Supplemental Materials Table of Contents

Supplemental Table 1. Dose conversion between mean weekly doses of short-acting rHuEPO or darbepoetin alfa before study registration and initial dose of roxadustat or darbepoetin alfa

	Prior ESA Dose		**Initial Study Medication Dose**
	rHuEPO (IU/week)	**Darbepoetin alfa (μg/week)**	**Roxadustat TIW (mg/intake)**
Roxadustat group	<4500	<20	70
	≥4500	≥20	100
	rHuEPO (IU/week)	**Darbepoetin alfa (μg/week)**	**Comparator: Darbepoetin alfa QW (μg/week)**
Darbepoetin alfa group	-	<12.5	10
	≤3000	≥12.5 to <17.5	15
	>3000 to ≤4500	≥17.5 to <25	20
	>4500 to ≤6000	≥25 to <35	30
	>6000	≥35 to <45	40
	-	≥45 to <55	50
	-	≥55	60

ESA, erythropoiesis-stimulating agents; QW, once weekly; rHuEPO, recombinant human erythropoietin; TIW, three times weekly.

Darbepoetin alfa (comparator) was intravenously administered once per week to patients at the completion of dialysis on the dialysis day after the longest dialysis interval, for a maximum of 24 weeks. The last dose was administered at completion of dialysis on the day of the Week 23 visit.

Supplemental Table 2. Dose-adjusting criteria

Roxadustat			
Change in Hb level from the previous 4 weeks to the current week	Weekly pre-dialysis Hb level		
	<10.5 g/dL	≥10.5 g/dL to ≤11.5 g/dL	>11.5 g/dL to ≤12.5 g/dL
< –1 g/dL	One-step increase	One-step increase	No change
≥ –1 g/dL to ≤1 g/dL	One-step increase	No change	One-step reduction
>1 g/dL	No change	One-step reduction	One-step reduction
Darbepoetin alfa			
	Hb Level*		
	<10.5 g/dL	>11.5 g/dL	>12.5 g/dL
	One-step increase	One-step decrease	No dosing

*Measured at the even week and the previous week; darbepoetin alfa dose was adjusted if both Hb measurements met the dose-adjusting criteria.

Supplemental Table 3. Dose-adjustment steps for roxadustat

Step	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Roxadustat dose (mg)	20	40	50	70	100	120	150	200	250	300

Supplemental Table 4. Dose-adjustment steps for darbepoetin alfa

Step	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Darbepoetin alfa dose (μg)	10	15	20	30	40	50	60	80	100	120	140	160	180

Supplemental Table 5. Sensitivity analysis: Change of average Hb levels of Weeks 18 to 24 from baseline (per protocol set)

Parameter	**Model**	**Treatment Group**	**LS Mean (SE) (95% CI)**	**Estimated Difference (SE) (95% CI)**
Change of average Hb levels of Weeks 18 to 24 from baseline (g/dL)	ANCOVA with MI	Darbepoetin alfa	–0.04 (0.05) (–0.14, 0.06)	-
		Roxadustat	–0.03 (0.06) (–0.13, 0.08)	0.01 (0.08) (–0.14, 0.16)
	PMM (Last Mean Carried Forward)	Darbepoetin alfa	–0.04 (0.05) (–0.14, 0.06)	-
		Roxadustat	–0.03 (0.06) (–0.14, 0.08)	0.01 (0.08) (–0.14, 0.16)
	PMM (Last Mean Carried Forward for roxadustat and randomized arm MAR for darbepoetin alpha)	Darbepoetin alfa	–0.04 (0.05) (–0.14, 0.06)	-
		Roxadustat	–0.03 (0.06) (–0.14,0.08)	0.01 (0.08) (–0.14, 0.16)

ANCOVA, analysis of covariance; CI, confidence interval; HB, hemoglobin; LS, least square; MAR, missing at random; MI, multiple imputation; PMM, pattern mixture model; SE, standard error.
Hb values in analysis visit windows at Weeks 18, 19, 20, 21, 22, 23, and 24 are used for calculating the average of Weeks 18 to 24. All the three rows (models) report results of prespecified analyses. A description of the multiple imputation approach is provided in the Supplemental Methods (Sensitivity Analysis for Missing Data).

