Molidustat for Renal Anemia in Nondialysis Patients Previously Treated with Erythropoiesis-Stimulating Agents: A Randomized, Open-Label, Phase 3 Study

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Keywords

Renal anemia · Hypoxia-inducible factor prolyl hydroxylase inhibitor · Molidustat · Chronic kidney disease

Abstract

Introduction: Erythropoiesis-stimulating agents (ESAs) are the current standard of care for anemia due to chronic kidney disease (CKD) in patients not undergoing dialysis. Molidustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is being investigated as an alternative treatment for renal anemia. Molidustat was evaluated in five phase 3 studies, the molidustat once daily improves renal anemia by inducing erythropoietin (MIYABI) program. The present study investigated the safety and efficacy of molidustat in Japanese patients with renal anemia not undergoing dialysis and previously treated with ESAs. **Methods:** This was a 52-week, active-controlled, randomized (1:1), open-label, parallel-group, multicenter, phase 3 study in Japanese patients with anemia due to CKD (stages 3–5). Molidustat was initiated at 25 mg or 50 mg once daily according to previous ESA dose. The ESA darbepoetin alfa (darbepoetin) was initiated at a starting dose in accordance with the previous ESA dose and injected subcutaneously once every 2 or 4 weeks. Doses

were regularly titrated to maintain hemoglobin (Hb) levels in the target range of 11.0–13.0 g/dL. The primary efficacy outcome was the mean Hb level and its change from baseline during the evaluation period (weeks 30–36). The safety outcomes included evaluation of all adverse events. **Results:** In total, 164 patients were randomized to receive molidustat ($n = 82$) or darbepoetin ($n = 82$). Baseline characteristics were well balanced. Mean (standard deviation) Hb levels at baseline were 11.31 (0.68) g/dL for molidustat and 11.27 (0.64) g/dL for darbepoetin. The mean (95% confidence interval [CI]) for mean Hb levels during the evaluation period for molidustat (11.67 [11.48–11.85] g/dL) and darbepoetin (11.53 [11.31–11.74] g/dL) was within the target range. Based on a noninferiority margin of 1.0 g/dL, molidustat was noninferior to darbepoetin regarding the change in mean Hb level during the evaluation period from baseline, with a least squares mean (95% CI) difference (molidustat-darbepoetin) of 0.13 (–0.15, 0.40) g/dL. The proportion of patients who reported at least 1 treatment-emergent adverse event (TEAE) was 92.7% for molidustat and 96.3% for darbepoetin. TEAEs leading to death were reported in 2 patients (2.4%) in the molidustat group and none in the darbepoetin group; serious TEAEs were reported in 32.9% and 26.8% of patients, respectively. **Discussion/Conclusion:** Molidustat was noninferior

to darbepoetin and maintained Hb levels in the prespecified target range in patients with renal anemia not undergoing dialysis and previously treated with ESA. Molidustat was well tolerated, and no new safety signal was observed.

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Introduction

Anemia is a frequent and important complication of chronic kidney disease (CKD) [1], and it has been associated with poor quality of life, increased risk of cardiovascular events, hospitalizations, and death [1–3]. As CKD progresses, the risk of anemia increases, with a prevalence of approximately 50–80% in patients with end-stage renal disease [4, 5]. Anemia is characterized by a reduced level of hemoglobin (Hb) in the blood. Thresholds of <13.5 g/dL and <11.5 g/dL in men and women, respectively, younger than 60 years old have been recommended by the Japanese Society for Dialysis Therapy for the diagnosis of anemia [6]. Insufficient erythropoietin (EPO) production in the kidneys is a key factor in the pathogenesis of anemia associated with CKD, also known as renal anemia [7]. Consequently, current management of renal anemia consists of a combination of erythropoiesis-stimulating agents (ESAs) and iron supplementation, with guidelines recommending that Hb levels should be maintained in the range 11–13 g/dL in Japanese patients with CKD not undergoing dialysis [6]. Although ESAs are generally effective in elevating Hb levels in patients with renal anemia [8], they are ineffective at raising Hb levels in approximately 10–20% of patients [9, 10]. Furthermore, ESAs have been associated with several potential safety concerns, including increased risk of cardiovascular events, stroke and death, which might be due to acute increases in Hb levels [8, 11–14]. These adverse outcomes are more prone to occur in inflamed or ESA-hyporesponsive patients, who are more likely to be exposed to high doses of ESA and iron [11]. Finally, some patients may experience a fear of injections that may be a barrier to the optimal management of renal anemia in patients receiving ESAs. Therefore, the development of alternative therapy options could be beneficial.

