

Additional file 1

Table S1. Hemoglobin Over Time and Change from Baseline (ITT Population)

Hgb (g/dL)	Placebo	Daprodustat Total	Daprodustat Dose			
			10 mg	15 mg	25 mg	30 mg
Baseline,^a n	18	79	20	18	21	20
Mean±SD	10.6±0.75	10.6±0.69	10.6±0.71	10.7±0.77	10.4±0.59	10.5±0.73
Day 15, n	18	79	20	18	21	20
Mean±SD	10.3±0.97	10.7±0.93	10.5±1.19	10.6±0.87	10.9±0.78	10.9±0.85
Change from Baseline						
Mean±SD	-0.3±0.52	0.2±0.91	-0.1±0.84	0.0±0.97	0.5±0.79	0.4±0.93
Day 29, n	17	67	19	16	17	15
Mean±SD	10.0±1.12	10.8±1.40	10.4±1.83	10.5±0.93	11.1±1.33	11.3±1.15
Change from Baseline						
Mean±SD	-0.6±0.65	0.2±1.43	-0.2±1.75	-0.1±1.09	0.6±1.45	0.6±1.17
Day 29 (imputed),^b n	18	79	20	18	21	20
Mean±SD	9.8±1.34	11.0±1.54	10.5±1.85	10.4±1.22	11.3±1.36	11.7±1.39
Change from Baseline						
Mean±SD	-0.7±0.83	0.5±1.68	-0.1±1.73	-0.2±1.36	0.9±1.47	1.2±1.74

Hgb, hemoglobin; *ITT*, intention-to-treat; *SD*, standard deviation.

^aThe average of hemoglobin measured by the central lab at week -2 and day 1 visits.

^bIncluding participants (1 on placebo and 12 on daprodustat) who had a day 15 hemoglobin value but were missing a day 29 value.

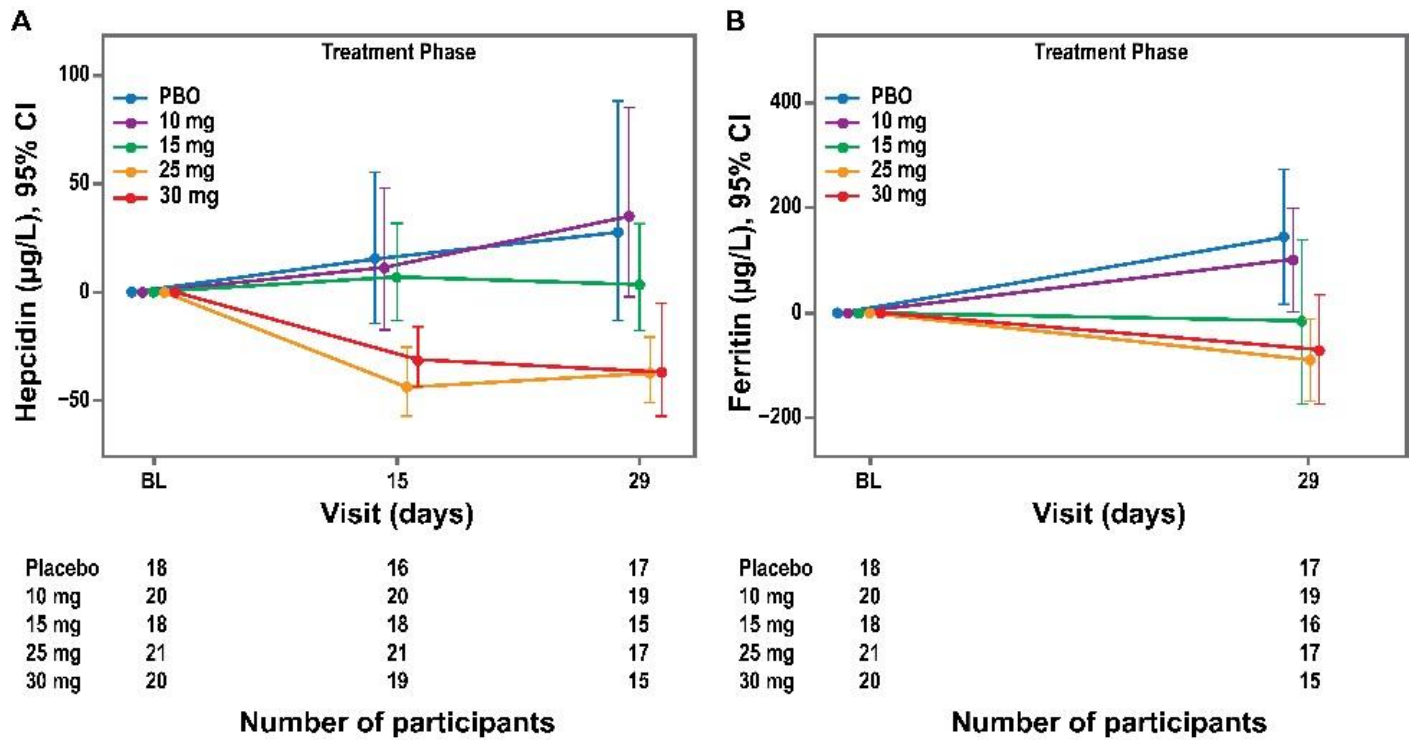
Table S2. Repeated Measure Analysis for Hemoglobin Change from Baseline at Day 29 (ITT Population)

