Supplementary Material

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Supplementary Table 1. Institutional Review Board

Institution	Name of Institutional Review Board/ Ethics Committee
Sunagawa City Medical Center	Sunagawa City Medical Center, Institutional Review Board Nishi4jokita, Sunagawa-shi, Hokkaido, Japan
Takikawa Municipal Hospital	Takikawa Municipal Hospital, Institutional Review Board Omachi, Takikawa-shi, Hokkaido, Japan
JR Sapporo Hospital	JR Sapporo Hospital, Institutional Review Board Kita3johigashi, Chuou-ku, Sapporo-shi, Hokkaido, Japan
Higashinaebo Hospital	Sapporo Dermatology Clinic, Institutional Review Board Minami3jonishi, Chuou-ku, Sapporo-shi, Hokkaido, Japan
Tenshi Hospital Yamato Municipal Hospital Japan Organization of Occupational Health and Safety Toyama Rosai Hospital Kyoto City Hospital	Jimbo Orthopedic Surgery, Institutional Review Board Hon-cho, Koganei-shi, Tokyo, Japan
Iwate Prefectural Central Hospital	Iwate Prefectural Hospital Joint, Institutional Review Board Ueda, Morioka-shi, Iwate, Japan
Southern TOHOKU Medical Clinic	Southern TOHOKU General Hospital, Institutional Review Board Yatsuyamada, Koriyama-shi, Fukushima, Japan
Mito Kyodo General Hospital JA Toride Medical Center Ibaraki Seinan Medical Center Hospital Ina Central Hospital	Review Board of Human Rights and Ethics for Clinical Studies, Institutional Review Board Ichiban-chou, Chiyoda-ku, Tokyo, Japan
Todachuo General Hospital	Todachuo General Hospital, Institutional Review Board Hon-cho, Toda-shi, Saitama, Japan
Japanese Red Cross Saitama Hospital	Japanese Red Cross Saitama Hospital, Institutional Review Board Shintoshin, Chuou-ku, Saitama-shi, Saitama, Japan
Chiba East Hospital Kyoto Medical Center National Hospital Organization Osaka Minami Beppu Medical Center	National Hospital Organization Central Review Board, Institutional Review Board Higashigaoka, Meguro-ku, Tokyo, Japan
Kobari General Clinic Kawahara Clinic	Sugiura Hospital, Institutional Review Board Hon-cho, Kawaguchi-shi, Saitama, Japan
NTT Medical Center Tokyo	NTT Medical Center Tokyo, Institutional Review Board Higashigotanda, Shinagawa-ku, Tokyo, Japan
Fujisawa City Hospital	Fujisawa City Hospital, Institutional Review Board Fujisawa, Fujisawa-shi, Kanagawa, Japan
Saiseikai Yokohamashi Nanbu Hospital	Saiseikai Yokohamashi Nanbu Hospital , Institutional Review Board Kounandai, Kounan-ku, Yokohama-shi, Kanagawa, Japan
Koukan Clinic	Koukan Hospital, Institutional Review Board Koukandori, Kawasaki-ku, Kawasaki-shi, Kanagawa, Japan
Kurobe City Hospital	Kurobe City Hospital, Institutional Review Board Mikkaichi, Kurobe-shi, Toyama, Japan
Hokuriku Central Hospital	Toyama Medical Association, Institutional Review Board Ninagawa, Toyama-shi, Toyama, Japan
Saiseikai Kanazawa Hospital	Saiseikai Kanazawa Hospital , Institutional Review Board Akatsuchimachi, Kanazawa-shi, Ishikawa, Jap
Ishikawa Prefectural Central Hospital	Ishikawa Prefectural Central Hospital, Institutional Review Board Kuratsukihigashi, Kanazawa-shi, Ishikawa, Japan

