Supplemental Material Table of Contents

Supplemental Item 1. Full Inclusion and Exclusion Criteria

Inclusion Criteria: A participant was eligible for inclusion in this study only if all of the following criteria applied at screening and day 1 (unless otherwise specified):

- Age (at informed consent): ≥20 years of age
- On hemodialysis or hemodiafiltration given 3 times weekly for at least 12 weeks before screening
- Use of the same ESA for at least 10 weeks before screening
    - ESA dose: Darbepoetin alfa 10 to 60 µg per week, epoetin (including biosimilars) ≤9000 IU per week, or epoetin beta pegol up to 250 µg per 4 weeks. Note: ESA dose must have been greater than the minimum ESA dose if hemoglobin >12.0 g/dL to 12.5 g/dL (minimum ESA dose: epoetins [including biosimilars], 1500 U per week; darbepoetin alfa, 10 µg per week; and epoetin beta pegol, 25 µg every 4 weeks)
- Hemoglobin: ≥9.5 g/dL and ≤12.5 g/dL, determined by a hemoglobin analyzer (HemoCue) at the site
- Ferritin >100 ng/mL or TSAT >20% (screening verification only)
- Not pregnant, having no childbearing potential, and not breastfeeding
- Females of childbearing potential had to agree to comply with one of the contraception methods from 28 days prior to the first dose of study drug

until the completion of the follow-up visit

- Written informed consent, including adherence to the requirements and conditions specified in the consent form and the protocol, must have been obtained from each participant as specified in the protocol, Section 10.2

Exclusion Criteria: A participant was not eligible for inclusion in this study if any of the following criteria applied at screening or day 1 unless otherwise specified:

CKD-related criteria

- Planned living-related kidney transplant during the study

Anemia-related criteria

- History of bone marrow hypoplasia or pure red cell aplasia
- Other causes of anemia including pernicious anemia, thalassemia, sickle cell anemia, or myelodysplastic syndromes
- Evidence of actively bleeding gastric, duodenal, or esophageal ulcer or clinically significant gastrointestinal bleeding within 10 weeks before screening or during a period from screening to day 1

Cardiovascular disease-related criteria

- Myocardial infarction, acute coronary syndrome, stroke, or transient ischemic attack: Diagnosed within 10 weeks before screening or during a period from screening to day 1
- Chronic Class IV heart failure, as defined by the New York Heart

Association (NYHA) functional classification system

- Corrected QT (QTc) interval (screening verification only): QTc >500 msec; or QTc >530 msec in patients with bundle branch block. QT interval corrected using the Bazett formula (QTcB) was used, and ECG could be mechanically or manually read

Other disease-related criteria

- Liver disease (if any of the following occurred):
    - Alanine aminotransferase (ALT) >2×upper limit of normal (ULN) (screening verification only)
    - Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN was acceptable if bilirubin was fractionated and direct bilirubin was <35%) (screening verification only)
    - Current unstable active liver or biliary disease (generally defined by the onset of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal/gastric varices, persistent jaundice, or cirrhosis)

  Note: Stable liver disease (including asymptomatic gallstones, chronic hepatitis B/C, or Gilbert's syndrome) was acceptable if the patient otherwise met entry criteria

- History of malignancy within 2 years before screening, currently receiving treatment for cancer, or complex kidney cyst >3 cm (II F, III, or IV based on the Bosniak classification)

Note: The only exception was localized squamous cell or basal cell carcinoma of the skin that had been definitively treated ≥10 weeks before screening

Concomitant medication and other study treatment-related criteria

- Planned use of IV iron during the screening phase or during a period from day 1 to week 4. Note: Oral iron was acceptable. However, the same dose regimen must have been used throughout the screening phase and from day 1 to week 4. Antihyperphosphatemic agents containing iron (eg, ferric citrate hydrate) were also acceptable only if used for at least 12 weeks before screening. However, they must have been continued throughout the screening phase and from day 1 to week 4
- History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (see the daprodustat investigator's brochure [IB] or the prescribing information for darbepoetin alfa)
- Use or planned use of any prescription or nonprescription drugs or dietary supplements that was prohibited during the study period (prohibited medications: strong inducers and inhibitors of cytochrome P450 [CYP] 2C8)
- Use of an investigational agent within 30 days or 5 half lives of the investigational agent (whichever was longer)
- Any prior treatment with daprodustat for a treatment duration of >30 days
- Any other condition, clinical or laboratory abnormality, or examination

finding considered by the investigator (or sub-investigator) would put the patient 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:

Participants were withdrawn from the study if their hemoglobin levels fell below 7.5 g/dL (based on the average of 2 HemoCue hemoglobin values of the same sample). Other withdrawal criteria included kidney transplant, pregnancy, new or recurrent cancer, liver chemistry abnormalities exceeding threshold criteria, and the need for chronic use of prohibited medication (ie, CYP2C8 inhibitors/inducers).

Supplemental Table 1. Dose Adjustment Algorithm (Daprodustat)

Hemoglobin (g/dL)	Hemoglobin increase over 4 weeks (g/dL)	Treatment
>13.0	NA	Interrupt treatment (and administer placebo) until hemoglobin decreases to less than 12.0 g/dL, and resume treatment at the one lower dose level (If interrupted [and placebo administered] at 1 mg, resume treatment at 1 mg after the one-step dose increase criterion is met)
≥12.0 and ≤13.0	NA	One-step dose reduction
≥10.0 and <12.0	>2.0	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
≥7.5 and <10.0	>2.0	One-step dose reduction
	0.5–2.0	Continue treatment at the current dose level
	<0.5	One-step dose increase
<7.5	NA	Discontinue treatment permanently[a] and initiate another appropriate treatment

[a]If an initial hemoglobin value was < 7.5 g/dL, measurement was repeated at the same study visit (using the same sample) to calculate the average. If the average met the hemoglobin stopping criteria, study treatment was required to be permanently discontinued.

Supplemental Table 2. Dose Adjustment Algorithm (Darbepoetin Alfa)

Hemoglobin (g/dL)	Treatment
>13.0	Interrupt treatment (and administer placebo) until Hgb decreases to less than 12.0 g/dL, and resume treatment at the one lower dose level (If interrupted [and placebo administered] at 10 µg, resume treatment at 10 µg after the one-step dose increase criterion is met)
≥12.0 and ≤13.0	One-step dose reduction
≥10.0 and <12.0	Continue treatment at the current dose level[a]
≥7.5 and <10.0	One-step dose increase[b]
<7.5	Discontinue treatment permanently[c] and initiate another appropriate treatment

[a]If hemoglobin >1 g/dL increase over 2 weeks, the dose was reduced to the one-step lower dose level.
[b]If hemoglobin >1 g/dL increase over 2 weeks, treatment was continued at the same dose level. If there was a safety concern, however, the dose reduction was allowed at the investigator's (or sub-investigator's) discretion to the one-step lower dose level.
[c]If an initial hemoglobin value was <7.5 g/dL, measurement was repeated at the same study visit (using the same sample) to calculate the average. If the average met the hemoglobin stopping criteria, study treatment was required to be permanently discontinued.

Supplemental Table 3. Number (%) of Participants with a Hemoglobin Increase of >2.0 g/dL over Any 4 Weeks (ITT Population)

	Daprodustat (N = 133)	Darbepoetin alfa (N = 134)
Number of participants, n (%)	1 (<1)	2 (1)

CI, confidence interval; ITT, intent-to-treat.

Supplemental Table 4. Number (%) of Participants with a Hemoglobin Level >13.0 g/dL and Number of Episodes (ITT Population)

	Daprodustat (N = 133)	**Darbepoetin alfa (N = 134)**
Number of participants, n (%)	7 (5)	8 (6)
Number of episodes	9	12

Includes hemoglobin values measured during both scheduled and unscheduled visits.
ITT, intent-to-treat.