Supplemental Table 6. Hepcidin (ng/mL) levels by visit (full analysis set)

Parameter	Roxadustat (n=150)	Darbepoetin alfa (n=151)
Week 0	26.441 (21.502)	24.446 (20.988)
Week 4	25.344 (26.584)	21.605 (19.694)
Week 12	25.469 (24.711)	22.490 (28.579)
Week 24	27.665 (24.640)	23.241 (26.472)
EoT	28.749 (28.220)	23.845 (26.127)
Change from Week 0 to EoT	2.308 (27.279)	–0.600 (27.061)

Data are presented as mean (SD).
EoT, end of treatment.

Supplemental Table 7. Serious TEAEs (safety analysis set)

MedDRA version 19.0 **System Organ Class** Preferred Term	**Roxadustat (n=150)**	**Darbepoetin alfa (n=152)**
Overall[a]	31 (20.7)	22 (14.5)
Cardiac disorder	5 (3.3)	4[b] (2.6)
Angina pectoris	1 (0.7)	2 (1.3)
Acute myocardial infarction	1 (0.7)	0
Aortic valve stenosis	0	1 (0.7)
Atrioventricular block complete	0	1 (0.7)
Bradycardia	1 (0.7)	0
Cardiac failure	0	1 (0.7)
Cardiac failure congestive	1 (0.7)	0
Coronary artery stenosis	1 (0.7)	0
Myocardial ischemia	0	1 (0.7)
Ear and labyrinth disorders	1 (0.7)	0
Sudden hearing loss	1 (0.7)	0
Gastrointestinal disorders	1 (0.7)	0
Gastrointestinal hemorrhage	1 (0.7)	0
General disorders and administration site conditions	1 (0.7)	0
Vascular stent occlusion	1 (0.7)	0
Infections and infestations	3 (2.0)	0
Cellulitis	2 (1.3)	0
Urinary tract infection	1 (0.7)	0
Injury, poisoning, and procedural complications	11 (7.3)	10 (6.6)
Shunt stenosis	6 (4.0)	7 (4.6)
Shunt occlusion	3 (2.0)	2 (1.3)
Joint dislocation	1 (0.7)	0
Subcutaneous hematoma	0	1 (0.7)
Spinal column injury	1 (0.7)	0
Investigations	2 (1.3)	1 (0.7)
Arteriogram coronary	1 (0.7)	0
Hemoglobin decreased	0	1 (0.7)
Investigation	1 (0.7)	0
Musculoskeletal and connective tissue disorders	1 (0.7)	0
Lumbar spinal stenosis	1 (0.7)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.7)	4 (2.6)
Basal cell carcinoma	0	1 (0.7)
Gastric cancer	1 (0.7)	0
Malignant neoplasm of renal pelvis	0	1 (0.7)
Transitional cell carcinoma	0	1 (0.7)
Lip and/or oral cavity cancer	0	1 (0.7)
Nervous system disorders	1 (0.7)	0
Cerebral infarction	1 (0.7)	0

Psychiatric disorders	0	1 (0.7)
Suicidal ideation	0	1 (0.7)
Respiratory, thoracic, and mediastinal disorders	1 (0.7)	1 (0.7)
Asthma	1 (0.7)	0
Pulmonary edema	0	1 (0.7)
Surgical and medical procedures	1 (0.7)	2 (1.3)
Angioplasty	0	1 (0.7)
Coronary angioplasty	1 (0.7)	0
Large intestinal polypectomy	0	1 (0.7)
Vascular disorders	5 (3.3)	1 (0.7)
Deep vein thrombosis	2 (1.3)	0
Orthostatic hypotension	1 (0.7)	0
Venous occlusion	1 (0.7)	0
Peripheral arterial occlusive disease	0	1 (0.7)
Subclavian vein stenosis	1 (0.7)	0

Data are presented as n (%).

[a]These data correspond to serious treatment-emergent adverse events presented in Table 3 of the manuscript.

[b]Two patients experienced more than one event.

TEAE, treatment-emergent adverse event.