Fukui Prefectural Hospital	Fukui Prefectural Hospital, Institutional Review Board Yotsui, Fukui-shi, Fukui, Japan
Red Cross Society Azumino Hospital	Red Cross Society Azumino Hospital, Institutional Review Board Toyoshina, Azumino-shi, Nagano, Japan
Gifu Prefectural General Medical Center	Gifu Prefectural General Medical Center, Institutional Review Board Noisshiki, Gifu-shi, Gifu, Jap
Asahi University Hospital	Asahi University Hospital , Institutional Review Board Hashimoto-cho, Gifu-shi, Gifu, Japan
Yaizu City Hospital	Yaizu City Hospital, Institutional Review Board Dobara, Yaizu-shi, Shizuoka, Japan
Masuko Memorial Hospital	Masuko Memorial Hospital , Institutional Review Board Takebashi-cho, Nakamura-ku, Nagoya-shi, Aichi, Japan
Chubu Rosai Hospital	Chubu Rosai Hospital, Institutional Review Board Komei, Minato-ku, Nagoya-shi, Aichi, Japan
Kasugai Municipal Hospital	Kasugai Municipal Hospital, Institutional Review Board Takaki-cho, Kasugai-shi, Aichi, Japan
Daido Clinic	Daido Hospital, Institutional Review Board Hakusui-cho, Minami-ku, Nagoya-shi, Aichi, Japan
Ehime Prefectural Central Hospital	Ehime Prefectural Central Hospital, Institutional Review Board Kasugamachi, Matsuyama-shi, Ehime, Japan
Omihachiman Community Medical Center	Omihachiman Community Medical Center, Institutional Review Board Tsuchida-cho, Omihachiman-shi, Shiga, Japan
Uji Tokushukai Medical Center	Tokushukai Group Joint, Institutional Review Board Kojimachi, Chiyoda-ku, Tokyo, Japan
Kitano Hospital The Tazuke Kofukai Medical Research Institute	Kitano Hospital The Tazuke Kofukai Medical Research Institute, Institutional Review Board Ogimachi, Kita-ku, Osaka-shi, Osaka, Japan
Osaka Saiseikai Nakatsu Hospital	Osaka Saiseikai Nakatsu Hospital, Institutional Review Board Shibata, Kita-ku, Osaka-shi, Osaka, Japan
Osaka General Medical Center	Osaka General Medical Center, Institutional Review Board Bandaihigashi, Sumiyoshi-ku, Osaka-shi, Osaka, Japan
Osaka Rosai Hospital	Osaka Rosai Hospital, Institutional Review Board Nagasone-cho, Kita-ku, Sakai-shi, Osaka, Japan
Chibune Clinic	Chibune General Hospital, Institutional Review Board Fukumachi, Nishiyodogawa-ku, Osaka-shi, Osaka, Japan
Sanin Rosai Hospital	Sanin Rosai Hospital, Institutional Review Board Kaikeshinden, Yonago-shi, Tottori, Japan
Saiki Jin Clinic	Brain Attack Center Ota Memorial Hospital, Institutional Review Board Okinogami-cho, Fukuyama-shi, Hiroshima, Japan
Kawashima Hospital	Kawashima Hospital, Institutional Review Board Kitasakoichiban-cho, Tokushima-shi, Tokushima, Japan
Iizuka Hospital	Iizuka Hospital, Institutional Review Board Yoshiomachi, Iizuka-shi, Fukuoka, Japan
Kokura Memorial Hospital	Kokura Memorial Hospital, Institutional Review Board Asano, Kokurakita-ku, Kitakyushu-shi, Fukuoka, Japan
Japanese Red Cross Kumamoto Hospital	Japanese Red Cross Kumamoto Hospital, Institutional Review Board Nagamine-minami, Higashi-ku, Kumamoto-shi, Kumamoto,
Kumamoto City Hospital	Kumamoto City Hospital, Institutional Review Board Koto, Higashi-ku, Kumamoto-shi, Kumamoto, Japan
Medical Corporation Seijinkai Ikeda Hospital Medical Corporation Jinaikai Ueyama Hospital	Medical Corporation Seijinkai Ikeda Hospital, Institutional Review Board Shimoharaigawa-cho, Kanoya-shi, Kagoshima, Japan