Supplemental Table 5 Adverse Events of Special Interest (Safety Population)

AE, n (%)	Daprodustat (N = 136)	Darbepoetin Alfa (N = 135)
Death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access	**9 (7)**	**10 (7)**
Arteriosclerosis coronary artery	0	1 (<1)
Cardiac failure[a]	1 (<1)	2 (1)
Cerebral infarction	1 (<1)	1 (<1)
Pulmonary edema	0	1 (<1)
Retinal vein occlusion	2 (1)	1 (<1)
Retinal artery occlusion	0	1 (<1)
Shunt events[b]	4 (3)	4 (3)
Venous occlusion	1 (<1)	0
Esophageal and gastric erosions	**3 (2)**	**5 (4)**
Gastritis erosive	2 (1)	2 (1)
Chronic gastritis	0	1 (<1)
Duodenal perforation	1 (<1)	0
Gastric ulcer	0	1 (<1)
Hemorrhagic erosive gastritis	0	1 (<1)
Proliferative retinopathy, macular edema, choroidal neovascularization	**4 (3)**	**4 (3)**
Macular edema	2 (1)	2 (1)
Anterior chamber angle neovascularization	2 (1)	1 (<1)
Retinal hemorrhage	0	1 (<1)
Cardiomyopathy	**0**	**1 (<1)**
Hypertensive cardiomyopathy	0	1 (<1)
Pulmonary artery hypertension	**1 (<1)**	**0**
Pulmonary hypertension	1 (<1)	0
Cancer-related mortality and tumor progression and recurrence	**0**	**1 (<1)**

Pancreatic carcinoma	0	1 (<1)
Exacerbation of rheumatoid arthritis	**0**	**1 (<1)**
Rheumatoid arthritis	0	1 (<1)
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	**0**	**0**

[a]Cardiac failure and cardiac failure congestive.
[b]Shunt malfunction, shunt occlusion, shunt stenosis, shunt thrombosis.
AE, adverse event

Supplemental Table 6. Systolic and Diastolic Blood Pressure at Week 52 (Safety Population)

	Daprodustat (N = 136) Post Dialysis	Darbepoetin Alfa (N = 135) Post Dialysis
Systolic blood pressure (mmHg)		
Baseline, n	**136**	**135**
Mean ± SD	139 (23)	137 (23)
Change from baseline at week 52, n	**115**	**119**
Mean ± SD	-1 (24)	2 (27)
Diastolic blood pressure (mmHg)		
Baseline, n	**136**	**135**
Mean ± SD	78 (14)	78 (13)
Change from baseline at week 52, n	**115**	**119**
Mean ± SD	-1 (13)	1 (15)
HTN medications changed due to increased BP, n (%)	**51 (38)**	**66 (49)**

BP, blood pressure; HTN, hypertension; SD, standard deviation.

Supplemental Table 7. Change from Baseline in Potassium (mmol/L) (Safety Population)

	Daprodustat (N = 136)	Darbepoetin alfa (N = 135)
Baseline		
n	136	135
Mean (SD)	5.0 (0.8)	5.0 (0.7)
Change from Baseline at Week 4		
n	133	134
Mean (SD)	0.0 (0.5)	0.0 (0.5)
Change from Baseline at Week 16		
n	123	129
Mean (SD)	-0.1 (0.5)	-0.1 (0.6)
Change from Baseline at Week 28		
n	122	126
Mean (SD)	-0.1 (0.6)	-0.1 (0.6)
Change from Baseline at Week 40		
n	120	125
Mean (SD)	-0.1 (0.6)	-0.1 (0.6)
Change from Baseline at Week 52		
n	115	120
Mean (SD)	-0.1 (0.6)	-0.1 (0.6)

Note: Baseline value is derived from the latest pre-dose assessment.
SD, Standard deviation.

Supplemental Table 8. Potassium Results: Post-Baseline Relative to Baseline (Safety Population)

Change Category (lower/upper boundary of clinical concern)	Daprodustat (N = 136)	Darbepoetin Alfa (N = 135)
n	136	134
Low (>0.5 mmol/L below LLRR), n (%)	1 (<1)	0
Within range or no change, n (%)	120 (88)	109 (81)
High (>1.0 mmol/L above ULRR), n (%)	15 (11)	25 (19)

Note: Participants are counted in the category that their value changes to (low, within range or no change, or high), unless there is no change in their category. Participants whose lab value category was unchanged (eg, high to high), or whose value became within range, are recorded in the “To within range or no change” category. Participants are counted twice if they had values that changed “To low” and ”To high", so the percentages may not add to 100%. Participants with a missing baseline value are assumed to have a within range value.
ULRR, Upper limit of normal range; LLRR, Lower limit reference range.