Supplemental Table 8. Hemoglobin levels by category (full analysis set)

Analysis Visit	Assessment	Roxadustat	Darbepoetin alfa
		(N=150)	(N=151)
Prescreening	n	150	150
	<10.0 g/dL	12 (8.0%)	9 (6.0%)
	>=10.0 g/dL to <=12.0 g/dL	129 (86.0%)	128 (85.3%)
	>12.0 g/dL	9 (6.0%)	13 (8.7%)
Screening	n	150	150
	<10.0 g/dL	2 (1.3%)	9 (6.0%)
	>=10.0 g/dL to <=12.0 g/dL	146 (97.3%)	138 (92.0%)
	>12.0 g/dL	2 (1.3%)	3 (2.0%)
Week 0	n	150	151
	<10.0 g/dL	9 (6.0%)	5 (3.3%)
	>=10.0 g/dL to <=12.0 g/dL	131 (87.3%)	131 (86.8%)
	>12.0 g/dL	10 (6.7%)	15 (9.9%)
Week 1	n	145	148
	<10.0 g/dL	9 (6.2%)	14 (9.5%)
	>=10.0 g/dL to <=12.0 g/dL	121 (83.4%)	126 (85.1%)
	>12.0 g/dL	15 (10.3%)	8 (5.4%)
Week 2	n	146	148
	<10.0 g/dL	7 (4.8%)	13 (8.8%)
	>=10.0 g/dL to <=12.0 g/dL	115 (78.8%)	123 (83.1%)
	>12.0 g/dL	24 (16.4%)	12 (8.1%)
Week 3	n	143	147
	<10.0 g/dL	16 (11.2%)	9 (6.1%)
	>=10.0 g/dL to <=12.0 g/dL	96 (67.1%)	128 (87.1%)
	>12.0 g/dL	31 (21.7%)	10 (6.8%)
Week 4	n	143	146
	<10.0 g/dL	15 (10.5%)	12 (8.2%)
	>=10.0 g/dL to <=12.0 g/dL	98 (68.5%)	122 (83.6%)
	>12.0 g/dL	30 (21.0%)	12 (8.2%)
Week 5	n	141	145
	<10.0 g/dL	16 (11.3%)	11 (7.6%)
	>=10.0 g/dL to <=12.0 g/dL	95 (67.4%)	119 (82.1%)
	>12.0 g/dL	30 (21.3%)	15 (10.3%)
Week 6	n	140	143
	<10.0 g/dL	16 (11.4%)	13 (9.1%)
	>=10.0 g/dL to <=12.0 g/dL	102 (72.9%)	118 (82.5%)
	>12.0 g/dL	22 (15.7%)	12 (8.4%)
Week 7	n	137	143
	<10.0 g/dL	14 (10.2%)	7 (4.9%)

	>=10.0 g/dL to <=12.0 g/dL	101 (73.7%)	121 (84.6%)
	>12.0 g/dL	22 (16.1%)	15 (10.5%)
Week 8	n	137	142
	<10.0 g/dL	12 (8.8%)	7 (4.9%)
	>=10.0 g/dL to <=12.0 g/dL	106 (77.4%)	122 (85.9%)
	>12.0 g/dL	19 (13.9%)	13 (9.2%)
Week 9	n	136	142
	<10.0 g/dL	16 (11.8%)	8 (5.6%)
	>=10.0 g/dL to <=12.0 g/dL	109 (80.1%)	116 (81.7%)
	>12.0 g/dL	11 (8.1%)	18 (12.7%)
Week 10	n	132	141
	<10.0 g/dL	14 (10.6%)	11 (7.8%)
	>=10.0 g/dL to <=12.0 g/dL	99 (75.0%)	119 (84.4%)
	>12.0 g/dL	19 (14.4%)	11 (7.8%)
Week 11	n	135	142
	<10.0 g/dL	12 (8.9%)	10 (7.0%)
	>=10.0 g/dL to <=12.0 g/dL	106 (78.5%)	117 (82.4%)
	>12.0 g/dL	17 (12.6%)	15 (10.6%)
Week 12	n	135	142
	<10.0 g/dL	9 (6.7%)	4 (2.8%)
	>=10.0 g/dL to <=12.0 g/dL	111 (82.2%)	122 (85.9%)
	>12.0 g/dL	15 (11.1%)	16 (11.3%)
Week 13	n	133	141
	<10.0 g/dL	9 (6.8%)	12 (8.5%)
	>=10.0 g/dL to <=12.0 g/dL	110 (82.7%)	117 (83.0%)
	>12.0 g/dL	14 (10.5%)	12 (8.5%)
Week 14	n	131	140
	<10.0 g/dL	8 (6.1%)	8 (5.7%)
	>=10.0 g/dL to <=12.0 g/dL	112 (85.5%)	120 (85.7%)
	>12.0 g/dL	11 (8.4%)	12 (8.6%)
Week 15	n	130	139
	<10.0 g/dL	11 (8.5%)	11 (7.9%)
	>=10.0 g/dL to <=12.0 g/dL	102 (78.5%)	117 (84.2%)
	>12.0 g/dL	17 (13.1%)	11 (7.9%)
Week 16	n	127	137
	<10.0 g/dL	11 (8.7%)	8 (5.8%)
	>=10.0 g/dL to <=12.0 g/dL	100 (78.7%)	118 (86.1%)
	>12.0 g/dL	16 (12.6%)	11 (8.0%)
Week 17	n	125	138
	<10.0 g/dL	10 (8.0%)	6 (4.3%)
	>=10.0 g/dL to <=12.0 g/dL	105 (84.0%)	118 (85.5%)