Hgb (g/dL)	Daprodustat Dose				
	Placebo	10 mg	15 mg	25 mg	30 mg
<i>Model-Adjusted Change from Baseline at Day 29^a</i>					
Adjusted mean±SE (95% CI)	-0.7±0.32 (-1.33 to -0.06)	-0.1±0.30 (-0.73-0.48)	-0.2±0.32 (-0.83-0.46)	0.8±0.31 (0.16-1.38)	1.0±0.32 (0.33-1.61)
<i>Model-Adjusted Difference from Placebo^a</i>					
Adjusted mean (95% CI)	--	0.6 (-0.31-1.45)	0.5 (-0.40-1.42)	1.5 (0.59-2.35)	1.7 (0.77-2.57)

CI, confidence interval; Hgb, hemoglobin; ITT, intention-to-treat; SE, standard error.

^aUsing a repeated measures model with terms included for baseline, treatment, time, and treatment*time. Least squares mean estimates and treatment differences of daprodustat group to placebo along with 95% CI are provided.

Figure S1. A) Geometric Mean Change from Baseline and 95% CI for Hepcidin (ITT Population) and B) Mean Change from Baseline and 95% CI for Ferritin (ITT Population)



BL, baseline; CI, confidence interval; ITT, intention-to-treat; PBO, placebo.

Table S3. Change from Baseline in Markers of Iron Metabolism at Day 29 (ITT Population)

	Placebo	Daprodustat Total	Daprodustat Dose			
			10 mg	15 mg	25 mg	30 mg
Transferrin (g/L)						
Baseline^a, n	18	79	20	18	21	20
Mean±SD	1.6±0.36	1.6±0.30	1.6±0.28	1.6±0.39	1.6±0.29	1.6±0.26
Day 29, n	17	67	19	16	17	15
Mean±SD	1.7±0.33	1.7±0.40	1.6±0.25	1.9±0.44	1.7±0.40	1.9±0.44
Absolute Change from Baseline						
Mean±SD	0.06±0.265	0.12±0.313	-0.01±0.238	0.15±0.246	0.08±0.379	0.31±0.309
TIBC (μmol/L)						
Baseline^a, n	18	79	20	18	21	20
Mean±SD	39.8±7.97	37.7±6.47	36.7±6.51	38.1±8.66	37.9±5.29	38.1±5.60
Day 29, n	17	67	19	16	17	15
Mean±SD	39.2±7.00	41.3±7.44	36.9±5.85	43.8±8.54	41.1±6.55	44.6±6.73
Absolute Change from Baseline						
Mean±SD	0.1±3.42	3.7±4.52	0.5±4.72	4.3±3.11	3.5±3.36	7.2±4.13
UIBC (μmol/L)						
Baseline^a, n	18	79	20	18	21	20
Mean±SD	25.9±6.50	25.5±6.21	25.3±6.05	25.8±7.04	26.0±6.09	25.1±6.13
Day 29, n	17	67	19	16	17	15
Mean±SD	23.6±7.58	27.5±8.20	24.6±6.84	27.8±10.91	29.1±7.30	28.9±7.13
Absolute Change from Baseline						
Mean±SD	-1.9±6.67	2.1±7.51	-0.4±7.38	1.1±8.56	3.6±5.04	4.6±8.28
CHr (pg)						
Baseline^a, n	18	79	20	18	21	20
Mean±SD	32.1±2.19	31.4±1.86	31.6±1.84	31.1±2.06	31.2±1.57	31.5±2.05
Day 29, n	16	64	19	14	16	15
Mean±SD	31.6±2.03	31.7±1.89	32.0±1.41	31.4±1.95	31.5±2.04	32.0±2.27
Absolute Change from Baseline						
Mean±SD	-0.2±1.38	0.3±1.22	0.2±1.34	0.3±1.10	0.2±1.04	0.6±1.44
Total Iron (μmol/L)						
Baseline^a, n	18	79	20	18	21	20
Mean±SD	13.9±4.38	12.1±4.62	11.4±4.32	12.3±4.35	11.9±5.33	13.0±4.54
Day 29, n	17	67	19	16	17	15

Mean±SD	15.6±6.85	13.9±6.19	12.4±5.59	16.0±6.44	11.9±4.53	15.7±7.51
Absolute Change from Baseline						
Mean±SD	2.0±6.08	1.6±6.97	0.9±6.72	3.2±8.11	-0.1±5.85	2.6±7.27
TSAT (%)						
Baseline^a, n	18	79	20	18	21	20
Geometric mean (CV%)	33.7 (26.95)	30.7 (35.66)	28.9 (42.76)	31.4 (29.03)	29.9 (38.66)	32.7 (31.61)
Day 29, n	17	67	19	16	17	15
Geometric mean (CV%)	36.9 (42.82)	30.6 (49.05)	30.0 (54.01)	34.5 (45.38)	26.9 (46.69)	31.8 (49.99)
Relative % Change from Baseline						
geometric mean	9.9	-1.7	2.7	9.7	-12.9	-4.9

CHr, reticulocyte hemoglobin; *CV*, coefficient of variation; *ITT*, intention-to-treat; *SD*, standard deviation; *TIBC*, total iron binding capacity; *TSAT*, transferrin saturation; *UIBC*, unsaturated iron binding capacity.