Supplementary Table 2. Inclusion/exclusion/withdrawal criteria

Inclusion criteria	Eligibility
Age	≥20 years of age
CKD stage at screening	Stages G3, G4, and G5 as defined by eGFR using the Japanese Society of Nephrology Chronic Kidney Disease Initiatives formula
Dialysis	ND for at least 12 weeks before screening
Use of ESA	
ESA-naïve	Have not used ESAs for at least 8 weeks before screening
ESA users	Have used the same ESA for at least 8 weeks before screening. However, the dose of darbepoetin alfa or CERA must have been stable (administered once every 4 weeks and up to a 1-step dose change at least 8 weeks before screening).
Hemoglobin	ESA-naïve: ≥8.0 g/dL and <11.0 g/dL ESA users: ≥9.0 g/dL and ≤13.0 g/dL
Iron parameters at screening	Ferritin >100 ng/mL or TSAT >20%
Gender	Male or female[a]
Disease-related exclusion criteria	**Ineligibility**
CKD-related	
Dialysis	Start or plan to initiate dialysis during the study
Kidney transplant	Planned living-related kidney transplant during the study
Anemia-related	
Aplasia	History of bone-marrow hypoplasia or pure red cell aplasia
Other causes of anemia	Pernicious anemia, thalassemia, sickle cell anemia, or myelodysplastic syndromes
GI bleeding	Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease or clinically significant GI bleeding within 8 weeks of screening through day 1
Cardiovascular disease-related	
MI, ACS, stroke, TIA	Diagnosed within 8 weeks before screening through day 1
Heart failure	Class IV heart failure, as defined by the New York Heart Association functional classification system
QTc interval at screening	QTc >500 msec or QTc >530 msec in participants with bundle branch block. QT interval corrected using the Bazett's formula was used, and ECG could be mechanically or manually read
Liver disease[b]	ALT >2×ULN at screening Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN was acceptable if bilirubin was fractionated and direct bilirubin was <35%) at screening

	Current unstable active liver or biliary disease (generally defined by the onset of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal/gastric varices, persistent jaundice, or cirrhosis)
Malignancy[c]	History of malignancy within 2 years before Screening, or currently receiving treatment for cancer
Other	If, in the opinion of the investigator, hemoglobin increase to the target range (11.0 – 13.0 g/dL) was medically risky, patients were excluded
Concomitant medication-related and other study-treatment related criteria	Ineligibility
Iron[d,e,f]	Planned use of IV iron during the screening phase through week 4
Severe allergic reactions	History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the daprodustat or CERA
Drugs and supplements	Use or planned use of strong inducers or inhibitors of CYP2C8 was prohibited from screening until 7 days after the last dose of study treatment Use of ESA (e.g., epoetin/darbepoetin alfa/epoetin beta pegol) was prohibited from 8 weeks before screening until the last dose of study treatment in ESA-naïve participants and during study treatment in ESA user; excluding epoetin beta pegol (brand name: Mircera Injection Syringe) supplied by GSK.
Prior exposure any other investigational drugs or treatment with daprodustat	Use of any other investigational drugs within 30 days or 5 half-lives of any other investigational drugs (whichever was longer) Any prior treatment with daprodustat for a treatment duration of >30 days
General health-related criteria	Ineligibility
Other conditions	Any other condition, clinical or laboratory abnormality, or examination finding considered by the investigator (or sub-investigator) that would put the participant at unacceptable risk and could affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study
Withdrawal criteria	
Hemoglobin	< 7.5 g/dL based on the average of 2 HemoCue hemoglobin values of the same sample
Other	Necessity of maintenance dialysis, kidney transplant, pregnancy, new or recurrent cancer, liver chemistry abnormalities exceeding threshold criteria, and more than 14 days use of strong inhibitors/inducers of CYP2C8

[a]Not pregnant, having no childbearing potential, and not breast-feeding. Female participants of childbearing potential had to agree to comply with one of the contraception methods from at least 28 days prior to the first dose of study drug until the completion of the follow-up visit.
[b]Stable liver disease (including asymptomatic gallstones, chronic hepatitis B/C, or Gilbert's syndrome) was acceptable if the participant otherwise met entry criteria.
[c]Squamous cell or basal cell carcinoma of the skin that had been definitively treated ≥8 weeks before screening was not considered an exclusion.
[d]Oral iron was acceptable. However, the same dose regimen must have been used throughout the Screening phase through week 4. Iron-containing phosphate binders (e.g., ferric citrate hydrate) were acceptable only if used for at least 12 weeks before screening. However, participants with iron-containing phosphate binders must have continued from screening through week 4.