	>12.0 g/dL	10 (8.0%)	14 (10.1%)
Week 18	n	124	135
	<10.0 g/dL	6 (4.8%)	11 (8.1%)
	>=10.0 g/dL to <=12.0 g/dL	111 (89.5%)	115 (85.2%)
	>12.0 g/dL	7 (5.6%)	9 (6.7%)
Week 19	n	122	135
	<10.0 g/dL	5 (4.1%)	8 (5.9%)
	>=10.0 g/dL to <=12.0 g/dL	107 (87.7%)	119 (88.1%)
	>12.0 g/dL	10 (8.2%)	8 (5.9%)
Week 20	n	121	134
	<10.0 g/dL	7 (5.8%)	8 (6.0%)
	>=10.0 g/dL to <=12.0 g/dL	104 (86.0%)	115 (85.8%)
	>12.0 g/dL	10 (8.3%)	11 (8.2%)
Week 21	n	120	131
	<10.0 g/dL	11 (9.2%)	8 (6.1%)
	>=10.0 g/dL to <=12.0 g/dL	102 (85.0%)	118 (90.1%)
	>12.0 g/dL	7 (5.8%)	5 (3.8%)
Week 22	n	120	130
	<10.0 g/dL	9 (7.5%)	7 (5.4%)
	>=10.0 g/dL to <=12.0 g/dL	101 (84.2%)	117 (90.0%)
	>12.0 g/dL	10 (8.3%)	6 (4.6%)
Week 23	n	120	131
	<10.0 g/dL	7 (5.8%)	7 (5.3%)
	>=10.0 g/dL to <=12.0 g/dL	103 (85.8%)	115 (87.8%)
	>12.0 g/dL	10 (8.3%)	9 (6.9%)
Week 24	n	118	131
	<10.0 g/dL	14 (11.9%)	6 (4.6%)
	>=10.0 g/dL to <=12.0 g/dL	97 (82.2%)	115 (87.8%)
	>12.0 g/dL	7 (5.9%)	10 (7.6%)
End of Treatment	n	150	151
	<10.0 g/dL	20 (13.3%)	11 (7.3%)
	>=10.0 g/dL to <=12.0 g/dL	118 (78.7%)	129 (85.4%)
	>12.0 g/dL	12 (8.0%)	11 (7.3%)

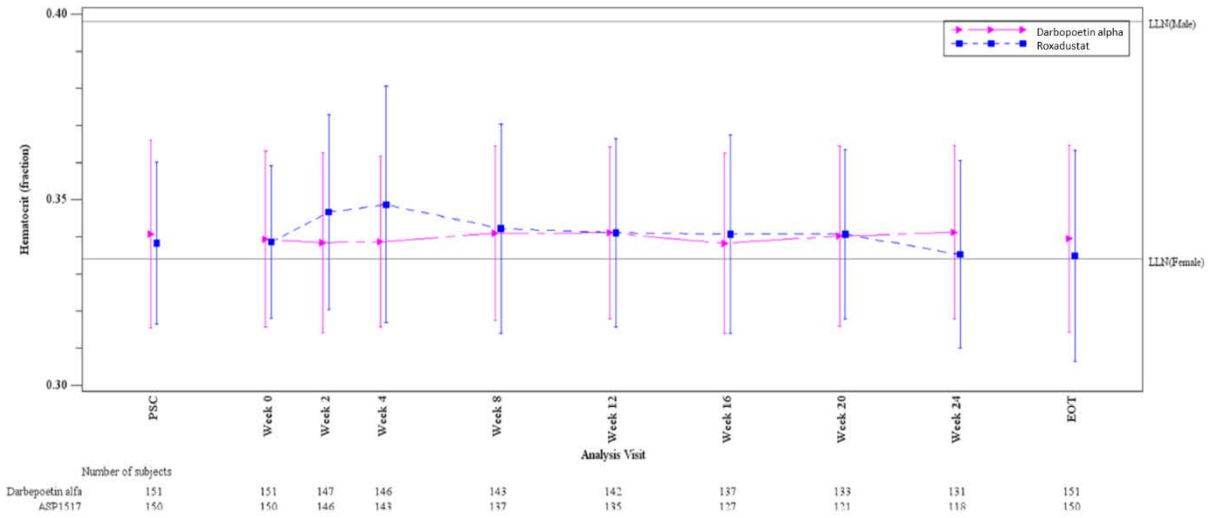
Supplemental Figure 1. Schedule of assessments

