SUPPLEMENTAL MATERIAL

Effects of Molidustat in the Treatment of Anemia in Chronic Kidney Disease

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Statistical Analysis:

A stratified block randomization procedure via an interactive response system was used to achieve a balance among stratifying factors[a)] between treatment groups across the studies. The size of the permuted blocks was two times the number of treatment groups, with equal allocation ratio per treatment group. The allocation ratio in DIALOGUE 4 was changed after the introduction of the 150 mg dose group through a protocol amendment. A 1:1:1:6:1 (150 mg was six times overrepresented) allocation ratio was used to achieve a reasonable number of patients in the 150 mg group from thereon. This resulted in a final allocation ratio of 1:1:1:0.6:1. At the randomization visit, the investigator had to check the patient's eligibility and stratification factor levels; an interactive response system subsequently randomly assigned the treatment group according to computer generated randomization lists.

Data were planned to be analyzed by descriptive statistics and listings. No formal statistical comparisons were planned. Descriptive statistics included summary tables of the endpoints showing mean and standard deviation as well as minimum, median and maximum or frequencies and percentages. Box-plots, line-plots and bar-charts were generated to support interpretation of the results.

Model-based analyses were added during the conduct of the studies to support the prespecified descriptive analyses. Inferential analyses, such as analysis of covariance (ANCOVA) and constrained longitudinal data analysis (cLDA), were evaluated using observed case data. The ANCOVA was repeated after imputation of missing data through last observation carried forward (c.f. supplemental table 5). An additional method, missing value imputation via linear interpolation from the values obtained during the 4-week period before the missing record, was also explored. Pairwise comparison of the molidustat doses to the comparators was performed within the context of these models. Furthermore, a subgroup

analysis was conducted, using baseline characteristics and treatment emergent findings to define these subgroups. In general, adjustments for multiplicity were not performed.

These analyses confirmed the results obtained by descriptive analyses.

The statistical evaluation was performed by using the Hosted SAS version release 9.3 (SAS Institute Inc., Cary, North Carolina, US). The authors had access to all data and planned analyses.

[a)] Strata used were as follows:

1) All studies
   Prior thromboembolic events (excluding hemodialysis vascular access events: arteriovenous fistula and arteriovenous graft events)
2) Dialogue 2 and 4
   Hypo-responsiveness to darbepoetin (i.e., total dose ≥ 1.8 μg/kg/week) / epoetin alfa / beta (i.e., total dose ≥ 260 IU/kg/week)

Supplemental Table 1. Key inclusion and exclusion criteria for DIALOGUEs 1, 2, and 4

<table>
<tr><th>DIALOGUE 1</th><th>DIALOGUE 2</th><th>DIALOGUE 4</th></tr>
<tr><td colspan="3">Inclusion criteria</td></tr>
<tr><td colspan="3">• Diagnosis of anemia of CKD
• Men and women ≥18 years of age
• Serum ferritin levels ≥100 μg/L and <1000 μg/L or transferrin saturation ≥20%
• Folate and vitamin B_{12} values above the lower limit of normal</td></tr>
<tr><td colspan="2">• eGFR <60 ml/min/1.73 m^2
• Not undergoing dialysis or expected to begin dialysis during the study (at least 16 weeks after randomization)</td><td>• Undergoing dialysis, defined as regular long-term hemodialysis with the same modality of dialysis for ≥3 months preceding randomization</td></tr>
<tr><td rowspan="2">• Not treated with ESA in the 8 weeks before randomization (ESA-naïve)</td><td>• Treated with stable [a] darbepoetin alfa in the 8 weeks before randomization</td><td>• Treated with stable [a] epoetin alfa/beta in the 8 weeks before randomization</td></tr>
<tr><td colspan="2">• At least one kidney</td></tr>
</table>

• Mean Hb level <10.5 g/dl	• Mean Hb level 9.0–12.0 g/dl	• Mean Hb level 9.0–11.5 g/dl
Exclusion criteria • Significant acute or chronic bleeding • Hereditary hemoglobinopathies • Aplastic anemia • Chronic inflammatory disease that could impact erythropoiesis • History of cardiovascular or cerebrovascular events in previous 6 months • Poorly controlled hypertension or hypotension [b] • Severe rhythm or conduction disturbances • Congestive heart failure (New York Heart Association class III or IV) • Severe hepatic insufficiency [c] • Treatment with immuno- or myelosuppressant therapy within 8 weeks before randomization (DIALOGUEs 1 and 4) or immunosuppressant therapy during the 7 days before randomization (DIALOGUE 2) • Previous or concurrent cancer except cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors (Ta, Tis, and T1), or any cancer curatively treated > 3 years prior to randomization		

- Use of UGT1A1 inhibitors during the 7 days before randomization

CKD, chronic kidney disease; DIALOGUE, DaIly orAL treatment increasing endOGenoUs Erythropoietin; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agents; Hb, hemoglobin; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1.

[a] DIALOGUE 2: no more than one dose change within 8 weeks prior to randomization. DIALOGUE 4: < 50% change from the maximum prescribed weekly dose with no change in the prescribed frequency during the last 8 weeks prior to randomization.

[b] Poorly controlled hypertension was defined as a mean BP ≥ 180/110 mmHg or systolic BP < 95 mmHg, respectively.

[c] Severe hepatic insufficiency was defined as alanine aminotransferase [ALT], aspartate aminotransferase [AST], or gamma-glutamyl transferase > 3 x the upper limit of normal [ULN], total bilirubin > 2 mg/dL, or Child-Pugh B or C), or active hepatitis in the investigator's opinion.

Supplemental Table 2. Daily average dosages of molidustat in (A) DIALOGUE 2 and (B) DIALOGUE 4

A Daily average dose (units[a])[b]	Molidustat Starting Dose Groups			
	25 mg N=30	50 mg N=30	75 mg N=32	Combined N=92
mean	26.3	45.6	63.1	45.4
SD	12.4	17.1	26.2	24.6
min	10	22	20	10
median	23.8	46.0	61.0	43.2
max	58	93	119	119

B Daily average dose (units[a])[b]	Molidustat Starting Dose Groups				
	25 mg N=44	50 mg N=40	75 mg N=44	150 mg N=29	Combined N=157
mean	36.6	57.5	71.7	114.5	66.2
SD	16.2	23.6	27.0	40.5	37.6
min	10	13	17	25	10
median	31.7	58.5	72.2	112.2	61.1
max	72	94	120	188	188

[a] Unit is 'mg' for molidustat groups.