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors potentially offer such an alternative. Indeed, the Asian Pacific Society of Nephrology, which includes Japan, has recently published recommendations regarding the use of HIF-PH inhibitors for the treatment of renal anemia, which state that the use of HIF-PH inhibitors should be considered in patients who are non-

ESA adherent due to fear of injections and in patients who are unresponsive to ESA therapy [15]. Moreover, 4 HIF-PH inhibitors (roxadustat, vadadustat, daprodustat, and enarodustat) have recently been approved in Japan for the treatment of renal anemia. EPO transcription is activated by HIFs in response to hypoxia. In the presence of oxygen, HIF-PH tags the HIF- α subunit for proteasomal degradation, preventing EPO synthesis [16]. Inhibition of HIF-PH results in stabilization of HIF, which leads to endogenous production of EPO and, ultimately, stimulation of erythropoiesis [17]. Molidustat is an orally bioavailable HIF-PH inhibitor that increases circulating levels of EPO close to the normal physiological range [18, 19]. Based on positive results from the phase 2 daily oral treatment increasing endogenous EPO (DIALOGUE) clinical program [20, 21], the molidustat once daily improves renal anemia by inducing EPO (MIYABI) program of five phase 3 trials was designed to investigate the efficacy and safety of molidustat in Japanese patients with renal anemia. Two trials were conducted in patients not undergoing dialysis who were ESA-naïve or previously treated with ESA, respectively [22]. Another 2 trials were conducted in patients undergoing hemodialysis who were either ESA-naïve or previously treated with ESA, while the last trial was performed in patients undergoing peritoneal dialysis who were treated or not with ESAs [23, 24]. Here, we present the results of the MIYABI Non-Dialysis Maintenance (MIYABI ND-M) study, which was conducted to evaluate the efficacy and safety of molidustat in Japanese patients who were not undergoing hemodialysis and who were previously treated with ESA [22].

Material and Methods

Study Design

The design of the MIYABI ND-M study (NCT03350347) has been previously described [22]. Briefly, this was a 52-week, active-controlled, randomized, open-label, parallel-group, multicenter, phase 3 study to investigate the efficacy and safety of molidustat in comparison with darbepoetin alfa (darbepoetin) in Japanese patients with renal anemia who were not undergoing dialysis and who were receiving ESA therapy. Study visits took place every 2 weeks for the first 4 weeks (weeks 0–4), every 4 weeks until week 28, every 2 weeks from week 28 and during the evaluation period (weeks 30–36), and then every 4 weeks until week 52, followed by a 4-week follow-up period. Efficacy was assessed after 30, 32, 34, and 36 weeks of treatment (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000518072).

Study Population

The target population was 150 patients with a pre-randomization Hb level of ≥ 10.0 g/dL and <13.0 g/dL. Men and women aged

20 years or older with a diagnosis of renal anemia who were not undergoing dialysis and who were treated with ESAs were eligible for inclusion. Eligible patients had to have an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (CKD stages 3–5) using the Matsuo et al. [25] formula. Key exclusion criteria included any current condition leading to significant blood loss, active hemolysis or hemolytic syndrome, and diagnosis of cardiovascular or cerebrovascular events in the 6 months before study drug assignment. A complete list of patient eligibility criteria is presented in online suppl. Table 1.

Treatments

Eligible patients were randomized 1:1 to receive molidustat or darbepoetin, and stratified according to previous ESA dose (high or low) and thromboembolic events (yes or no). Molidustat was administered orally once daily at a starting dose of 25 mg or 50 mg in accordance with the previous ESA dose. The cutoff value for patients previously treated with darbepoetin was fixed at 7.5 µg/week based on the PK/PD analysis of the phase 2 DIALOGUE studies. For patients receiving epoetin beta pegol, a conversion ratio for darbepoetin to epoetin beta pegol of 1/1.2 was used to determine the cutoff value between high or low dose based on published data [26, 27]; this value was rounded down to 6.25 µg/week, which corresponded to the closest formulation available. For patients who were previously treated with epoetin alfa or beta, a cutoff value of 1,500 IU/week was used according to the darbepoetin label. Darbepoetin was injected subcutaneously at a starting dose in accordance with the previous ESA dose and given once every 2 weeks (Q2W) or once every 4 weeks (Q4W). Doses were titrated individually based on the patient's Hb response to the previous dose during visits to maintain the Hb level within the target range of ≥ 11.0 g/dL– <13.0 g/dL. Dose titration visits for molidustat were scheduled every 4 weeks after the first 4 weeks of the treatment, and every 2 weeks or 4 weeks for darbepoetin during the treatment period. Patients with iron, folate or vitamin B12 deficiency were to be treated before study enrollment and throughout the study. Supplements were administered at the investigator's discretion in line with current guidelines. During the treatment period and when possible, iron supplements were administered orally with the goal to achieve serum ferritin levels of ≥ 100 ng/mL or transferrin saturation of $\geq 20\%$, in line with Japanese guidelines [28]. Rescue treatment (i.e., a red blood cell [RBC] transfusion to treat renal anemia or any ESA treatment due to lack of efficacy) was administered at the investigator's discretion but was not recommended for patients with Hb levels of ≥ 8.0 g/dL.