	Screening		Treatment (week)																									
	PSC	**SC**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**D**
Hb	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum iron parameters*	x		x		x		x				x				x				x				x				x	x
Hepcidin, sTfR, hsCRP			x				x								x												x	x
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmological tests	x		x												x												x	x
Monitoring of patient diary				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

*Serum iron, transferrin, total iron binding capacity, transferrin saturation, reticulocytes, ferritin, hemoglobin in reticulocyte.

D, discontinuation; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; PSC, prescreening; SC, screening; sTfR, soluble transferrin receptor.

Supplemental Figure 2. Mean and standard deviation plot of hematocrit (fraction) (full analysis set)



EOT, end of treatment; LLN, lower limit of normal; PSC, prescreening.

Supplemental Methods

Full Inclusion and Exclusion Criteria

Inclusion Criteria

The patient was eligible for the study if all of the following applied:

1. Patients who had given written informed consent by themselves
2. Patients who were diagnosed with chronic kidney disease (CKD), had been receiving stable chronic maintenance hemodialysis (HD) three times a week for more than 12 weeks before the prescreening assessments, and were scheduled to undergo HD three times a week during the study period
3. Patients with renal anemia who had been receiving intravenous treatment of recombinant human erythropoietin (rHuEPO) (twice a week or 3 times a week) or darbepoetin alfa within the doses approved in Japan for more than 8 weeks before the prescreening assessments
4. Mean of the patient's two most recent hemoglobin (Hb) levels just before registration (before dialysis after the longest dialysis interval) during the screening period had to be 10.0 to 12.0 g/dL (two Hb levels had to be measured with at least a week interval)
5. Patients with either transferrin saturation (TSAT) of ≥20% or serum ferritin of ≥100 ng/mL during the screening period
6. Patients aged 20 years or more at informed consent acquisition
7. Patients had been receiving HD via arteriovenous fistula or graft or subcutaneously fixed superficial artery
8. Female patients had to fulfill the following conditions:
    a. Non-childbearing potential female patients:
        i. Post-menopausal (defined as at least 1 year without any menses) prior to the prescreening assessments, or
        ii. Documented surgically sterile
    b. Childbearing potential female patients (patients who did not correspond above):
        i. Agreed not to try to become pregnant during the study after informed consent acquisition and for 28 days after the final study drug administration
        ii. And had a negative pregnancy test at the prescreening assessments
        iii. And, if heterosexually active, agreed to consistently use two forms of highly effective birth control† (at least one of which had to be a barrier method)

starting at screening and throughout the study period and for 28 days after the final study drug administration

9. Female patients had to agree not to breastfeed starting at screening and throughout the study period, and for 28 days after the final study drug administration
10. Female patients had to agree not to donate ova starting at screening and throughout the study period, and for 28 days after the final study drug administration
11. Male patients and their female spouse/partners who were of childbearing potential had to be using two forms of highly effective birth control† (at least one of which had to be a barrier method) starting at screening and continue throughout the study period, and for 12 weeks after the final study drug administration
12. Male patients had to agree not to donate sperm starting at screening and throughout the study period, and for 12 weeks after the final study drug administration

† Highly effective forms of birth control included:

- Consistent and correct usage of established oral contraception
- Established intrauterine device or intrauterine system
- Barrier methods of contraception: condom or occlusive cap
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method)

Exclusion Criteria

The patient was excluded from participation if any of the following applied:

1. Concurrent retinal neovascular lesion untreated (proliferative diabetic retinopathy, exudative age-related macular degeneration, retinal vein occlusion, etc.) and macular edema untreated, and patients with any condition that significantly compromises the ability to visualize the retina, based on assessment at the prescreening of central reading
2. Concurrent autoimmune disease with inflammation that could have impacted erythropoiesis (systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, celiac disease, etc.)
3. History of gastric/intestinal resection considered influential on the absorption of drugs in the gastrointestinal tract (excluding resection of gastric or colon polyps) or concurrent gastroparesis
4. Uncontrolled hypertension (more than one-third of identifiable diastolic blood pressure values above 100 mmHg within 12 weeks prior to and including the prescreening assessments)
5. Concurrent congestive heart failure (New York Heart Association [NYHA] Class III or greater)

6. History of hospitalization for treatment of stroke, myocardial infarction, or pulmonary embolism within 12 weeks before the prescreening assessments
7. Positive for hepatitis B virus surface antigen or hepatitis C virus antibody at the prescreening assessments or positive for human immunodeficiency virus in a past test
8. Concurrent other form of anemia than renal anemia (hemolytic anemia, pancytopenia, hemorrhagic anemia, etc.)
9. History of pure red cell aplasia
10. Had received treatment with protein anabolic hormone, testosterone enanthate, or mepitiostane within 6 weeks before the prescreening assessments
11. Aspartate aminotransferase, alanine aminotransferase, or total bilirubin that was greater than the criteria below, or previous or concurrent another serious liver disease (acute or active chronic hepatitis, cirrhosis, etc.) at the prescreening assessments
    a. Aspartate aminotransferase: 2 × upper limit of normal
    b. Alanine aminotransferase: 2 × upper limit of normal
    c. Total bilirubin: 1.5 × upper limit of normal
12. Previous or current malignant tumor (no recurrence for at least 5 years was eligible)
13. Had undergone red blood cell transfusion or a surgical procedure considered to promote anemia (excluding shunt reconstruction surgery for vascular access) and ophthalmological surgery within 4 weeks before the prescreening assessments
14. Had a scheduled kidney transplantation in the study period
15. Had a previous history of treatment with Roxadustat
16. History of serious drug allergy including anaphylactic shock
17. Participation in another clinical study or post marketing clinical study (including that of a medical device) within 12 weeks before informed consent acquisition
18. Employed by the sponsor, or contract research organizations (CROs), site management organizations (SMOs) or study sites involved in this study
19. Other patients considered ineligible for the study by the investigator or sub-investigator

Rational for Sample Size

In confirming the noninferiority to darbepoetin alfa for the average Hb change from baseline to the evaluation period (Weeks 18 to 24) as a primary endpoint, with the assumption listed below, the sample size securing 90% power for the lower limit of 95% confidence interval (CI) in the difference between roxadustat and darbepoetin alfa, exceeding the noninferiority margin of –0.75 g/dL, was 103 patients for roxadustat and 103 patients for darbepoetin alfa, using an allocation rate of 1:1. The power of ≥99% was achieved, confirming the efficacy of roxadustat (the 95% CI of average Hb levels in the evaluation period was included in 10.0 to 12.0 g/dL, assuming 11.0 g/dL of the average Hb levels during the evaluation period).

Assuming a conservative per protocol set dropout rate of 30%, 150 patients for roxadustat and 150 patients for darbepoetin alfa were planned to be enrolled in this study.

Assumption for sample size:

- The difference between roxadustat and darbepoetin alfa in the average Hb change from baseline during the evaluation period was conservatively assumed to be –0.25 g/dL.
- The standard deviation for roxadustat and darbepoetin alfa in the average Hb change from baseline during the evaluation period in the phase 2 study result was 0.91 g/dL and 1.02 g/dL, respectively. The standard deviation for the Hb change from baseline at the final visit for cohorts administered the study drug thrice weekly (Cohorts A, C, and D) in the FGCL-4592-041 study was 0.83 g/dL (Week 17), 1.00 g/dL (Week 25), and 1.14 g/dL (Week 25), respectively. From these results, the standard deviation for the average Hb change from baseline during the evaluation period in this study was conservatively assumed to be 1.10 g/dL.
- The target Hb level in this study was 10.0 to 12.0 g/dL, as designated by the “Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012” (Japanese Society of Nephrology, 2012), and the doses of both roxadustat and darbepoetin alfa were adjusted to be maintained within a 2-g/dL range of the target Hb level. Therefore, the effect of maintaining a value within this designated range ± darbepoetin alfa was considered clinically significant and as an allowable difference between the two drug agents; the noninferiority margin for this study was designated as 0.75 g/dL, which was less than half of a 2-g/dL range of the target Hb level. The domestic phase 3 comparative study with epoetin beta pegol designated the noninferiority margin as 0.75 g/dL.