^aThe day 1 pre-dose value.

Table S4. Change from Baseline in Indices of Hematopoiesis (ITT Population)

	Placebo	Daprodustat Total	Daprodustat Dose			
			10 mg	15 mg	25 mg	30 mg
Hematocrit (%)						
Baseline^a, n	18	79	20	18	21	20
Mean±SD	33.0±3.39	32.8±3.02	33.1±2.31	33.7±4.31	32.5±2.78	32.1±2.43
Day 15, n	17	77	19	18	20	20
Mean±SD	32.4±2.88	33.3±3.25	32.4±3.71	32.6±2.82	34.2±3.09	33.9±3.15
Absolute Change from Baseline						
Mean±SD	-1.0±2.00	0.5±3.63	-0.7±2.19	-1.2±4.94	1.7±2.75	1.8±3.38
Day 29, n	16	64	19	14	16	15
Mean±SD	31.3±3.61	33.2±4.62	31.7±6.19	32.4±2.97	34.1±4.00	34.9±3.73
Absolute Change from Baseline						
Mean±SD	-2.2±2.47	0.2±5.01	-1.3±5.40	-1.5±5.38	1.5±4.51	2.2±3.85
RBC Count (10¹²/L)						
Baseline^a, n	18	79	20	18	21	20
Mean±SD	3.4±0.37	3.5±0.38	3.5±0.30	3.6±0.49	3.4±0.31	3.4±0.38
Day 15, n	17	76	19	17	20	20
Mean±SD	3.4±0.31	3.5±0.38	3.4±0.41	3.5±0.34	3.5±0.29	3.5±0.47
Absolute Change from Baseline						
Mean±SD	-0.1±0.18	0.0±0.32	-0.1±0.21	-0.1±0.46	0.1±0.25	0.10±0.30
Day 29, n	16	64	19	14	16	15
Mean±SD	3.3±0.43	3.5±0.51	3.3±0.57	3.5±0.46	3.6±0.40	3.6±0.55
Absolute Change from Baseline						
Mean±SD	-0.2±0.26	0.0±0.45	-0.1±0.49	-0.1±0.50	0.1±0.42	0.2±0.34
Reticulocyte Count (%)						
Baseline^a, n	18	79	20	18	21	20
Mean±SD	1.6±0.57	1.7±0.68	1.7±0.53	1.6±0.70	1.6±0.65	1.8±0.86
Day 15, n	17	76	20	16	20	20
Mean±SD	1.2±0.53	2.0±1.14	1.4±0.73	1.8±0.82	2.5±1.46	2.4±1.03
Absolute Change from Baseline						
Mean±SD	-0.4±0.94	0.3±1.18	-0.3±0.83	0.1±0.56	0.9±1.56	0.7±1.12
Day 29, n	16	63	18	14	16	15
Mean±SD	1.5±0.62	1.8±0.82	1.6±0.78	1.7±0.98	1.9±0.75	1.9±0.81
Absolute Change from Baseline						
Mean±SD	-0.1±0.85	0.1±0.69	-0.1±0.80	0.0±0.58	0.4±0.55	0.1±0.70

ITT, intention-to-treat; *RBC*, red blood cells; *SD*, standard deviation.

^aThe day 1 pre-dose value.

Table S5. Summary of Plasma Daprodustat Pharmacokinetic Parameters Following Dose Administration of Daprodustat (PK Population)

Daprodustat Dose	PK Parameter ^a					
	n	C _{max} (ng/mL)	AUC _(0-t) (ng.h/mL)	AUC _(0-∞) (ng.h/mL)	t _{max} ^b (h)	t _{1/2} (h)
10 mg	19	140 (104.0)	312 (91.4)	348 (78.2) ^c	2.9 (1.0–12.5)	2.1 (50.0) ^c
15 mg	15	141 (248.8)	417 (168.6)	384 (142.7) ^d	2.0 (0.8–8.3)	1.9 (62.3) ^d
25 mg	16	247 (311.5)	514 (396.1)	1214 (41.6) ^e	2.0 (0.9–10.1)	1.4 (58.4) ^e
30 mg	14	387 (99.4)	1010 (92.3)	1369 (59.3) ^f	1.9 (0.9–3.1)	2.9 (38.7) ^f

AUC_{0-t}, area under the concentration-time curve from time 0 to time t; AUC_{0-∞}, area under the concentration-time curve from time 0 to time infinity; C_{max}, maximum observed plasma concentration; t_{1/2}, half-life; t_{max}, time to maximum observed plasma concentration.

^aGeometric mean (%CV).

^bMedian (range).

^cn = 12.

^dn = 9.

^en = 8.

^fn = 11.