Outcomes

The primary efficacy outcomes were the mean Hb level during the evaluation period, with a target Hb range of ≥ 11.0 g/dL– <13.0 g/dL, and its change from baseline. The change in mean Hb level was defined as the difference in the mean Hb level at baseline and during the evaluation period. Other efficacy outcomes included Hb levels at each visit. Subgroup analysis by baseline eGFR and by previous ESA dosage (low or high) were performed. High dosage was defined as: darbepoetin >15 µg Q2W or >30 µg Q4W; epoetin beta pegol >25 µg Q4W; or epoetin alfa/beta $>1,500$ IU every week or $>3,000$ IU Q2W. Low dosage was defined as previous dosage equal to, or lower than, these limits. The responder rate in each treatment group was also investigated and was defined as the proportion of patients who met the following criteria: (1) the mean Hb level was within the target range of ≥ 11.0 g/dL and <13.0 g/dL dur-

ing the evaluation period; (2) $\geq 50\%$ of the Hb levels were in the target range during the evaluation period; and (3) no rescue treatment was received up to the end of the evaluation period.

Safety outcomes assessed by the investigator during the 52 weeks of treatment included treatment-emergent adverse events (TEAEs), coded using the Medical Dictionary for Regulatory Activities version 22.0. The incidence of major adverse cardiovascular events (MACEs), adjudicated by an independent committee, was also assessed. MACEs were defined as cardiovascular or undetermined death, myocardial infarction, unstable angina pectoris, ischemic stroke (ischemic stroke or ischemic stroke with hemorrhagic transformation), pulmonary thromboembolism, and acute limb ischemia. Finally, parameters of renal function, including eGFR, were investigated as exploratory variables up to week 52.

Statistical Analysis

Analyses of efficacy and safety were performed in the full analysis set and safety analysis set (SAF), respectively. The full analysis set comprised all randomized patients who had at least 1 baseline Hb level recorded before the first dose of the study drug. The SAF included all patients who received at least 1 dose of the study drug. The baseline Hb level was defined as the mean of all Hb levels during the screening period and the Hb level at week 0 (baseline visit). The mean Hb level during the evaluation period was calculated using the central Hb levels collected at scheduled visits during the evaluation period (weeks 30–36; i.e., visits 10–13). If rescue treatment was started before week 36, the latest available Hb level (central or local) before the start of rescue treatment was used as the mean Hb level during the evaluation period. If fewer than 2 valid central Hb levels were available during the evaluation period, post-baseline Hb levels were used for imputation until 1 valid determination was available at each visit; post-baseline Hb levels were used in the following priority order: (1) the local Hb level at the scheduled visit; (2) the latest unscheduled central Hb level in the week prior to the scheduled visit; and (3) the latest unscheduled local Hb level in the week prior to the scheduled visit.

For the primary efficacy analysis, the mean Hb level during the evaluation period and the respective 2-sided 95% confidence intervals (CIs) were estimated using 1-sample *t*-statistics. The difference in the changes between the treatment groups (molidustat-darbepoetin) and the respective 2-sided 95% CIs were estimated using an analysis of covariance model, including the treatment group, previous ESA dose group (low/high), and prior thromboembolic events (yes/no) as fixed effects and baseline Hb levels as a covariate. The noninferiority of molidustat to darbepoetin was established if the lower limit of the 2-sided 95% CI for the difference (molidustat-darbepoetin) was above -1.0 g/dL, with a noninferiority margin of 1.0 g/dL. Data were analyzed for subgroups defined by characteristics such as age, sex, baseline weight, prior thromboembolic events, main cause of CKD, previous ESA dose, and rescue medication used during the trial.