[b] Daily average dose = Total cumulative dose / Treatment duration.

Supplemental Table 3. Secondary efficacy variables in the DIALOGUE program

DIALOGUE 1	DIALOGUE 2	DIALOGUE 4
• Change in local Hb level from baseline to post-baseline during the first 12-week treatment period • Rate of change of Hb level over time	• Response defined as meeting all three of the following criteria: – mean Hb level in the target range 10.0–12.0 g/dl[a] – ≥50% of Hb levels in the target range 10.0–12.0 g/dl[a] – no RBC-containing transfusion during the active treatment	• Response defined as meeting all three of the following criteria: – mean Hb level in the target range 10.0–11.0 g/dl[a] – ≥50% of Hb levels in the target range 10.0–11.0 g/dl[a] – no RBC-containing transfusion during the active treatment

• Study treatment exposure measured as duration of exposure (in days) between the dates of the first and last dose	• Time in the target range (10.0–12.0 g/dl) measured as number of days and percentage of time within range • Change from baseline in Hb level during treatment • Number and proportion of patients with: – ≥50% of Hb levels below the lower limit of 10.0 g/dl[a] – mean Hb level below the lower limit of 10.0 g/dl[a] – ≥50% of Hb levels above the upper limit of 12.0 g/dl[a] – mean Hb level above the upper limit of 12.0 g/dl[a]	• Time in the target range (10.0–11.0 g/dl) measured as number of days and percentage of time within range • Time in the target range (9.5–11.5 g/dl) measured as number of days and percentage of time within range • Number and proportion of patients with: – ≥50% of Hb levels below the lower limit of 10.0 g/dl[a] – mean Hb level below the lower limit of 10.0 g/dl[a] – ≥50% of Hb levels above the upper limit of 11.0 g/dl[a] – mean Hb level above the upper limit of 11.0 g/dl[a] • Number and proportion of patients with: – ≥50% of Hb levels below the lower limit of 9.5 g/dl[a] – mean Hb level below the lower limit of 9.5 g/dl[a]

		– ≥50% of Hb levels above the upper limit of 11.5 g/dl[a] – mean Hb level above the upper limit of 11.5 g/dl[a]
	• Patient treatment exposure by dose level (*eg* starting dose, interim titrated dose, and final titrated dose/duration of exposure on each level) • Number and percentage of patients requiring down-titration • Number and percentage of patients requiring up-titration • Change from baseline in: – reticulocyte count – RBC count • Hematocrit	

[a]During the evaluation period of the parent study (*ie*, the final 4 weeks of study treatment).

Hb, hemoglobin; RBC, red blood cell.

Supplemental Table 4. Baseline demographics and clinical characteristics in DIALOGUEs 1, 2, and 4

	Molidustat Dose Group[a]							Control Group[b]	Total
	25 mg o.d.	50 mg o.d.	75 mg o.d.	150 mg o.d.	25 mg b.i.d.	50 mg b.i.d.	Combined		
DIALOGUE 1	*n*=19	*n*=21	*n*=22	–	*n*=19	*n*=20	*n*=101	*n*=20	*n*=121
Mean age, years (SD)	69 (12)	68 (13)	71 (10)	–	70 (12)	65 (13)	69 (12)	67 (16)	68 (13)
Women, *n* (%)	5 (26)	12 (57)	9 (41)	–	9 (47)	10 (50)	45 (45)	11 (55)	56 (46)
Race, *n* (%)									
White	14 (74)	11 (52)	13 (59)	–	15 (79)	10 (50)	63 (62)	15 (75)	78 (64)
Asian	5 (26)	10 (48)	9 (41)	–	4 (21)	10 (50)	38 (38)	5 (25)	43 (36)
Black	0	0	0	–	0	0	0	0	0

Other	0	0	0	–	0	0	0	0	0
Mean CKD duration, years (SD)	3.8 (4.1)	6.6 (6.2)	4.2 (3.5)	–	2.2 (2.9)	5.1 (4.3)	4.5 (4.5)	3.5 (2.7)	4.3 (4.3)
CKD etiology, *n* (%)[c]									
Diabetes	12 (63)	8 (38)	9 (41)	–	9 (47)	7 (35)	45 (45)	9 (45)	54 (45)
Hypertension	9 (47)	12 (57)	12 (55)	–	7 (37)	5 (25)	45 (45)	6 (30)	51 (42)
Mean eGFR, ml/min/1.73 m^2 (SD)[d]	25 (14)	23 (11)	24 (10)	–	25 (12)	21 (14)	23 (12)	23 (12)	23 (12)
Mean Hb level, g/dl (SD)	9.4 (0.7)	9.5 (0.7)	9.6 (0.6)	–	9.3 (0.5)	9.5 (1.1)	9.5 (0.7)	9.5 (0.6)	9.5 (0.7)

Mean CRP, mg/L (SD)	8.8 (12.6)	4.9 (10.1)	6.0 (9.8)	- -	13.3 (31.8)	3.5 (6.0)	7.2 (16.4)	4.3 (5.1)	6.7 (15.2)
DIALOGUE 2	*n*=30	*n*=30	*n*=32	–	–	–	*n*=92	*n*=32	*n*=124
Mean age, years (SD)	66 (9)	65 (10)	73 (11)	–	–	–	68 (11)	69 (9)	68 (10)
Women, *n* (%)	18 (60)	13 (43)	16 (50)	–	–	–	47 (51)	14 (44)	61 (49)
Race, *n* (%)									
White	21 (70)	23 (77)	25 (78)	–	–	–	69 (75)	25 (78)	94 (76)
Asian	9 (30)	7 (23)	6 (19)	–	–	–	22 (24)	6 (19)	28 (23)
Black	0	0	1 (3)	–	–	–	1 (1)	1 (3)	2 (2)
Other	0	0	0	–	–	–	0	0	0

