lower for the roxadustat group versus the DA group in NDD patients with CKD, including those with no RH at baseline and those without diabetes mellitus, at some time points, suggesting further investigation in these patient populations is warranted as these findings should be considered hypothesis generating. Last, significant differences were not consistently observed in retinal thickness, visual acuity, hard exudates, cotton wool spots, intraretinal fluid, or subretinal fluid in either treatment group at any given time point.

Limitations in the current analysis include a limited number of patients in each study, which may limit the generalizability of the current results. In addition, exclusion criteria of both studies dictated that some patients with some ophthalmologic diseases (e.g., concurrent untreated retinal neovascular lesion or untreated macular edema or any condition that significantly compromised the ability to visualize the retina) be excluded from enrollment, which may influence these findings. Furthermore, these studies (up

to 24 weeks) are short term; as such, the long-term ophthalmologic-related safety of roxadustat is still unclear. The assessment of ophthalmologic safety in both studies was part of the safety evaluation and powering considerations for the studies were based on demonstration of noninferiority in efficacy and not equivalence in terms of ophthalmologic safety. Because of the relatively wide CIs owing to the sample size, no previously established noninferiority margin for ophthalmologic safety evaluations, and baseline imbalance in proportions for some abnormalities, such as cotton wool spots, these results should be interpreted with caution. Last, these studies were limited to the Japanese population, which may influence the generalizability of these findings.

In conclusion, data from this analysis do not suggest a safety signal or that treatment with roxadustat, compared with treatment with DA, is associated with an increased risk of new or worsening RHs, retinal thickness, visual acuity, hard exudates, cotton wool spots, intraretinal fluid, or subretinal fluid in Japanese patients with NDD or DD CKD. Long-term safety data may help fully elucidate the risk of treatment with roxadustat as it pertains to ophthalmologic adverse events in this patient population.

DISCLOSURE

YJS and QDN have served on the scientific advisory board for Astellas Pharma, Inc. QDN has also served on the scientific advisory board for AsclepiX Therapeutics, Genentech, Regeneron, among others. YY, TO, and YM are employees of Astellas Pharma, Inc. MR is an employee of Astellas Pharma Europe B.V. TA has received personal fees from Astellas, Bayer, Chugai, Fuso, GlaxoSmithKline, JT Pharmaceuticals, KKC, Kissei, NIPRO Corporation, Ono, Otsuka, Torii, and Sanwa Chemical Industrial Co., Ltd.

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DATA SHARING 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.

AUTHOR CONTRIBUTIONS

MR, TA, and TO created the concept and design of the study. TO and TA acquired the data. YJS, QDN, YY, TO, YM, MR, and TA analyzed and interpreted the data, and drafted and made critical revisions of the manuscript for important intellectual content.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Dose conversion between mean weekly doses of rHuEPO or darbepoetin alfa before study registration and initial dose of roxadustat at the start of the treatment period for DD and NDD patients.

Table S2. Dose conversion between mean weekly doses of rHuEPO or darbepoetin alfa before study registration and initial dose of darbepoetin alfa at the start of the treatment period.

Table S3. Dose-adjusting criteria.

Table S4. Dose-adjustment steps for roxadustat.

Table S5. Dose-adjustment steps for darbepoetin alfa.

Table S6. Difference of proportion of patients (roxadustat vs. darbepoetin alfa) with new or worsening retinal hemorrhage.

Table S7. Difference of change from baseline in retinal thickness (μm) (roxadustat vs. darbepoetin alfa).

Table S8. Difference of change from baseline in visual acuity (roxadustat vs. darbepoetin alfa).

Table S9. Difference of change from baseline in total number of retinal hemorrhages (roxadustat vs. darbepoetin alfa).

Table S10. Difference of proportion of patients (roxadustat vs. darbepoetin alfa) for hard exudates.

Table S11. Difference of proportion of patients (roxadustat vs. darbepoetin alfa) for cotton wool spots.

Table S12. Difference of proportion of patients (roxadustat vs. darbepoetin alfa) for presence of subretinal fluid.

Table S13. Difference of proportion of patients (roxadustat vs. darbepoetin alfa) for presence of intraretinal fluid (PDF).

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