[e]From week 4 and onwards, supplemental iron therapy was to be performed according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] if ferritin was ≤100 ng/mL and TSAT was ≤20%. The investigator (or sub-investigator) could select the route of administration and dose of prescription iron.
[f]Iron-containing phosphate binders (e.g., ferric citrate hydrate) could be initiated from week 4 and onwards unless any other antihyperphosphatemic agents were appropriate. Once initiated, iron-containing phosphate binders were to be continued until the end of the study wherever possible.
ALT, alanine aminotransferase; CERA, continuous erythropoietin receptor activator (epoetin beta pegol); CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; GI, gastrointestinal; IV, intravenous; MI, myocardial infarction; ND, not on dialysis; QTc, QT corrected; TIA, transient ischemic attack, TSAT, transferrin saturation; ULN, upper limit of normal.

Supplementary Table 3. Dose adjustment algorithm for daprodustat[a,b]

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment[c]
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the 1-step lower dose level (If interrupted at 1 mg: resume treatment at 1 mg once the 1-step dose increase criteria are met)
≥12.5 to ≤13.0	NA	1-step dose reduction
≥11.5 to <12.5	>2.0[d]	1-step dose reduction
	≤2.0	Continue treatment at the current dose level
≥7.5 to <11.5	>2.0[d]	1-step dose reduction
	≥0.5 to ≤2.0	Continue treatment at the current dose level[d]
	<0.5	1-step dose increase
<7.5[e]	NA	Discontinue treatment permanently and initiate another appropriate treatment

[a]Both ESA users and ESA-naïve participants originally initiated treatment with daprodustat at a starting dose of 4 mg once-daily on day 1 and remained on the same regimen until week 4. After a higher than expected percentage of ESA-naïve participants with a Hgb increase of >2.0 g/dL from baseline was observed at week 4, the protocol was amended. ESA-naïve participants with Hgb <9.0 g/dL continued to start at 4 mg once-daily but ESA-naïve participants with Hgb ≥9.0 g/dL at baseline initiated at 2 mg of daprodustat once-daily.
[b]For both ESA-naïve participants and ESA users, maintenance dose ranged from 1 to 24 mg every 4 weeks in the daprodustat group.
[c]Daprodustat was dosed regardless of food intake.
[d]At Week 4 (after the protocol was amended), if Hgb increased >1.0 g/dL over 2 weeks, the dose of daprodustat was reduced by 1 dose step; if Hgb increased ≤1.0 g/dL over 2 weeks, treatment was continued as specified in the dose adjustment algorithm except for 1-step dose reduction for a Hgb increase of >2.0 g/dL over 4 weeks.
[e]If an initial Hgb value was <7.5 g/dL the measurement was repeated at the same study visit (using the same sample) to calculate the average. If the average met the Hgb stopping criteria, study treatment was to be permanently discontinued.
ESA, erythropoiesis- stimulating agent; Hgb, hemoglobin; NA, not applicable.

Supplementary Table 4. Dose conversion for CERA

Dosing interval change (ESA-naïve)[a]	
CERA dose before interval change (given once every 2 weeks)	Dose conversion of CERA (given once every 4 weeks)
25 µg	50 µg
50 µg	100 µg
75 µg	150 µg
100 µg	200 µg
150 µg	250 µg

Dose conversion for replacement with CERA initial dose (ESA users)		
Prior ESA		CERA
Epoetin	<4500 IU per week	100 µg once every 4 weeks
	≥4500 IU per week	150 µg once every 4 weeks
Darbepoetin alfa	30 µg once every 4 weeks[b]	25 µg once every 4 weeks
	60 µg once every 4 weeks[b]	50 µg once every 4 weeks
	90 µg once every 4 weeks[b]	75 µg once every 4 weeks
	120 µg once every 4 weeks[b]	100 µg once every 4 weeks
	180 µg once every 4 weeks[b]	150 µg once every 4 weeks
CERA	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks[b]	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks

[a]After hemoglobin was confirmed in the target range (11.0–13.0 g/dL), hemoglobin change ≤2.0 g/dL over the past 4 weeks, and equivalent dose was given twice, dosing interval was changed from once every 2 weeks to once every 4 weeks.
[b] Allowance of ±1 week.
CERA, continuous erythropoietin receptor activator (epoetin beta pegol); ESA, erythropoietin-stimulating agent.