Mean CKD duration, years (SD)	6.6 (7)	8.2 (8)	5.5 (3)	–	–	–	6.7 (6)	5.8 (5)	6.5 (6)
CKD etiology, *n* (%)[c]									
Diabetes	12 (40)	6 (20)	13 (41)	–	–	–	31 (34)	10 (31)	41 (33)
Hypertension	10 (33)	15 (50)	6 (19)	–	–	–	31 (34)	13 (41)	44 (36)
Mean eGFR, ml/min/1.73 m^2 (SD)[d]	20 (10)	18 (9)	23 (14)	–	–	–	20 (11)	22 (12)	21 (12)
Mean Hb level, g/dl (SD)	10.9 (0.7)	10.7 (0.7)	10.7 (0.7)	–	–	–	10.8 (0.7)	10.9 (0.7)	10.8 (0.7)
Mean prior ESA dose	0.2 (0.2)	0.2 (0.1)	0.2 (0.3)	-	-	-	0.2 (0.2)	0.3 (0.2)	0.2 (0.2)

(µg/kg/week) prior to randomization (SD)									
Mean CRP, mg/L (SD)	5.9 (7.6)	7.7 (15.4)	8.7 (19.2)	- -	- -	- -	7.4 (14.9)	6.5 (11.2)	7.2 (14.0)
DIALOGUE 4	*n*=44	*n*=40	*n*=44	*n*=29	–	–	*n*=157	*n*=42	*n*=199
Mean age, years (SD)	63 (11)	59 (13)	58 (13)	58 (14)	–	–	59 (13)	59 (9)	59 (12)
Women, *n* (%)	18 (41)	17 (43)	20 (45)	11 (38)	–	–	66 (42)	13 (31)	79 (40)
Race, *n* (%)									
White	20 (45)	19 (48)	28 (64)	17 (59)	–	–	84 (54)	18 (43)	102 (51)
Asian	10 (23)	8 (20)	6 (14)	5 (17)	–	–	29 (18)	7 (17)	36 (18)

Black	13 (30)	13 (33)	8 (18)	6 (21)			40 (25)	17 (40)	57 (29)
Other	1 (2)	0	2 (5)	1 (3)	–	–	4 (3)	0	4 (2)
Mean CKD duration, years (SD)	8 (6.8)	6 (6.0)	6 (6.0)	5 (5.5)	–	–	6 (6.2)	6 (4.3)	6 (5.8)
Mean dialysis therapy duration, years (SD)	6 (5.9)	5 (5.6)	4 (3.6)	5 (5.3)	–	–	5 (5.2)	5 (4.0)	5 (5.0)
CKD etiology, *n* (%)[c]									
Diabetes	29 (66)	16 (40)	25 (57)	16 (55)	–	–	86 (55)	24 (57)	110 (55)
Hypertension	10 (23)	21 (53)	10 (23)	7 (24)	–	–	48 (31)	18 (43)	66 (33)

Mean Hb level, g/dl (SD)	10.4 (0.6)	10.4 (0.6)	10.4 (0.7)	10.7 (0.6)	–	–	10.5 (0.6)	10.6 (0.5)	10.5 (0.6)
Mean prior ESA dose (IU/kg/week) prior to randomization (SD)	104 (72.4)	108 (131.0)	117 (94.8)	134 (83.6)	-	-	114 (97.9)	103 (88.7)	112 (95.9)
Mean CRP, mg/L (SD)	0.9 (1.7)	0.6 (0.8)	0.8 (1.2)	0.8 (1.7)	-	-	0.8 (1.4)	0.7 (1.1)	0.8 (1.3)

[a]For DIALOGUEs 2 and 4, doses represent starting doses only
[b]Patients in the control group received placebo in DIALOGUE 1, continued darbepoetin treatment in DIALOGUE 2, and continued epoetin treatment in DIALOGUE 4.
[c]Patients could have more than one etiology of CKD and the two most common etiologies are shown here. Other etiologies included autoimmune disease, cardiac diseases, glomerulonephritis, infection, and polycystic kidney disease.
[d]eGFR was calculated using the Modification of Diet in Renal Disease formula.
b.i.d., twice daily; CKD, chronic kidney disease; DIALOGUE, DaIly orAL treatment increasing endOGenoUs Erythropoietin; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; o.d., once daily; SD, standard deviation.

Supplemental Table 5. Changes from baseline in mean local haemoglobin at evaluation period by starting dose in DIALOGUE 1, DIALOGUE 2 and DIALOGUE 4 (last observation carry forward)

A. DIALOGUE 1

				Within group change from baseline		Between group comparison	
Starting Dose Group	n	Baseline mean	Evaluation period mean	LS mean change	95% CI for LS mean change	Difference in LS mean change	95% CI for difference
Molidustat 25 mg o.d.	19	9.4	10.6	1.2	(0.4, 2.0)	1.1	(0.2, 1.9)
Molidustat 50 mg o.d.	21	9.6	11.0	1.5	(0.9, 2.2)	1.3	(0.7, 2.0)
Molidustat 75 mg o.d.	22	9.6	11.6	1.9	(1.3, 2.5)	1.9	(1.2, 2.5)
Molidustat 25 mg b.i.d.	19	9.4	11.0	1.6	(0.9, 2.2)	1.5	(0.8, 2.2)

Molidustat 50 mg b.i.d.	20	9.5	11.5	2.1	(1.4, 2.9)	1.9	(1.1, 2.7)
Molidustat Combined	101	9.5	11.1	1.7	(1.3, 2.1)	1.5	(0.9, 2.1)
Placebo	20	9.5	9.6	0.1	(-0.5, 0.8)		

n = number of subjects

LS (least square) mean and difference in LS mean are based on ANCOVA model including treatment, randomization stratification factors, and baseline as a covariate; CI, confidence interval; b.i.d., twice daily; o.d., once daily.

B. DIALOGUE 2

				Within group change from baseline		Between group comparison	
Starting Dose Group	n	Baseline mean	Evaluation period mean	LS mean change	95% CI for LS mean change	Difference in LS mean change	95% CI for difference
Molidustat 25 mg o.d.	30	10.9	10.9	0.1	(-0.5, 0.7)	-0.2	(-0.7, 0.3)
Molidustat 50 mg o.d.	30	10.7	10.9	0.4	(-0.1, 0.8)	-0.0	(-0.4, 0.4)
Molidustat 75 mg o.d.	32	10.7	11.4	0.9	(0.4, 1.3)	0.4	(-0.0, 0.9)
Molidustat Combined	92	10.8	11.1	0.4	(0.1, 0.8)	0.1	(-0.3, 0.5)
Darbepoetin	32	10.9	11.1	0.3	(-0.1, 0.8)		

n = number of subjects.
LS (least square) mean and difference in LS mean are based on ANCOVA model including treatment, randomization stratification factors, and baseline as a covariate; CI, confidence interval; o.d., once daily.