Results

Patient Disposition and Baseline Characteristics

In total, 164 patients were randomized to molidustat ($n = 82$) or darbepoetin ($n = 82$). Of these, 133 patients

Fig. 1. Patient disposition. Completed study: completed both treatment and follow-up.

completed treatment up to week 36 (65 [79.3%] in the molidustat group and 68 [82.9%] in the darbepoetin group) and 120 patients completed treatment up to week 52 (57 [69.5%] in the molidustat group and 63 [76.8%] in the darbepoetin group) (Fig. 1). Demographic and baseline characteristics were well balanced between the 2 groups except for the proportion of males, which was higher in the darbepoetin group (Table 1).

Treatment Exposure

Over the 52 weeks of treatment, the mean (standard deviation [SD]) treatment duration was 307.8 (93.0) days in the molidustat group and 317.7 (90.5) days in the darbepoetin group. Up to week 52, mean (SD) dosages were 51.21 (32.35) mg/day in the molidustat group and 22.01 (13.13) µg/week in the darbepoetin group. Online suppl. Figure 2 summarizes the mean actual dosage of study drug at each study visit in the SAF and in subgroups according to prior ESA dosage. The most common maximum dose in the molidustat group was 50 mg (30 patients

[36.6%]), followed by 75 mg (15 patients [18.3%]), and 100 mg and 150 mg (11 patients [13.4%] each). In the darbepoetin group, the most common maximum dosage was 45 µg/week (21 patients [25.6%]), followed by 15 µg/week and 22.5 µg/week (14 patients [17.1%] each), and 7.5 µg/week and 30 µg/week (9 patients [11.0%] each).

Dose adjustments were required in 78 patients (96.3%) in the molidustat group and in 76 patients (93.8%) in the darbepoetin group. A post hoc analysis explored the mean dosage by visit according to baseline eGFR subgroups (eGFR <15 mL/min/1.73 m², eGFR ≥15 and <30 mL/min/1.73 m², and eGFR ≥30 mL/min/1.73 m²) for molidustat and darbepoetin (online suppl. Fig. 3). In both treatment groups, the mean actual dosage for the patients in the eGFR <15 mL/min/1.73 m² subgroup was numerically higher than in the other 2 eGFR subgroups.

Over the 52 weeks of treatment, oral iron treatment (excluding iron treatment which was not intended to supply iron) was administered to 56.1% (46/82) of patients in the molidustat group and 39.0% (32/82) of patients in the

Table 1. Patient demographic and baseline characteristics (FAS)

Parameter	Molidustat (n = 82)	Darbepoetin (n = 82)	Total (N = 164)
Male, n (%)	45 (54.9)	54 (65.9)	99 (60.4)
Age, mean (SD), years	69.0 (10.3)	72.4 (10.3)	70.7 (10.4)
Weight, mean (SD), kg	60.67 (11.31)	60.18 (11.06)	60.43 (11.16)
Previous ESA dosage, n (%)			
Low ^a	26 (31.7)	24 (29.3)	50 (30.5)
High ^a	56 (68.3)	58 (70.7)	114 (69.5)
Previous ESA dosage recorded in IxRS, n (%)			
Low ^a	27 (32.9)	27 (32.9)	54 (32.9)
High ^a	55 (67.1)	55 (67.1)	110 (67.1)
Hb level, mean (SD), g/dL	11.31 (0.68)	11.27 (0.64)	11.29 (0.66)
eGFR, mean (SD), mL/min/1.73 m ²	18.7 (10.7)	17.5 (9.0)	18.1 (9.9)
Ferritin, mean (SD), ng/mL	118.2 (106.2)	124.5 (79.0)	121.4 (93.3)
Transferrin saturation, mean (SD), %	34.0 (13.6)	34.2 (9.7)	34.1 (11.8)
Vitamin B12, mean (SD), pmol/L	287.3 (139.3)	307.2 (177.7)	297.4 (159.7)
Folate, mean (SD), nmol/L	80.5 (397.0)	42.7 (193.0)	61.7 (312.4)
Serum CRP, mean (SD), mg/dL	0.211 (0.441)	0.194 (0.479)	0.203 (0.459)
CKD stage based on eGFR, n (%)			
G3a, ≥45 and <60 mL/min/1.73 m ²	1 (1.2)	1 (1.2)	2 (1.2)
G3b, ≥30 and <45 mL/min/1.73 m ²	13 (15.9)	8 (9.8)	21 (12.8)
G4, ≥15 and <30 mL/min/1.73 m ²	29 (35.4)	40 (48.8)	69 (42.1)
G5, <15 mL/min/1.73 m ²	39 (47.6)	33 (40.2)	72 (43.9)
Main cause of CKD, n (%)			
Diabetic nephropathy	29 (35.4)	22 (26.8)	51 (31.1)
Nephrosclerosis	27 (32.9)	25 (30.5)	52 (31.7)
Chronic glomerulonephritis	17 (20.7)	24 (29.3)	41 (25.0)
Polycystic kidney disease	4 (4.9)	1 (1.2)	5 (3.0)
Others	5 (6.1)	10 (8.2)	15 (9.1)
Duration of CKD, mean (SD), years	7.3 (7.2)	7.8 (8.5)	7.5 (7.8)
Prior thromboembolic events, n (%)	10 (12.2)	10 (12.2)	20 (12.2)
SBP, mean (SD), mm Hg	132.3 (16.1)	132.9 (16.5)	132.6 (16.3)
DBP, mean (SD), mm Hg	71.5 (13.3)	70.4 (10.6)	71.0 (12.0)