Sensitivity Analysis for Missing Data

ANCOVA with MI

The MI ANCOVA model was used to compare roxadustat and darbepoetin alfa groups in a fixed sequence procedure:

1. Generate 1000 datasets, using seed 9254122, where intermittent missing hemoglobin data are imputed for each treatment, relying on non-missing data from all subjects within each randomization arm using the Monte Carlo Markov Chain (MCMC) imputation model with treatment and the available non-missing hemoglobin for each scheduled week. The MCMC statement in the SAS PROC MI procedure with monotone option is used. As a result, each dataset only has missing ending data, or a monotone missing data pattern.
2. For each dataset from step 1, missing ending data (hemoglobin up through end of evaluation period) are imputed using seed 2798375. As a result, 1000 imputed complete datasets are generated.

    - Missing data at Week 1 are imputed using the regression imputation model with baseline assignment factor, and baseline and hemoglobin from Week 1, using the SAS PROC MI procedure with the REGRESSION option in the MONOTONE statement.
    - The SAS PROC MI procedure uses data separately from each treatment subject to impute the missing data for a specific week (i.e., only those that need the imputation for the week). Since subjects from the different randomization arms for that week are excluded from the step, they do not contribute to the imputation for the week.
    - Repeat for all other scheduled weeks sequentially (Week 2 to the end of evaluation period). Subjects whose missing data were imputed for previous weeks contribute to the imputation for the current week.

    The regression imputation model includes an intercept and the slopes of the hemoglobin from previous weeks, as well as the stratification factors.

3. Analyze each imputed dataset with the ANCOVA, using the mean of all observed or imputed hemoglobin values within the evaluation period. The model contains terms for baseline hemoglobin measurement as a covariate and randomization arm and the other randomization stratification factors as fixed effects.
4. Combine estimates from the results of each of the 1000 ANCOVA runs using SAS PROC MIANALYZE.

Report the results of the least-squares mean estimates of the change from baseline in hemoglobin during the evaluation period, the estimates of treatment effect (e.g., least-squares mean change from baseline in hemoglobin for roxadustat group minus the least-squares mean change from baseline in hemoglobin for the darbepoetin alfa group) and the corresponding 95% CIs during the evaluation period.

Pattern Mixture Models (PMM)

PMMs were used as an alternative to impute missing values, using different assumptions for missing patterns.

PMMs provide a general and flexible framework for sensitivity analyses that allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner. This is expected to address the possibility of the data being missing not at random (MNAR).

The following aspects of data missingness may affect the estimates:

- Timing and extent of missingness
- Assumed underlying mechanism for data missingness

A. Timing and Extent of Missing Data

To assess the potential effect of data missingness on the estimate of treatment effect, subjects are classified as full data or missing data cases.

Patterns of missingness were based on non-missing hemoglobin before the end of the evaluation period.

- Full data cases are defined as subjects with non-missing hemoglobin for all scheduled weeks of the treatment period.
- Missing data cases are defined as subjects with missing hemoglobin on at least one scheduled week of the treatment period. The missing data cases are further grouped into intermittent missing and monotone missing cases.
    - Intermittent missing hemoglobin cases are defined as subjects with missing hemoglobin for at least one scheduled week, but not on consecutive scheduled weeks, up to end of the evaluation period.
    - Monotone missing hemoglobin cases are defined as subjects who have consecutive scheduled weeks with missing hemoglobin up to the end of the evaluation period. A subject who is a monotone missing case could have intermittent missing hemoglobin prior to the ending week.

Subjects were grouped as follows:

- Full data cases
- Intermittent missing data cases
- Monotone missing data cases

If the incidence of monotone missing data cases and intermittent missing data cases were relatively small, then those cases were combined so that the groups are full data cases and missing data cases.

B. Assumptions on Missing Data Mechanism

In addition to the extent of data missingness, the mechanism under which missing data occur may affect the estimate of the parameter of interest.

The potential impact of missing efficacy endpoints on the estimates of treatment effects was assessed using alternative statistical models with different underlying assumptions on the missing data mechanism for MNAR (Little and Rubin, 2002).