C. DIALOGUE 4

				Within group change from baseline		Between group comparison	
Starting Dose Group	n	Baseline mean	Evaluation period mean	LS mean change	95% CI for LS mean change	Difference in LS mean change	95% CI for difference
Molidustat 25 mg o.d.	44	10.4	9.4	-1.7	(-2.5, -1.0)	-0.9	(-1.4, -0.4)
Molidustat 50 mg o.d.	40	10.4	9.7	-2.3	(-3.5, -1.1)	-0.6	(-1.1, -0.1)
Molidustat 75 mg o.d.	44	10.4	9.9	-1.0	(-1.8, -0.2)	-0.3	(-0.8, 0.3)
Molidustat 150 mg o.d.	29	10.7	10.5	-1.0	(-1.7, -0.2)	0.3	(-0.2, 0.8)
Molidustat Combined	157	10.5	9.8	-1.2	(-1.7, -0.6)	-0.4	(-0.9, 0.0)

Epoetin	42	10.6	10.3	-0.7	(-1.4, -0.1)

n = number of subjects

LS (least square) mean and difference in LS mean are based on ANCOVA model including treatment, randomization stratification factors, and baseline as a covariate; CI, confidence interval; o.d., once daily.

Supplemental Table 6. Time within the hemoglobin range during treatment with Molidustat and active treatment in DIALOGUE 2 and DIALOGUE 4

A. DIALOGUE 2

Target Range 10.0–12.0 g/dl	Dose Group	Statistics					
		n	Mean	SD	Min	Median	Max
Percentage of time within range (10.0–12.0 g/dl)[a]	Molidustat						
	25 mg o.d.	30	66	34.4	0.0	84.2	100.0
	50 mg o.d.	30	71	30.8	0.0	80.5	100.0
	75 mg o.d.	32	56	29.8	0.0	63.4	100.0
	Combined	92	64	31.9	0.0	72.0	100.0
	Darbepoetin	32	83	25.1	15.3	98.5	100.0

B. DIALOGUE 4

Target Range	Treatment Group	Statistics					
		n	Mean	SD	Min	Median	Max
Percentage of time within range (10.0 –12.0 g/dl)[a]	Molidustat						
	25 mg o.d. (*n*=44)	44	34	29.3	0.0	28.8	100.0
	50 mg o.d. (*n*=40)	39	27	24.9	0.0	18.1	98.4
	75 mg o.d. (*n*=44)	44	27	26.1	0.0	21.6	100.0
	150 mg o.d. (*n*=29)	29	38	27.9	0.0	36.9	95.0
	Combined (*n*=157)	156	31	27.2	0.0	24.4	100.0
	Epoetin (*n*=42)	42	47	26.2	0.0	45.5	100.0
	Total (*n*=199)	198	34	27.7	0.0	29.4	100.0
Percentage of time within target range (9.5–11.5 g/dl)[a]	Molidustat						
	25 mg o.d. (*n*=44)	44	60	33.2	0.0	59.6	100.0

50 mg o.d. (*n*=40)	39	54	32.1	0.6	54.6	100.0
75 mg o.d. (*n*=44)	44	53	31.1	0.0	52.0	100.0
150 mg o.d. (*n*=29)	29	69	31.4	6.2	86.2	100.0
Combined (*n*=157)	156	58	32.2	0.0	57.6	100.0
Epoetin (*n*=42)	42	80	20.5	23.4	86.5	100.0
Total (*n*=199)	198	63	31.4	0.0	67.4	100.0

[a]Percentage of time within the Hb target range = 100 × number of days in the target range/number of days on treatment.

max, maximum; min, minimum; o.d., once daily; SD, standard deviation.

Supplemental Table 7. Patients receiving red blood cell transfusion and ESA treatment for low haemoglobin as rescue treatment during the study by study and starting dose.

	Molidustat Dose Groups							Comparator [a]	Total
	25 mg o.d.	50 mg o.d.	75 mg o.d.	150 mg o.d.	25 mg b.i.d.	50 mg b.i.d.	Combined		
DIALOGUE 1	*n*=19	*n*=21	*n*=22	-	*n*=19	*n*=20	*n*=101	*n*=20	*n*=121
Patients receiving red blood cell transfusion (%)	2 (11%)	0	1 (5%)	-	0	0	3 (3%)	0	3 (3%)
Patients receiving ESA treatment (%)	2 (11%)	1 (5%)	0	-	3 (16%)	0	6 (6%)	1 (5%)	7 (6%)

DIALOGUE 2	*n*=30	*n*=30	*n*=32	-	-	*n*=	*n*=92	*n*=32	*n*=124
Patients receiving red blood cell transfusion (%)	0	1 (3%)	0	-	-	-	1 (1%)	1 (3%)	2 (2%)
Patients receiving ESA treatment (%)	0	0	0	-	-	-	0	1 (3%)	1 (0.8%)
DIALOGUE 4	*n*=44	*n*=40	*n*=44	*n*=29	–	–	*n*=157	*n*=42	*n*=199
Patients receiving red blood cell transfusion (%)	3 (7%)	4 (10%)	3 (7%)	1 (3%)	-	-	11 (7%)	2 (5%)	13 (7%)

Patients receiving ESA treatment (%)	2 (5%)	0	0	0	-	-	2 (1%)	0	2 (1%)

[a] Patients in the control group received placebo in DIALOGUE 1, continued darbepoetin treatment in DIALOGUE 2, and continued epoetin treatment in DIALOGUE 4.