Calculated percentages are subject to rounding. CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; FAS, full analysis set; Hb, hemoglobin; IxRS, interactive voice/web response system; SBP, systolic blood pressure; SD, standard deviation. ^a High dosage was defined as: darbepoetin >15 µg once every 2 weeks or >30 µg once every 4 weeks; epoetin beta pegol >25 µg once every 4 weeks; or epoetin alfa/beta >1,500 IU every week or >3,000 IU once every 2 weeks. Low dosage was defined as previous dosage equal to, or lower than, these limits.

darbepoetin group. Intravenous iron treatment was administered to 2 patients in each treatment group. The mean (SD) for the mean dosage of oral iron treatment during the 52-week treatment period was 44.54 (34.03) mg/day in the molidustat group and 50.58 (41.65) mg/day in the darbepoetin group. The mean (SD) for the mean dosage of intravenous iron treatment during the 52-week treatment period was 0.77 (1.09) mg/week in the molidustat group and 2.20 (3.12) mg/week in the darbepoetin group. Iron concentration, total iron binding capacity, unsaturated iron binding capacity, transferrin saturation,

and levels of hepcidin 25 and ferritin are presented in on-line suppl. Figure 4. In the molidustat group, there was a decrease in transferrin saturation, and in hepcidin and ferritin concentrations from baseline to week 52.

Efficacy Outcomes

The mean (95% CI) Hb level during the evaluation period was 11.67 (11.48–11.85) g/dL in the molidustat group and 11.53 (11.31–11.74) g/dL in the darbepoetin group. For both treatment arms, the mean Hb levels were in the target range (≥11.0 g/dL to <13.0 g/dL) throughout the

Fig. 2. Mean (SD) Hb levels at study visits (FAS): for the overall population (plus overall mean values during the evaluation period) (a); and for subgroups of patients with low or high ESA dosage at baseline in the molidustat group (b) and in the darbepoetin group (c). The baseline Hb level was defined as the mean of all Hb levels during the screening period and the Hb level at week 0. Molidustat: FAS ($n = 82$); ESA dosage, low ($n = 26$); ESA dosage, high ($n = 56$). Darbepoetin: FAS ($n = 82$); ESA dosage, low ($n = 24$); ESA dosage, high ($n = 58$). Gray dotted lines denote the target Hb range of ≥ 11 g/dL and < 13 g/dL. ^a High dosage was defined as: darbepoetin > 15 μg once every 2 weeks or > 30 μg once every 4 weeks; epoetin beta pegol > 25 μg once every 4 weeks; epoetin alfa/beta $> 1,500$ IU every week or $> 3,000$ IU once every 2 weeks. Low dosage was defined as previous dosage equal to, or lower than, these limits. BL, baseline; ESA, erythropoiesis-stimulating agent; FAS, full analysis set; Hb, hemoglobin; SD, standard deviation.

evaluation period (Fig. 2a). The least squares (LS) mean for the change in mean Hb level during the evaluation period from baseline was 0.36 g/dL for molidustat and 0.24 g/dL for darbepoetin. Molidustat was noninferior to darbepoetin, with a LS mean difference (95% CI) (molidustat-darbepoetin: 0.13 [−0.15, 0.40] g/dL) within the 1.0 g/dL prespecified noninferiority margin. In all the subgroup analyses according to baseline characteristics, the LS mean difference between treatments in the change in Hb level was above −1.0 g/dL (online suppl. Fig. 5). Mean Hb levels remained in the prespecified target range at each visit until week 52 in both treatment groups over-

all (Fig. 2a) and when stratified based on low or high ESA dosage at baseline (Fig. 2b, c). For molidustat, the mean Hb levels also remained within the target range in all the baseline eGFR subgroups, with the exception of weeks 2–8 in the subgroup with eGFR < 15 mL/min/1.73 m², for which mean Hb levels were < 11.0 g/dL (online suppl. Fig. 6). For darbepoetin, the mean Hb levels also remained within the target range in all the baseline eGFR subgroups, with the exception of weeks 4–12 in the subgroup with eGFR < 15 mL/min/1.73 m², for which mean Hb levels were < 11.0 g/dL (online suppl. Fig. 6). The responder rate during the evaluation period was 72.0% in the moli-