Supplementary Table 5. Dose adjustment algorithm for CERA

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment
Initial dose adjustment[b] (ESA-naïve participants)		
NA	<1.0	1-step dose increase
<10.0	≤2.0	1-step dose increase
NA	>2.0[a]	1-step dose reduction
Otherwise		Continue treatment at the current dose level
Maintenance dose adjustment (ESA users and ESA-naïve participants)[c]		
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the 1 lower dose level (resume treatment at 25 µg if interrupted at 25 µg)
≥12.5 to ≤13.0	NA	1-step dose reduction
≥11.5 to <12.5	>2.0	1-step dose reduction
	≤2.0	Continue treatment at the current dose level
≥7.5 to <11.5	>2.0	1-step dose reduction
	≥1.0 to ≤2.0	Continue treatment at the current dose level
	<1.0	1-step dose increase
<7.5[d]	NA	Discontinue treatment permanently and initiate another appropriate treatment

[a]After the protocol was amended Hgb was measured at week 2. If an increase of >1.0 g/dL over the past 2 weeks, CERA dose was to be reduced by 1 step (or treatment interrupted) at week 2 for ESA-naïve participants.
[b]Once Hgb increased to ≥11.0 g/dL, dose adjustments were made according to the pre-specified maintenance dose adjustment algorithm.
[c]For both ESA users and ESA-naïve participants, maintenance dose ranged from 25 to 250 µg every 4 weeks in the CERA group.
[d]If an initial Hgb value was <7.5 g/dL, the measurement was repeated at the same study visit (using the same sample) to calculate the average. If the average met the Hgb stopping criteria, study treatment was to be permanently discontinued.
CERA, continuous erythropoietin receptor activator (epoetin beta pegol); ESA, erythropoietin-stimulating agent; Hgb, hemoglobin; NA, not applicable.

Supplementary Table 6. Supplementary efficacy analysis of mean hemoglobin during the primary efficacy evaluation period

	Hgb (g/dL), Mean (95% CI)		Treatment difference (g/dL), (95% CI)
	Daprodustat	CERA	
Efficacy ND population[a,b]	*n* = 148 12.0 (11.9–12.1)	*n* = 150 11.9 (11.8–12.0)	0.1 (–0.0 to 0.3)
ITT population using evaluable Hgb[b,c]	*n* = 108 12.0 (11.9–12.1)	*n* = 109 11.9 (11.8–12.0)	0.1 (–0.1 to 0.3)
Modified ITT population[d]	*n* = 88 12.0 (11.9–12.1)	*n* = 87 11.9 (11.8–12.0)	0.1 (–0.1 to 0.3)
Per-protocol population[e]	*n* = 84 12.0 (11.9–12.1)	*n* = 81 11.9 (11.7–12.0)	0.1 (–0.1 to 0.3)

[a]Efficacy ND population included participants with at least 1 Hgb measurement at baseline and 1 scheduled visit thereafter.
[b]Participants who had Hgb only at baseline and week 2 were not included in the analysis.
[c]Evaluable Hgb was based on Hgb values that were not taken within the 8 weeks following a transfusion or a nonrandomized ESA medication during treatment period.
[d]Modified ITT population included ITT participants with at least 1 Hgb measurement during the efficacy evaluation period.
[e]Per-protocol population included all modified ITT participants with no major protocol deviations.
CERA, continuous erythropoietin receptor activator (epoetin beta pegol); CI, confidence interval; Hgb, hemoglobin, ITT, intent-to-treat population; ND, not on dialysis.