Supplemental Table 8. TEAEs reported in >10% of patients in any group in DIALOGUEs 1, 2, and 4 by Molidustat dose group

TEAE	Molidustat Dose Group							Control Group [a]	Total
	25 mg o.d.	50 mg o.d.	75 mg o.d.	150 mg o.d.	25 mg b.i.d.	50 mg b.i.d.	Combined		
DIALOGUE 1	*n*=19	*n*=21	*n*=22	–	*n*=19	*n*=20	*n*=101	*n*=20	*n*=121
Hypertension	3 (16)	1 (5)	2 (9)	–	2 (11)	2 (10)	10 (10)	5 (25)	15 (12)
Nasopharyngitis	1 (5)	0	2 (9)	–	1 (5)	3 (15)	7 (7)	2 (10)	9 (7)
Dizziness	1 (5)	0	2 (9)	–	1 (5)	1 (5)	5 (5)	3 (15)	8 (7)
Urinary tract infection	1 (5)	2 (10)	0	–	0	1 (5)	4 (4)	3 (15)	7 (6)
Hyperkalemia	1 (5)	2 (10)	0	–	0	1 (5)	4 (4)	3 (15)	7 (6)
Constipation	2 (11)	1 (5)	2 (9)	–	0	0	5 (5)	1 (5)	6 (5)
Diarrhea	2 (11)	2 (10)	0	–	0	0	4 (4)	1 (5)	5 (4)

Hyperparathyroidism, secondary	0	0	0	–	0	1 (5)	1 (1)	3 (15)	4 (3)
Vomiting	2 (11)	0	0	–	0	0	2 (2)	1 (5)	3 (3)
DIALOGUE 2	*n*=30	*n*=30	*n*=32	–	–	–	*n*=92	*n*=32	*n*=124
Hypertension	3 (10)	6 (20)	5 (16)	–	–	–	14 (15)	4 (13)	18 (15)
Edema, peripheral	2 (7)	4 (13)	2 (6)	–	–	–	8 (9)	2 (6)	10 (8)
Chronic kidney disease	2 (7)	2 (7)	6 (19)	–	–	–	10 (11)	0	10 (8)
Diarrhea	1 (3)	4 (13)	0	–	–	–	5 (5)	1 (3)	6 (5)
DIALOGUE 4	*n*=44	*n*=40	*n*=44	*n*=29	–	–	*n*=157	*n*=42	*n*=199
Hypertension	1 (2)	3 (8)	10 (23)	3 (10)	–	–	17 (11)	8 (19)	25 (13)
Hemoglobin decreased	5 (11)	4 (10)	5 (11)	1 (3)	–	–	15 (10)	2 (5)	17 (9)
Hemoglobin increased	2 (5)	2 (5)	4 (9)	5 (17)	–	–	13 (8)	2 (5)	15 (8)
Diarrhea	1 (2)	2 (5)	9 (21)	0	–	–	12 (8)	2 (5)	14 (7)

Nasopharyngitis	4 (9)	5 (13)	0	0	–	–	9 (6)	1 (2)	10 (5)
Nausea	1 (2)	0	3 (7)	4 (14)	–	–	8 (5)	2 (5)	10 (5)
Vomiting	1 (2)	0	2 (5)	3 (10)	–	–	6 (4)	0	6 (3)

All data are given as *n* (%).

[a] Patients in the control group received placebo in DIALOGUE 1, continued darbepoetin treatment in DIALOGUE 2, and continued epoetin treatment in DIALOGUE 4.

b.i.d., twice daily; Hb, hemoglobin; TEAE, treatment-emergent adverse event; o.d., once daily.

A blinded Central Adjudication Committee was implemented; judgment aimed at whether the events reported was clinically correct (based on clinical data), not on relatedness to study procedure or treatment.

Supplemental Table 9. Baseline values of measures of iron metabolism in DIALOGUE 1, DIALOGUE 2, and DIALOGUE 4

A. DIALOGUE 1

Measure of Iron Metabolism	Mean (SD) values at Baseline	
	Molidustat (*n*=101)	Placebo (*n*=20)
Ferritin, μg/L	201 (150)	221 (164)
Hepcidin, ng/ml	36 (30)	38 (31)
Iron, μg/dl	81 (34)	83 (22)
TIBC, μmol/L	43 (10)	42 (7)
Transferrin saturation, %	34 (13)	35 (10)
UIBC, μmol/L	29 (10)	27 (7)

B. DIALOGUE 2

Measure of iron metabolism	Mean (SD) values at Baseline	
	Molidustat (*n*=92)	Darbepoetin (*n*=32)
Ferritin, μg/L	203 (175)	249 (270)
Hepcidin, ng/ml	35 (29)	37 (29)
Iron, μg/dl	82 (53)	78 (27)
TIBC, μmol/L	44 (10)	43 (8)
Transferrin saturation, %	32 (13)	34 (12)
UIBC, μmol/L	29 (9)	28 (9)

C. DIALOGUE 4

Measure of iron metabolism	Mean (SD) values at Baseline	
	Molidustat (n=157)	Epoetin (n=42)
Ferritin, μg/L	557 (315)	542 (331)
Hepcidin, ng/ml	72 (40)	70 (36)
Iron, μg/dl	68 (25)	64 (21)
TIBC, μmol/L	36 (6)	35 (7)
Transferrin saturation, %	34 (11)	33 (12)
UIBC, μmol/L	24 (5)	24 (7)

SD, standard deviation; TIBC, total iron binding capacity; UIBC, unsaturated iron binding capacity.

Normal ranges for serum hepcidin values: 3.1-43.5 ng/mL for males, 1.1-25.7 ng/mL for pre-menopausal females, and 2.0-46.9 ng/mL for post-menopausal females.