Table 2. Summary of TEAEs up to week 52 (SAF)

	Molidustat (<i>n</i> = 82)	Darbepoetin (<i>n</i> = 82)	Total (<i>N</i> = 164)
Any TEAE, <i>n</i> (%)	76 (92.7)	79 (96.3)	155 (94.5)
Mild	40 (48.8)	54 (65.9)	94 (57.3)
Moderate	18 (22.0)	11 (13.4)	29 (17.7)
Severe	18 (22.0)	14 (17.1)	32 (19.5)
Any serious TEAE, <i>n</i> (%)	27 (32.9)	22 (26.8)	49 (29.9)
TEAE leading to death, <i>n</i> (%)	2 (2.4)	0	2 (1.2)
Common (≥5%) TEAEs by primary system organ class and preferred term			
Eye disorders, <i>n</i> (%)			
Conjunctivitis allergic	4 (4.9)	5 (6.1)	9 (5.5)
GI disorders, <i>n</i> (%)			
Constipation	7 (8.5)	7 (8.5)	14 (8.5)
Diarrhea	7 (8.5)	10 (12.2)	17 (10.4)
Large intestine polyp	0	5 (6.1)	5 (3.0)
General disorders and administration site conditions, <i>n</i> (%)			
Edema peripheral	7 (8.5)	2 (2.4)	9 (5.5)
Infections and infestations, <i>n</i> (%)			
Influenza	6 (7.3)	1 (1.2)	7 (4.3)
Nasopharyngitis	28 (34.1)	33 (40.2)	61 (37.2)
Pneumonia	4 (4.9)	5 (6.1)	9 (5.5)
Metabolism and nutrition disorders, <i>n</i> (%)			
Hyperkalemia	2 (2.4)	7 (8.5)	9 (5.5)
Hypoglycemia	6 (7.3)	0	6 (3.7)
Musculoskeletal and connective tissue disorders, <i>n</i> (%)			
Back pain	6 (7.3)	3 (3.7)	9 (5.5)
Psychiatric disorders, <i>n</i> (%)			
Insomnia	5 (6.1)	4 (4.9)	9 (5.5)
Renal and urinary disorders, <i>n</i> (%)			
CKD worsening ^a	15 (18.3)	8 (9.8)	23 (14.0)
Vascular disorders, <i>n</i> (%)			
Hypertension	2 (2.4)	5 (6.1)	7 (4.3)

A patient was counted only once within each preferred term or any primary SOC. CKD, chronic kidney disease; GI, gastrointestinal; SAF, safety analysis set; SOC, system organ class; TEAEs, treatment-emergent adverse events. ^aThe term “CKD worsening” is a collection of a variety of reported terms in the Medical Dictionary for Regulatory Activities (MedDRA). Specifically, “CKD worsening” includes the following terms: “chronic kidney disease exacerbation, chronic kidney disease progression, deterioration of CKD, exacerbation of CKD, progression of chronic kidney disease, worsening of CKD, worsening of chronic kidney disease, worsening of chronic renal failure, progression of chronic kidney disease, renal failure chronic aggravated, worsening of CKD, and worsening of renal failure.” According to the study protocol, the worsening of kidney function as a natural course of CKD was not recorded as a TEAE.

dustat group and 76.8% in the darbepoetin group, with a treatment difference (molidustat-darbepoetin) of -4.9 (95% CI; $-18.3, 8.6$) % (online suppl. Table 2).

After randomization and before the end of the evaluation period, the proportion of patients who received any ESA treatment or RBC transfusion was 1.2% (1/82) in the molidustat group and 3.7% (3/82) in the darbepoetin group. The main reason for the ESA treatment was initiation of maintenance dialysis (1 patient in the molidustat group), and adverse event and rescue treatment (2 pa-

tients in the darbepoetin group). The main reasons for RBC transfusion were rescue treatment (1 patient in the darbepoetin group) and an adverse event (1 patient in the darbepoetin group). On or after the end of the evaluation period and before the end of the treatment period, the proportion of patients who received any ESA treatment, HIF-PH inhibitor other than molidustat or RBC transfusion was 2.4% (2/82) in the molidustat group. The reason for the ESA treatment was initiation of maintenance dialysis (2 patients in the molidustat group). The propor-

tion of patients who received any ESA treatment other than darbepoetin, HIF-PH inhibitor, or RBC transfusion was 0% in the darbepoetin group.