Supplementary Table 7. Mean hemoglobin during the primary efficacy evaluation period (ITT population)

Analysis of mean Hgb during the primary efficacy evaluation period			
	Mean Hgb (g/dL)[a], (95% CI)		Treatment difference (g/dL), (95% CI)
	Daprodustat	CERA	
	n = 108	*n* = 109	
Overall	12.0 (11.8–12.1)	11.9 (11.7–12.0)	0.1 (–0.1 to 0.3)
	n = 50	*n* = 50	
ESA-naïve	11.9 (11.8–12.0)	11.7 (11.5–11.8)	0.2 (0.0–0.5)
	n = 58	*n* = 59	
ESA User	12.0 (11.8–12.2)	12.0 (11.8–12.2)	-0.0 (–0.3 to 0.2)
Analysis of number (%) of participants with mean Hgb in the target range (11.0–13.0 g/dL) during the primary efficacy evaluation period			
	Responder[b], *n* (%)		Odds ratio (95% CI)
	n = 88	*n* = 87	
Overall	81 (92)	80 (92)	1.0 (0.3–3.0)
	n = 45	*n* = 36	
ESA-naïve	43 (96)	32 (89)	2.4 (0.4–14.2)
	n = 43	*n* = 51	
ESA User	38 (88)	48 (94)	0.5 (0.1–2.3)

[a]Participants with hemoglobin at only baseline and Week 2 are not included in the analysis.
[b]Responder is defined as a participant with the mean Hgb within the target range during the primary efficacy evaluation period.
CERA, continuous erythropoietin receptor activator (epoetin beta pegol). CI, confidence interval; ESA, erythropoietin-stimulating agent; Hgb, hemoglobin; ITT, intent-to-treat population.

Supplementary Table 8. Mean duration within the target range for hemoglobin level during the primary efficacy evaluation period (ITT population)

	Mean time within target range (weeks)[a], (SD)		
	Daprodustat	CERA	Treatment difference (Weeks)[b], (95% CI)
	n = 88	*n* = 87	
Overall	10.2 (2.8)	9.4 (3.3)	0.8 (–0.1 to 1.7)
	n = 45	*n* = 36	
ESA-naïve	10.5 (2.6)	8.7 (3.6)	1.8 (0.4–3.2)
	n = 43	*n* = 51	
ESA user	9.9 (2.9)	9.9 (3.0)	0.0 (–1.2 to 1.2)

[a]Time within range is calculated for participants with hemoglobin measurements observed in both scheduled and unscheduled visits on and after Week 40.
[b]Treatment difference (daprodustat – CERA) for the weeks within the target range is provided.
CERA, continuous erythropoietin receptor activator (epoetin beta pegol); CI, confidence interval; ESA, erythropoietin-stimulating agent; ITT, intent-to-treat; SD, standard deviation.

Supplementary Table 9. Distribution of dose[a,b] during the primary efficacy evaluation period (ITT population)

	Daprodustat		CERA	
	ESA-naïve (*n* = 50)	ESA user (*n* = 58)	ESA-naïve (*n* = 50)	ESA user (*n* = 59)
P25	2.3 mg	3.3 mg	62.5 μg	50.0 μg
Median	4.0 mg	5.3 mg	91.7 μg	91.7 μg
P75	6.0 mg	7.3 mg	133.3 μg	150.0 μg

[a]Dose of daprodustat is mg/day.
[b]Dose of CERA was μg per 4 weeks. Dose of CERA at a scheduled visit was converted to dose per 4 weeks when the dose frequency was every 2 weeks.
CERA, continuous erythropoietin receptor activator (epoetin beta pegol); ESA, erythropoietin-stimulating agent; ITT, intent-to-treat population; P25, 25th percentile; P75, 75th percentile.

Supplementary Table 10. Number of participants treated by each dose at Week 48 (ITT population)

Daprodustat (N = 58)		Participants at Week 48	0 mg	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
	Lower ERI (N = 28)	19	3	1	3	6	3	1	1	0	0
	Higher ERI (N = 30)	24	2	0	1	7	6	1	2	2	3
CERA (N = 59)		Participants at Week 48	0 µg	25 µg	50 µg	75 µg	100 µg	150 µg	200 µg	250 µg	
	Lower ERI (N = 34)	30	1	6	8	4	5	4	1	1	
	Higher ERI (N = 25)	19	1	0	0	4	3	3	2	6	

Lower ERI: <5.27 IU/kg/week/g/dL, Higher ERI: ≥5.27 IU/kg/week/g/dL
For participants taking darbepoetin alfa, standardized dose (IU/week) = 250 x darbepoetin alfa dose (µg/week).[1]
For participants taking CERA, standardized dose (IU/week) = 208 x CERA dose (µg/week).[2]
ERI was calculated based on standardized dose divided by weight at screening and hemoglobin on Day 1.
CERA, continuous erythropoietin receptor activator (epoetin beta pegol); ERI, Erythropoietin Resistance Index; ITT, intent-to-treat population