Supplemental Table 9. Institutional Review Board

Institutional Review Board List	
Institution Name	Name of IEC/IRB
Kasugai Municipal Hospital	Kasugai Municipal Hospital, Institutional Review Board 1-1-1, Takaki-cho, Kasugai-city, Aichi, 486-8510, Japan
Fukui-ken Saiseikai Hospital	Fukui-ken Saiseikai Hospital, Institutional Review Board 7-1, Funabashi, Wadanaka-cho, Fukui-city
Higashinaebo Hospital	Higashinaebo Hospital, Institutional Review Board
Japanese Red Cross Society Azumi Hospital	Japanese Red Cross Society Azumi Hospital, Institutional Review Board 5685, Toyoshina, Azumino-city, Nagano-ken
Kasaoka Daiichi Hospital	Jinbo Orthopedic Clinic, Institutional Review Board
Miyaji Clinic	
Hasegawa Hospital	
Kasugai Municipal Hospital	Kasugai Municipal Hospital, Institutional Review Board 1-1-1, Takaki-cho, Kasugai-city, Aichi, 486-8510, Japan
Kurobe City Hospital	Kurobe City Hospital, Institutional Review Board 1108-1, Mikkaichi, Kurobe-city, Toyama, 938-8502, Japan
Anjou Kyoritsu Clinic	Nagoya Kyoritsu Hospital, Institutional Review Board 1-172 Hokke, Nakagawa-ku, Nagoya-shi
Meiko Kyoritsu Clinic	
Kaikoukai Central Clinic	
Medical Corporation Kaikoukai Hekikai Kyoritsu Clinic	
Medical Corporation Jiyoukai Akagaki Clinic	Nihonbashi Sakura Clinic, Institutional Review Board 1-9-2 Nihonbashi Kayaba-cho, Chuo-ku, Tokyo, 103-0025, Japan
Kano Hospital Medical Corporation Houshikai	
Fukuoka Wajiro Hospital	
Takayama Hospital	
Meiyo Clinic	Review Board of Human Rights and Ethics for Clinical Studies Ethics Review Committee 13-2 Ichibancho, Chiyoda-ku, Tokyo
Matsumoto City Hospital	
Kanno Dialysis & Vascular Access Clinic	
Kohitsujikai Group Naganuma Clinic	
Yokohama Jin Clinic	
Suda Clinic	
Kamiiida Clinic	
Kyoto Okamoto Memorial Hospital	
Ora Hospital	
Kusunoki Hospital	
Isesaki Municipal Hospital	
Social medical corporation Seichokai Fuchu Hospital	
Nozaki Clinic	
Oda Clinic	

Kuwajima Clinic	Sugiura Clinic, Institutional Review Board Rm301, 4-4-16, Honcho, Kawaguchi-shi, Saitama
Jusendo Clinic	
Tsuchiura Beryl Clinic	
Medical Corporation Hakuyukai Kikuchi Internal Medicine Clinic	
Kinashi Obayashi Hospital	
Tenjin Clinic	
Futakotamagawaeki mae Clinic	
St. Hill Hospital	
Kawadairanaika Medical Clinic	
Houshinkai Yokodai Central Clinic	
Houshinkai Yokohama Minami Clinic	
Tachibanadai Hospital	
Tokiwa Clinic	
Suzuki Clinic	
Sunagawa City Medical Center	Sunagawa City Medical Center, Institutional Review Board 3-1-1, Nishi4-jo Kita, Sunagawa-city
Hosaka Clinic	Supporo Dermatology Clinic, Institutional Review Board Minami 3 Jo Nishi 2 Chome 1-1, Chuo-ku, Sapporo-shi
Takikawa Municipal Hospital	Takikawa Municipal Hospital, Institutional Review Board 2-2-34, Omachi, Takikawa-city
Social Welfare Organization Saiseikai Imperial Gift Foundation, Inc. Osaka prefecture branch of Saiseikai Tondabayashi Hospital	Tokai Memorial Hospital, Institutional Review Board 681-47 Ohhora Hazama-cho, Kasugai-shi, Aichi-ken
Yamagata Tokushukai Hospital	Tokushukai Group, Institutional Review Board 1-8-7, Koji-machi, Chiyoda-ku, Tokyo 102-0083, Japan
Hanyu General Hospital	