Safety

Overall, 94.5% of patients experienced at least 1 TEAE during the study: 92.7% of patients in the molidustat group and 96.3% in the darbepoetin group (Table 2). The most commonly reported TEAEs were nasopharyngitis (34.1% and 40.2% in the molidustat and darbepoetin groups, respectively), worsening of CKD (18.3% and 9.8%, respectively), and diarrhea (8.5% and 12.2%, respectively) (Table 2). TEAEs leading to death were reported in 2 patients (2.4%) in the molidustat group and none in the darbepoetin group, and serious TEAEs were reported in 32.9% and 26.8% of patients, respectively. MACEs that occurred after the start of the study drug were reported in 3.7% of patients treated with molidustat and 1.2% of patients receiving darbepoetin (online suppl. Table 3). Additionally, 3.7% of patients in the molidustat group and 1.2% in the darbepoetin group developed diabetic retinopathy, and 3.7% in the molidustat group and 4.9% in the darbepoetin group developed neoplasms (benign, malignant, or unspecified) (online suppl. Table 4). The mean serum eGFR appeared to remain stable in the molidustat group (online suppl. Fig. 7). Subgroup analyses of TEAEs by age group (<65 and ≥65 years old) and by sex are presented in online supplementary Table 5. The proportion of serious TEAEs was similar between the 2 groups in female patients but higher for males in the molidustat group than in the darbepoetin group.

Discussion/Conclusion

The MIYABI ND-M study is part of the phase 3 MIYABI program designed to evaluate the safety, efficacy, and tolerability of molidustat in patients with renal anemia who were previously treated with ESAs or were ESA-naïve, and who were undergoing dialysis or not [22, 23]. In this phase 3, randomized, open-label, active-controlled study, molidustat was noninferior to darbepoetin in maintaining Hb levels within the target range of ≥11.0 g/dL and <13.0 g/dL during the evaluation period. In both treatment groups, the mean Hb level during the evaluation period was within the prespecified target range. Additionally, over the 52-week treatment period, molidustat was well tolerated, with a similar incidence of TEAEs to that reported in the darbepoetin group.

The analysis of the treatment difference between molidustat and darbepoetin, with respect to the change in mean Hb levels during the evaluation period from baseline, demonstrated that molidustat was noninferior to darbepoetin in maintaining Hb levels in patients with renal anemia who were previously treated with ESA and not undergoing dialysis. Moreover, molidustat was able to maintain Hb levels not only during the evaluation period but also at each visit up to week 52. A small decrease in Hb levels was observed until week 4 in the molidustat group, followed by a steady increase until week 20 and then stabilization. This decrease in Hb levels was observed in the subgroup of patients previously treated with a high dosage of ESA but not in those previously receiving low dosage of ESA. It is therefore possible that further dose optimization might be required to reach a steady state more rapidly in this patient population. Hb levels in both subgroups of patients overlapped from week 20 until the end of the evaluation period. In the molidustat treatment group, a similar transient decrease in Hb levels was observed in the subgroup of patients with a baseline eGFR <15 mL/min/1.73 m². The lower baseline total iron concentration observed in this subgroup of patients compared with patients with eGFR ≥15 mL/min/1.73 m² may account for this small initial decrease in Hb levels. In the darbepoetin group, there was no decrease in Hb levels in the subgroup of patients with a baseline eGFR <15 mL/min/1.73 m². There was no difference in baseline total iron levels between subgroups of patients stratified by eGFR levels in the darbepoetin treatment arm (online suppl. Table 6). In the present study, higher dosages were required to maintain Hb levels in patients with lower baseline eGFR in both groups. Such a trend was not observed in the MIYABI Non-Dialysis Correction study (data presented in the accompanying manuscript published in the same issue). This difference might be due to the difference in study population and further investigations will be required to fully understand these data.