Supplementary Table 11. Summary of on-therapy AEs of special interest (safety population[a])

Adverse event	Daprodustat (*n* = 149)	CERA (*n* = 150)
Any event, n (%)	18 (12)	21 (14)
Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access		
Any event	4 (3)	10 (7)
Cardiac failure[b]	1 (<1)	6 (4)
Cerebral infarction	1 (<1)	1 (<1)
Aortic dissection	0	1 (<1)[c]
Arrhythmia	0	1 (<1)[c]
Deep vein thrombosis	1 (<1)	0
Pulmonary congestion	0	1 (<1)
Shock hemorrhagic	1 (<1)[c]	0
Proliferative retinopathy, macular edema, choroidal neovascularization[d]		
Any event	5 (3)	5 (3)
Macular edema	2 (1)	4 (3)
Diabetic retinopathy	2 (1)	1 (<1)
Neovascular age-related macular degeneration	1 (<1)	0
Esophageal and gastric erosions		
Any event	6 (4)	3 (2)
Gastric ulcer	1 (<1)	1 (<1)
Gastritis	1 (<1)	1 (<1)
Gastroesophageal reflux disease	1 (<1)	1 (<1)
Barrett's esophagus	1 (<1)	0
Chronic gastritis	0	1 (<1)
Duodenal ulcer	1 (<1)	0
Erosive Gastritis	1 (<1)	0
Cancer-related mortality and tumor progression and recurrence		
Any event	3 (2)	3 (2)
Lung neoplasm malignant	1 (<1)	1 (<1)
Breast cancer	1 (<1)	0
Metastasis to skin	0	1 (<1)
Ovarian cancer	1 (<1)	0
Rectal cancer	0	1 (<1)
Renal cancer	0	1 (<1)
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis[e]	0	0
Cardiomyopathy	0	0
Pulmonary artery hypertension	0	0
Exacerbation of rheumatoid arthritis	0	0

[a]The safety population included all participants who received ≥1 dose of study medication.
[b]Includes congestive cardiac failure.
[c]Indicates fatal event.
[d]Mandatory ophthalmologic exams included best corrected visual acuity, intraocular pressure, extraocular movement, slit-lamp exam, gonioscopy, and dilated funduscopic examination. Option exams (mandatory to report if done) included confrontation field test, ocular imaging (color fundus photographs, optical coherence tomography or fluorescein angiography.
[e]For AEs of special interest potentially related to thrombosis and/or tissue ischemia, hemoglobin >13 g/dL, hemoglobin increase >2 g/dL over 2 weeks for participants who enrolled after the protocol change, or hemoglobin >4 g/dL over 4 weeks occurring within 30 days prior to and 15 days after the start of an AE of special interest were considered criteria for excessive erythropoiesis.
AE, adverse event; CERA, continuous erythropoietin receptor activator (epoetin beta pegol); MI, myocardial infarction.

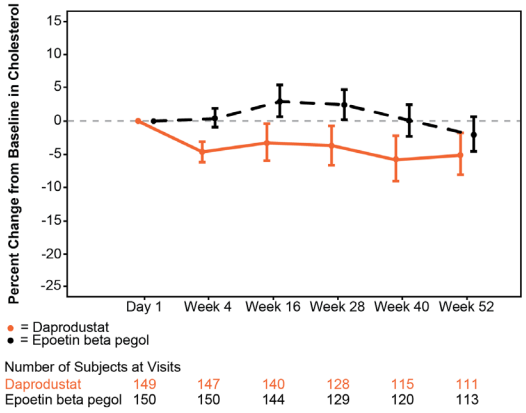
Supplementary Table 12. Mean change from baseline at week 52 in blood pressure and antihypertensive medications (safety population[a])