C. PMM - Last Mean Carried Forward

A pattern-mixture model using a last mean carried forward multiple imputation method (Carpenter et al., 2013) was used as another sensitivity analysis to explore the robustness of the MMRM and ANCOVA with MI results for the primary efficacy variables. Using this method, missing data after "ending week" were imputed based on the last non-missing mean from its own randomization arm.

D. PMM - Last Mean Carried Forward for Roxadustat and Randomized Arm MAR for Darbepoetin Alpha

This method is a combination of PMM-Last Mean Carried forward for roxadustat and PMM-Randomized Arm MAR for the darbepoetin alpha group. The imputation data were generated based on the last mean carried forward method described above for the roxadustat group, while for the darbepoetin alpha group, the imputation data were generated using the Randomized Arm MAR group described below.

The Randomized Arm MAR is similar to PMM-Last Mean Carried Forward except that the joint distribution of the patients' observed and missing data is multivariate normal with mean and covariance matrix from their randomized arms.

The ANCOVA model was then performed for each combined imputed complete data set. Similarly, the Rubin's method was then used to combine the estimates and the differences between the least square mean differences between the two randomization arms from each of the ANCOVA analyses.

References

Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: A framework for relevant, accessible assumption, and inference via multiple imputation. *J Biopharm Stat.* 2013;23:1352-1371.

Little RJA and Rubin DB. Statistical Analysis with Missing Data, Second Edition. John Wiley & Sons; New Jersey: 2002.

Compliance

Compliance (roxadustat)

For each subject, compliance of roxadustat in the treatment period was calculated in %, using the following formula:

$$\frac{\text{Actual number of times taking roxadustat in treatment period as directed}}{\text{Maximum number of opportunities taking roxadustat in treatment period}} \times 100$$

where

'Actual number of times taking roxadustat in treatment period' =

Number of times in which "Date of Dosing Study Drug" is described and "Medication Situation" is "DOSE AS DIRECTED" in the Diary Times eCRF, from the date of first dosing to the date of last dosing; and

'Maximum number of opportunities taking roxadustat in treatment period' =

Total number of times in which "Date of Dosing Study Drug" is described or "Medication Situation" is "NOT TAKEN" in the Diary Times eCRF, from the date of first planned dosing to the last date during which "Date of Dosing Study Drug" is described or "Medication Situation" is "NOT TAKEN" in the Diary Times eCRF.

Compliance (darbepoetin alfa)

For each subject, compliance of darbepoetin alfa in the treatment period was calculated in %, using the following formula:

$$\frac{\text{Actual number of times taking darbepoetin alfa in treatment period}}{\text{Maximum number of opportunities taking darbepoetin alfa in treatment period}} \times 100$$

where

'Actual number of times taking darbepoetin alfa in treatment period' =

Number of times in which "Dosing Date" is described and "Was the dose of study drug temporarily discontinued?" is "NO" in the Study Drug Dosing (darbepoetin alfa) eCRF, from the date of first dosing to the date of last dosing (see only the condition of "Dosing Date" at Week 0 visit); and

'Maximum number of opportunities taking darbepoetin alfa in treatment period' =

Total number of times in which "Dosing Date" is described or "Was the dose of study drug temporarily discontinued?" is "YES" and "Reason" is "OTHER" in the Study Drug Dosing (darbepoetin alfa) eCRF,

from the date of first planned dosing to the date of last dosing (see only the condition of “Dosing Date” at Week 0 visit).

Dynamic Allocation

The patient assignment was determined so that the imbalance between the numbers of patients in the two treatment groups was minimized on study site, following assignment factors. This was implemented by a dynamic allocation method using a biased-coin minimization approach. See Zelen (1974) and Pocock and Simon (1975) for references.

- Factor 1: Average Hb levels (less than 11.0 g/dL and 11.0 g/dL or more) of the two most recent points just before registration
- Factor 2: ESA dose just before registration (rHuEPO: less than 4500 IU/week and 4500 IU/week or more; darbepoetin alfa: less than 20 μg/week and 20 μg/week or more)
- Factor 3: Previous or concurrent retinal vascular disorder* (present or absent)
- Factor 4: Diabetes mellitus (present or absent)

*Refers to retinal hemorrhage, vitreous hemorrhage, non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, macular edema, retinal vein occlusion, and retinal artery occlusion.

A flowchart of the assignment procedure is shown below.

References

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis*. 1974;28:365-375.

Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics.* 1975;31:103-115.

Flowchart of dynamic allocation method using a biased-coin minimization approach