Supplemental Table 10. Changes in measures of iron metabolism between baseline and end of treatment in DIALOGUE 1, DIALOGUE 2, and DIALOGUE 4

A. DIALOGUE 1

Measure of Iron Metabolism	Mean (SD) Change Between Baseline and End of Treatment	
	Molidustat (*n*=101)	Placebo (*n*=20)
Ferritin, μg/L	−99 (125.7)	−8 (123)
Hepcidin, ng/ml	−18 (32.6)	2 (28.7)
Iron, μg/dl	−11 (45.8)	−13 (38.1)
TIBC, μmol/L	3 (6.7)	−1 (4.9)
Transferrin saturation, %	−7 (16.3)	−5 (13.0)
UIBC, μmol/L	5 (9.1)	0.8 (5.0)

B. DIALOGUE 2

Measure of iron metabolism	Mean (SD) Change Between Baseline and End of Treatment	
	Molidustat (*n*=92)	Darbepoetin (*n*=32)
Ferritin, μg/L	−15 (114.1)	−11 (102.2)
Hepcidin, ng/ml	−8 (27.8)	15 (28.5)
Iron, μg/dl	−8 (51.5)	1 (29.9)
TIBC, μmol/L	−0.1 (6.7)	−0.5 (5.6)
Transferrin saturation, %	−0.8 (13.9)	0.4 (11.0)
UIBC, μmol/L	1 (9.3)	−0.8 (5.6)

C. DIALOGUE 4

Measure of iron metabolism	Mean (SD) Change Between Baseline and End of Treatment	
	Molidustat (n=157)	Epoetin (n=42)
Ferritin, μg/L	54 (233.0)	49 (253.7)
Hepcidin, ng/ml	7 (48.6)	6 (37.7)
Iron, μg/dl	7 (30.9)	6 (26.3)
TIBC, μmol/L	3 (14.3)	2 (9.9)
Transferrin saturation, %	2 (15.4)	0.2 (12.9)
UIBC, μmol/L	2 (15.5)	0.7 (10.9)

SD, standard deviation; TIBC, total iron binding capacity; UIBC, unsaturated iron binding capacity.

Supplemental Table 11. Patients with thromboembolic events in any group in DIALOGUEs 1, 2, and 4 by Molidustat dose group

TEAE	Molidustat Dose Group							Control Group[a]	Total
	25 mg o.d.	50 mg o.d.	75 mg o.d.	150 mg o.d.	25 mg b.i.d.	50 mg b.i.d.	Combined		
DIALOGUE 1	*n*=19	*n*=21	*n*=22	–	*n*=19	*n*=20	*n*=101	*n*=20	*n*=121
Acute myocardial infarction	0	0	0	-	0	1 (5%)	1 (1%)	0	1 (1%)
Stroke	0	0	0	-	0	0	0	0	0
Arterial occlusive disease	0	0	1 (5%)	-	0	0	1 (1%)	0	1 (1%)
Peripheral arterial occlusive disease	0	0	0	-	0	0	0	1 (5%)	1 (1%)
Peripheral artery thrombosis	0	0	0	-	1 (5%)	0	1 (1%)	0	1 (1%)

Peripheral venous disease	0	0	0	-	0	0	0	1 (5%)	1 (1%)
Total	0	0	1 (5%)	-	1 (5%)	1 (5%)	3 (3%)	2 (10%)	5 (4%)
DIALOGUE 2	*n*=30	*n*=30	*n*=32	–	–	–	*n*=92	*n*=32	*n*=124
Acute myocardial infarction	0	0	0	–	–	–	0	0	0
Stroke	0	0	0	–	–	–	0	1 (3%)	1 (1%)
Arterial occlusive disease	0	0	0	–	–	–	0	0	0
Peripheral arterial occlusive disease	0	0	0	–	–	–	0	0	0
Peripheral artery thrombosis	0	0	0	–	–	–	0	0	0

Peripheral venous disease	0	0	0	–	–	–	0	0	0
Total	0	0	0	–	–	–	0	1 (3%)	1 (1%)
DIALOGUE 4	*n*=44	*n*=40	*n*=44	*n*=29	–	–	*n*=157	*n*=42	*n*=199
Acute myocardial infarction	0	0	2 (5%)	0	–	–	2 (1%)	0	2 (1%)
Stroke	2 (5%)	0	0	0	–	–	2 (1%)	0	2 (1%)
Arterial occlusive disease	0	0	0	0	–	–	0	0	0
Peripheral arterial occlusive disease	0	0	0	0	–	–	0	0	0
Peripheral artery thrombosis	0	0	0	0	–	–	0	0	0

Peripheral venous disease	0	0	0	0	–	–	0	0	0
Venous occlusion	0	1 (3%)	0	0	–	–	1 (1%)	0	1 (1%)
Total	2 (5%)	1 (3%)	0	0	-	-	5 (3%)	0	5 (3%)

All data are given as *n* (%).

[a]Patients in the control group received placebo in DIALOGUE 1, continued darbepoetin treatment in DIALOGUE 2, and continued epoetin treatment in DIALOGUE 4.

b.i.d., twice daily; Hb, hemoglobin; TEAE, treatment-emergent adverse event; o.d., once daily.

Supplemental Figure 1. | Study design of (A) DIALOGUE 1, (B) DIALOGUE 2, and (C) DIALOGUE 4.

Molidustat doses were suspended if Hb was >13.0 g/dL or if the rise in Hb was >1.0 g/dL in 2 weeks. Participants who required a dose suspension for ≥6 consecutive weeks had to be withdrawn from the study.