	Daprodustat (*n* = 149)	CERA (*n* = 150)
Systolic blood pressure (mmHg)		
Baseline		
n	149	150
Mean (SD)	135.5 (17.0)	136.7 (16.6)
Change from baseline at Week 52		
n	111	113
Mean (SD)	-1.5 (20.8)	-0.5 (19.1)
Diastolic blood pressure (mmHg)		
Baseline		
n	149	150
Mean (SD)	71.0 (12.7)	72.6 (11.7)
Change from baseline at Week 52		
n	111	113
Mean (SD)	2.2 (10.3)	1.6 (12.2)
Change in antihypertensive medications due to increased blood pressure		
Participants with change in antihypertensive medications during treatment period	57 (38)	68 (45)

[a]The safety population included all participants who received at least 1 dose of study medication.
CERA, continuous erythropoietin receptor activator (epoetin beta pegol); SD, standard deviation.

Supplementary Fig. 1. Percent change from baseline in lipid parameters over time (safety population).

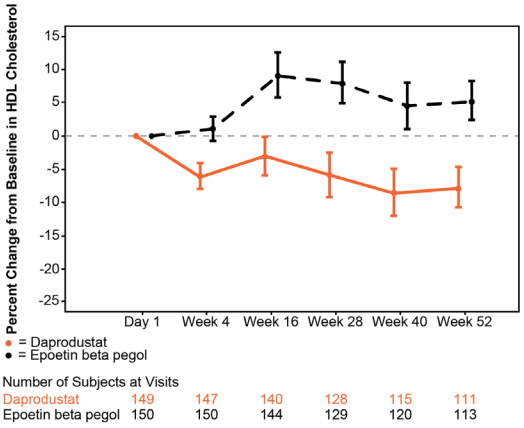
A. Total cholesterol



Number of Subjects at Visits

Daprodustat	149	147	140	128	115	111
Epoetin beta pegol	150	150	144	129	120	113

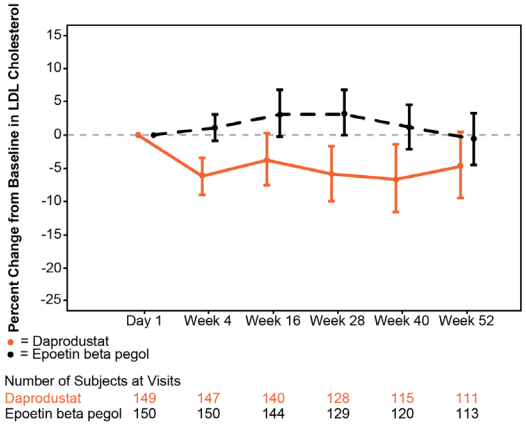
B. HDL cholesterol



Number of Subjects at Visits

Daprodustat	149	147	140	128	115	111
Epoetin beta pegol	150	150	144	129	120	113

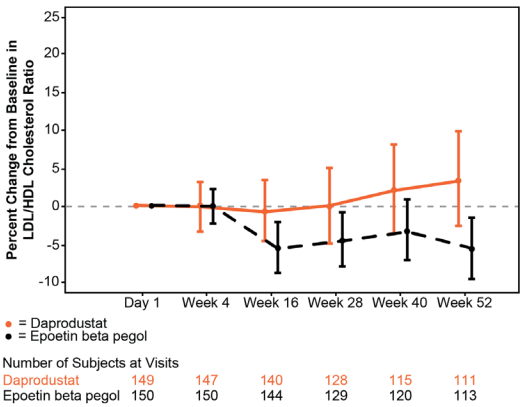
C. LDL cholesterol



Number of Subjects at Visits

Daprodustat	149	147	140	128	115	111
Epoetin beta pegol	150	150	144	129	120	113

D. LDL/HDL ratio



Number of Subjects at Visits

Daprodustat	149	147	140	128	115	111
Epoetin beta pegol	150	150	144	129	120	113

Orange solid lines represent time courses of values in Daprodustat users. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

References

1. Sterner G, Prutz KG. Conversion from epoetin beta to darbepoetin: what is the equivalent dose? Nephrol Dial Transplant. 2008 Aug; 23:4084.

2. Choi P, Farouk M, Manamley N, Addison J. Dose Conversion Ratio in Hemodialysis Patients Switched from Darbepoetin Alfa to PEG-Epoetin Beta: AFFIRM Study. Adv Ther. 2013 Oct;30:1007-1017.