In both treatment groups, similar proportions of patients reported at least 1 TEAE during the treatment period. The incidence of serious TEAEs was slightly higher in the molidustat group than in the darbepoetin group; however, none of the serious TEAEs were considered to be related to molidustat. In addition, the profile of molidustat observed in the present study was consistent with data from the long-term phase 2 DIALOGUE 3 study [20], and the safety profile of darbepoetin was consistent with previously published data [29]. In the molidustat group, the 2 TEAEs resulting in death were myocardial infarction and infectious pleural effusion. The TEAE of myocardial infarction leading to death

occurred in a 67-year-old female patient who had been smoking for 20 years and with a history of congenital cystic kidney disease, hypertension, and intracranial aneurysm. The patient's history of CKD, hypertension and smoking may represent a plausible cause for the occurrence of myocardial infarction. The TEAE of infectious pleural effusion occurred in a 75-year-old male patient with a history of CKD due to nephrosclerosis, aortic valve replacement, mitral valve replacement, heart failure (New York Heart Association functional class I), atrial fibrillation and infectious pleural effusion. Although no autopsies were performed, these 2 TEAEs were not considered by the investigator to be related to molidustat. Molidustat did not appear to affect eGFR during the study up to week 52, although no statistical analysis was performed to confirm this observation because no hypothesis and no statistical test were prespecified.

The development of potential new therapies for the treatment of renal anemia that have a different mechanism of action to ESA treatments may be beneficial for patients who are hyporesponsive or nonresponsive to ESA treatment or for patients with inflammation, as these patients are most likely to be exposed to high doses of ESA [11]. Additionally, as orally administered treatments, HIF-PH inhibitors have the potential to alleviate the burden imposed on patients due to regular injections of ESA.

The results presented here confirmed that molidustat offers an efficacious and well-tolerated alternative to ESA treatment in patients with renal anemia. However, further investigations in larger and longer trials would be required to fully characterize the incidence of MACE events associated with molidustat. In addition, there are theoretical concerns associated with the long-term use of HIF-PH inhibitors, such as enhanced retinal angiogenesis that might lead to retinopathy and activation of the tumor growth factor (e.g., VEGF) [15]. Although great caution and careful monitoring are warranted by these safety concerns, until now, no important safety signals associated with the use of HIF-PH inhibitors have been reported [11, 15]. In the present study, there were no major differences in the incidence of neoplasms, diabetic retinopathy, and retinal hemorrhage between treatment groups and these were considered unrelated to the study drugs by the investigator, except for 1 occurrence of diabetic retinopathy in a patient receiving molidustat.

A strength of this study is the inclusion of the standard of care, darbepoetin, as an active control. The results presented here should be interpreted in the context of several limitations. The open-label design may have introduced bias because of confounding variables, and is a limitation of this study. Another limitation is the lack of

generalizability of the safety results to the real-world CKD population due to the exclusion of patients with cardiovascular or cerebrovascular events in the 6 months before study drug assignment and of those with chronic inflammatory disease. Other limitations include the low number of patients and the short duration of the study. Finally, the stratification was based on a limited number of variables (previous ESA dose and thromboembolic events), which may have contributed to the observed imbalance in the safety outcomes.

In conclusion, molidustat was able to maintain Hb levels in the prespecified target range of >11.0 g/dL and <13 g/dL in patients with renal anemia not undergoing dialysis and previously treated with ESA, and was noninferior to the standard of care, darbepoetin. Overall, 52 weeks of treatment with dose-titrated molidustat were well tolerated in Japanese patients, and no new safety signal was observed.

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Statement of Ethics

The study protocol was approved by the Institutional Review Board and Ethics Committee for the participating center (online suppl. Tables 7 and 8). The study was conducted according to Good Clinical Practice guidelines from the International Council for Harmonisation and the principles detailed in the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from each participant before any study-related procedures were conducted.

Conflict of Interest Statement

H.Y. received consulting and lecture fees from Bayer Yakuhin, Ltd., during the conduct of the study. K.N., Y.M., Y.H., and T.H. are employees of Bayer Yakuhin, Ltd. T.A. received consulting and lecture fees from Bayer Yakuhin, Ltd., during the conduct of the study. He also received consulting, lecture, or manuscript fees outside the submitted work from Astellas, Chugai Pharmaceutical, FUSO Pharmaceutical Industries, GlaxoSmithKline, Japan Tobacco Pharmaceuticals, KISSEI, Kyowa Kirin, NIPRO, Ono Pharmaceutical, Otsuka Pharmaceutical, Sanwa Chemical, and Torii Pharmaceutical.

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Author Contributions

H.Y., K.N., Y.M., and T.A. participated in the study concept and design. All the authors were involved in the acquisition, analysis, and interpretation of data. All the authors participated in preparing the manuscript.

Data Availability Statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA Principles for Responsible Clinical Trial Data Sharing. This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the European Union and US, as necessary, for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the European Union and US regulatory agencies on or after January 1, 2014.

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