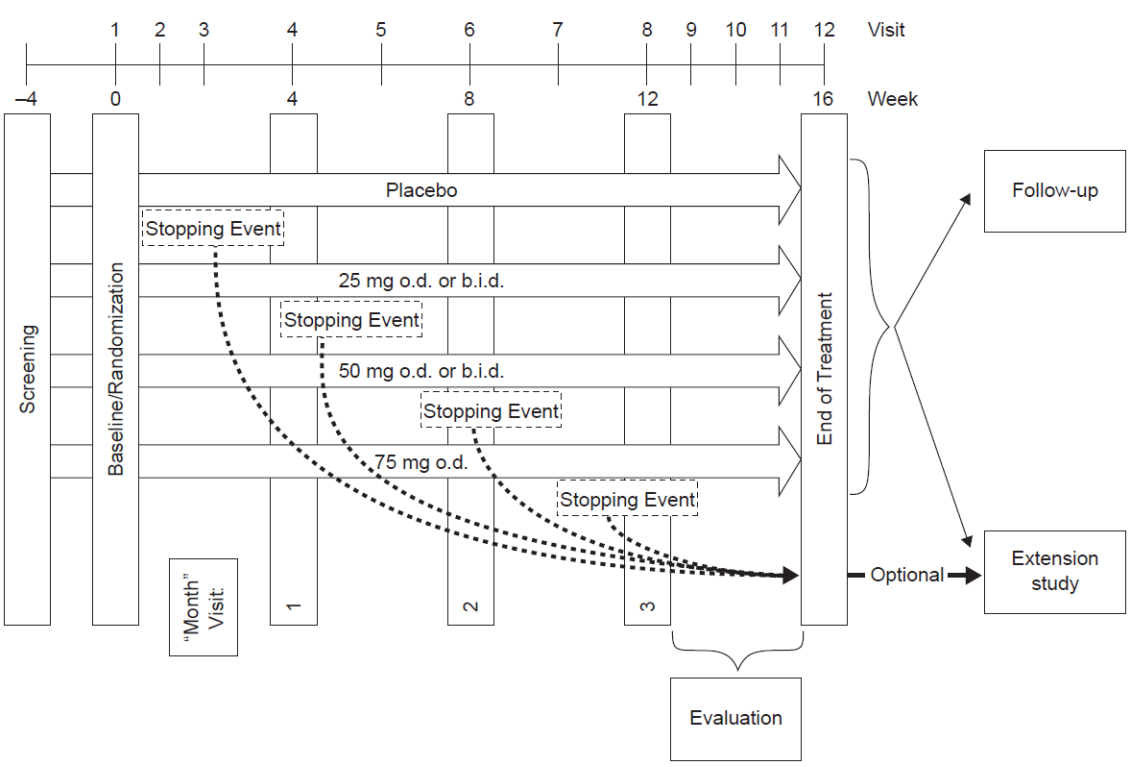
* Individuals who opted out of the long-term extension study were followed up for a minimum of 8 weeks. Follow-up did not apply to patients who opted in to the extension study; for these patients, in DIALOGUE 2, day 113 of this study (end of treatment) was day 1 of the extension study and in DIALOGUE 4 day 1 of the extension study was the day after day 113 of this study (end of treatment).

† Only Molidustat doses could be decreased on day 15, as individuals on darbepoetin (DIALOGUE 2) or epoetin (DIALOGUE 4) were on a stable dose at study entry.

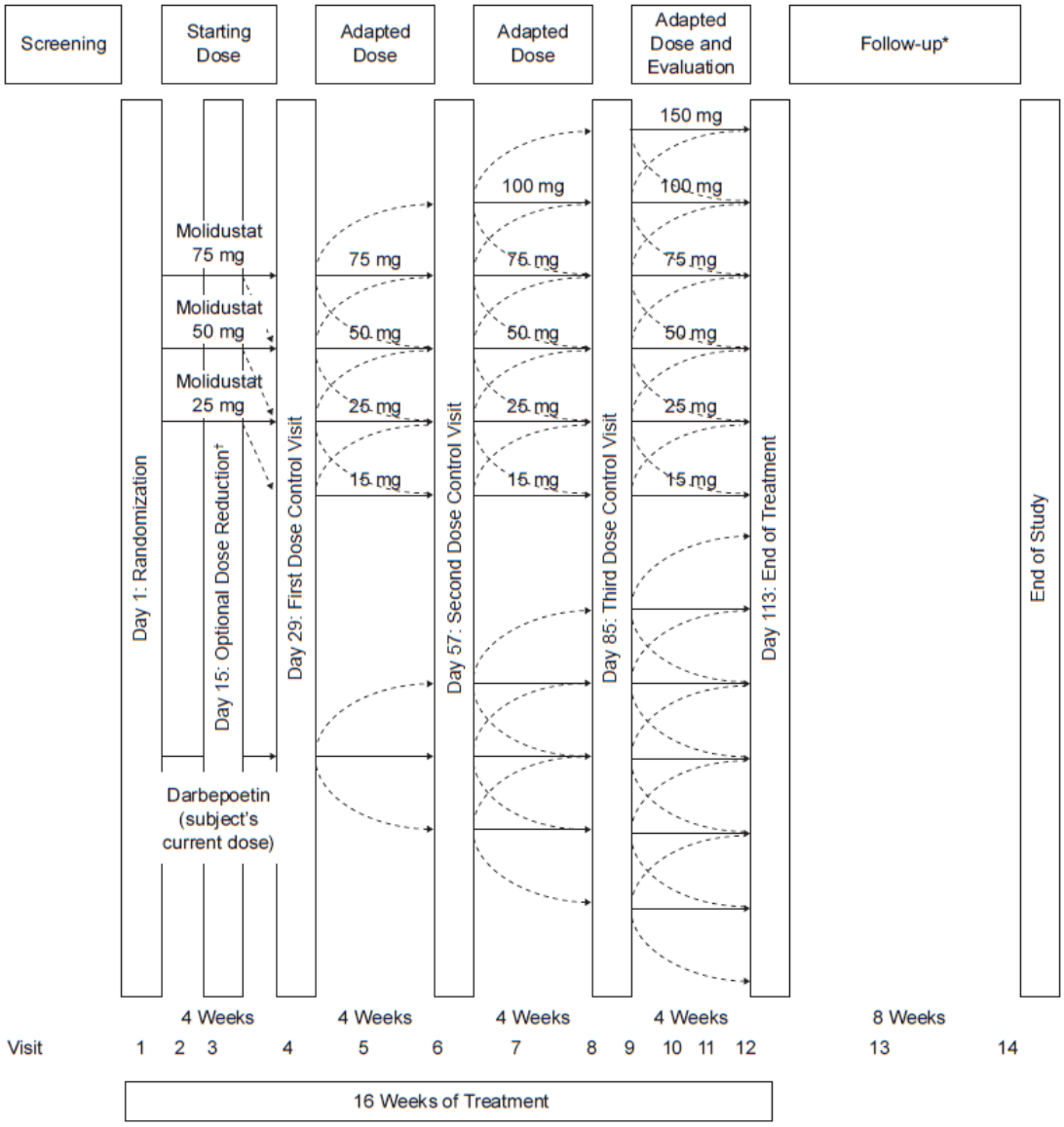
‡ Only individuals in the Molidustat 150 mg o.d. starting dose arm were able to up-titrate to 200 mg o.d..

ABPM, ambulatory blood pressure monitoring; b.i.d., twice daily; DIALOGUE, DaIly orAL treatment increasing endOGenoUs Erythropoietin; EPO, epoetin; Hb, hemoglobin; o.d., once daily; PD, pharmacodynamics; PK, pharmacokinetics.

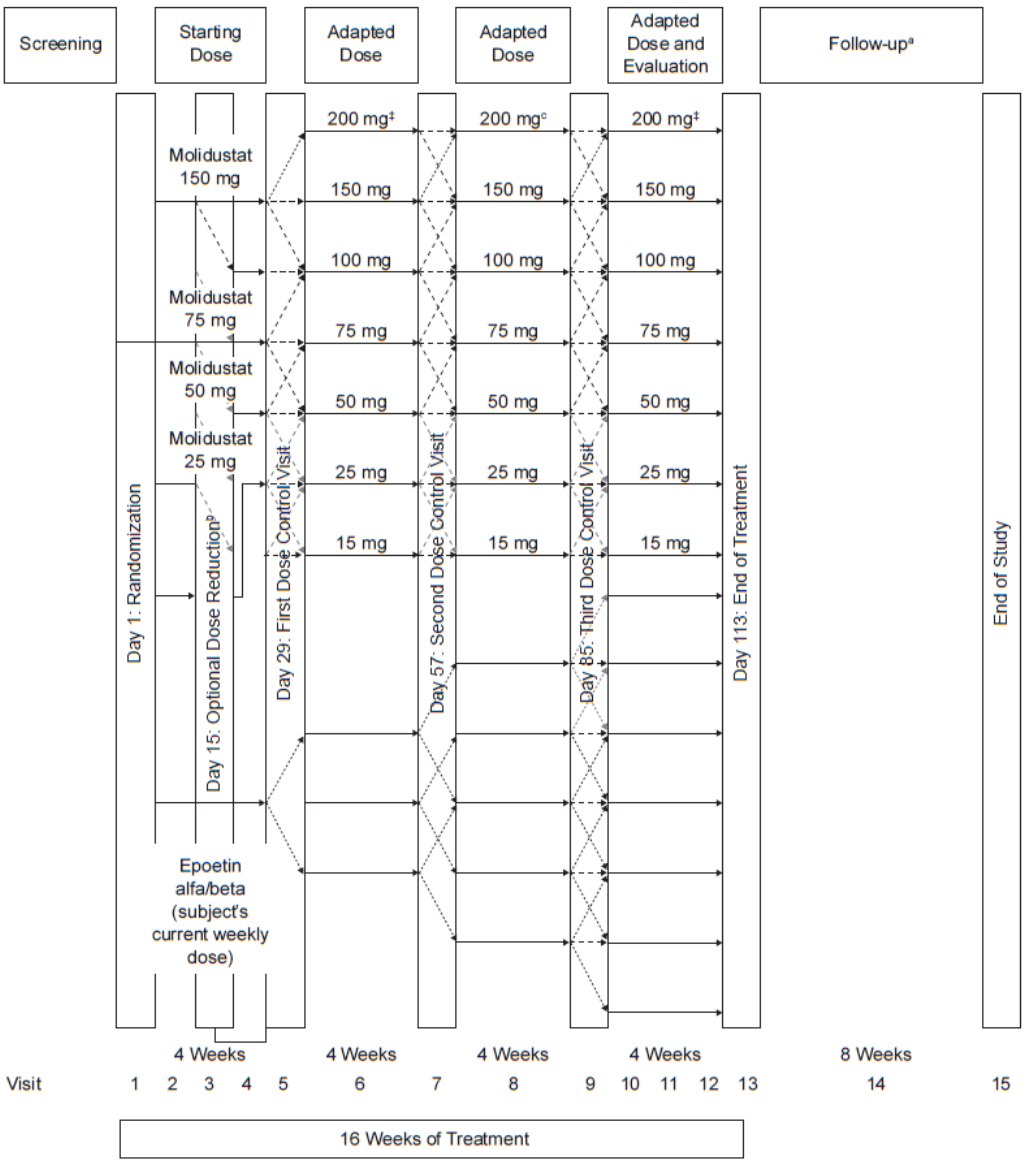
A


1 2 3 4 5 6 7 8 9 10 11 12 Visit
–4 0 4 8 12 16 Week
Screening
Baseline/Randomization
Placebo
Stopping Event
25 mg o.d. or b.i.d.
Stopping Event
50 mg o.d. or b.i.d.
Stopping Event
75 mg o.d.
Stopping Event
End of Treatment
Follow-up
Optional
Extension study
"Month" Visit:
1
2
3
Evaluation

B


Screening
Starting Dose
Adapted Dose
Adapted Dose
Adapted Dose and Evaluation
Follow-up*
Day 1: Randomization
Day 15: Optional Dose Reduction†
Day 29: First Dose Control Visit
Day 57: Second Dose Control Visit
Day 85: Third Dose Control Visit
Day 113: End of Treatment
End of Study
Molidustat 75 mg
Molidustat 50 mg
Molidustat 25 mg
Darbepoetin (subject's current dose)
75 mg
50 mg
25 mg
15 mg
100 mg
75 mg
50 mg
25 mg
15 mg
150 mg
100 mg
75 mg
50 mg
25 mg
15 mg
4 Weeks
4 Weeks
4 Weeks
4 Weeks
8 Weeks
Visit 1 2 3 4 5 6 7 8 9 10 11 12 13 14
16 Weeks of Treatment

C


Screening
Starting Dose
Adapted Dose
Adapted Dose
Adapted Dose and Evaluation
Follow-up[a]
Molidustat 150 mg
Molidustat 75 mg
Molidustat 50 mg
Molidustat 25 mg
200 mg‡
150 mg
100 mg
75 mg
50 mg
25 mg
15 mg
200 mg[c]
Day 1: Randomization
Day 15: Optional Dose Reduction[b]
Day 29: First Dose Control Visit
Day 57: Second Dose Control Visit
Day 85: Third Dose Control Visit
Day 113: End of Treatment
End of Study
Epoetin alfa/beta (subject's current weekly dose)
4 Weeks
4 Weeks
4 Weeks
4 Weeks
8 Weeks
Visit
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
16 Weeks of Treatment

Supplemental Figure 2. | Dose titration scheme for DIALOGUEs 2 and 4.

All doses are given in mg.

Molidustat doses were suspended if Hb was >13.0 g/dL or if the rise in Hb was >1.0 g/dL in 2 weeks. Participants who required a dose suspension for ≥6 consecutive weeks had to be withdrawn from the study.