Efficacy and Safety of Molidustat for Anemia in ESA-Naive Nondialysis Patients: A Randomized, Phase 3 Trial

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Renal anemia · Chronic kidney disease · Efficacy · Safety · Molidustat

Abstract
Introduction: Molidustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that predominantly induces renal production of erythropoietin (EPO). Molidustat was evaluated for the treatment of anemia associated with chronic kidney disease (CKD) in the “Molidustat Once Daily Improves Renal Anemia by Inducing EPO” (MIYABI) program, which comprises 5 phase 3 clinical trials. The present MIYABI Non-Dialysis Correction (ND-C) study investigated the efficacy and safety of molidustat in Japanese patients with renal anemia who were not undergoing dialysis and were not receiving erythropoiesis-stimulating agent (ESA) treatment.

Methods: This was a 52-week, randomized (1:1), open-label, active-control, parallel-group, multicenter, phase 3 study in Japanese patients with renal anemia associated with CKD (stages 3–5). Molidustat or the ESA darbepoetin alfa (herein-after referred to as darbepoetin) were initiated at 25 mg once daily or 30 μg every 2 weeks, respectively, and doses were regularly titrated to correct and to maintain hemoglobin (Hb) levels in the target range of ≥11.0 g/dL and <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, 162 patients were randomized to receive molidustat (n = 82) or darbepoetin (n = 80). Baseline characteristics were generally well balanced between treatment groups. The mean (standard deviation) Hb levels at baseline were 9.84 (0.64) g/dL for molidustat and 10.00 (0.61) g/dL for darbepoetin. The mean (95% confidence interval [CI]) for mean Hb levels during the evaluation period for molidustat (11.28 [11.07, 11.50] g/dL) and darbepoetin (11.70 [11.50, 11.90] g/dL) was within the target range. Based on a noninferiority margin of 1.0 g/dL, molidustat was non-inferior to darbepoetin in the change in mean Hb level during the evaluation period from baseline; the least-squares mean (95% CI) difference (molidustat-darbepoetin) was −0.38 (−0.67, −0.08) g/dL. The proportion of patients who reported at least 1 treatment-emergent adverse event (TEAE) was 93.9% for molidustat and 93.7% for darbepoetin. Most TEAEs were mild (54.9% for molidustat and 63.3% for darbepoetin) or moderate (22.0% for molidustat and 22.8% for darbepoetin) in intensity. There were 3 deaths in the molidustat group and 1 in the darbepoetin group.

Discussion/Conclusion: This is an Open Access article licensed under the Creative Commons Attribution-NonCommercial-4.0 International License (CC BY-NC) (http://www.karger.com/Services/OpenAccessLicense), applicable to the online version of the article only. Usage and distribution for commercial purposes requires written permission.

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**Conclusion:** In the MIYABI ND-C study, molidustat appeared to be an efficacious and generally well-tolerated alternative to darbepoetin for the treatment of renal anemia in Japanese patients who were not undergoing dialysis and were not receiving ESA treatment.

**Introduction**

Renal anemia is a frequent complication of chronic kidney disease (CKD) that worsens as CKD progresses; it is associated with increased risk of hospitalization, cardiovascular events and death, and with reduced quality of life and work productivity [1–4]. In the Japanese population, the prevalence of renal anemia among patients with CKD stages 3–5 has been estimated to be in the range of 8–60% [5–7]. Deficient synthesis of erythropoietin (EPO) in the kidneys is reported as the main cause of renal anemia [8]. Other factors that also contribute to renal anemia include shortened erythrocyte lifespan, dysregulated iron homeostasis, inflammation, and nutritional deficiencies of folate and vitamin B12 [8, 9]. For men and women younger than 60 years of age, the Japanese Society for Dialysis Therapy (JSDT) guidelines define the diagnostic criteria for renal anemia as hemoglobin (Hb) levels in the range of <13.5 g/dL and <11.5 g/dL, respectively [10].

Injection of erythropoiesis-stimulating agents (ESAs) is the standard of treatment for renal anemia, and the JSDT guidelines recommend adjusting the ESA dose to maintain Hb levels in the range of ≥11.0 g/dL and <13.0 g/dL in patients with CKD not undergoing dialysis [10, 11]. In contrast, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, commonly followed by Western countries, suggest that ESA treatment in adult patients with CKD should be adjusted to maintain Hb levels ≤11.5 g/dL [11]. Although ESAs are generally effective in increasing Hb levels, some patients respond poorly to treatment with ESAs and their use may be associated with an increased risk of death and cardiovascular events [12–15]. Furthermore, ESAs can cause functional iron deficiency, which may involve a need for concomitant intravenous iron supplementation, and their parenteral administration is often perceived as inconvenient by patients [11, 16]. Hence, the development of alternative therapies for the treatment of renal anemia could be highly beneficial for patients.

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors represent a potential alternative treatment to ESAs for renal anemia [17]. In normoxia, HIF-PH inhibits the transcription of the EPO gene in the kidneys by mediating the degradation of the hypoxia-inducible factor-α (HIF-α). HIF-PH inhibitors mimic the physiological response to hypoxia by stabilizing HIF-α and subsequently increasing the endogenous production of renal EPO [18]. HIF-PH inhibitors can also improve iron availability, by increasing iron export and iron mobilization, and reduce the expression of inflammatory markers associated with anemia [19, 20]. Molidustat, an oral HIF-PH inhibitor, is being investigated as a potential therapy for renal anemia, and its route of administration may also represent an advantage over injection of ESAs. Unlike the injection of recombinant human EPO (rhEPO), in preclinical studies molidustat increased the endogenous production of renal EPO – and to a lesser extent of hepatic EPO – close to the normal physiological range, leading to normal hematocrit and Hb levels [20, 21]. In the phase 2b “Daily Oral Treatment Increasing Endogenous EPO” (DIALOGUE) program, molidustat displayed similar efficacy and safety to the ESA darbepoetin alfa (hereinafter referred to as darbepoetin) for the treatment of patients with renal anemia who were not undergoing dialysis [22, 23]. Following the DIALOGUE phase 2 trials, the “Molidustat Once Daily Improves Renal Anemia by Inducing EPO” (MIYABI) phase 3 program comprising 5 studies was conducted in Japan to further investigate the efficacy and safety of molidustat for the treatment of Japanese patients with renal anemia [24, 25]. Three of the MIYABI studies were 52-week, randomized active-control trials evaluating the efficacy and safety of molidustat compared with darbepoetin according to dialysis and previous ESAs treatment status (ND-C: nondialysis correction, ND-M: nondialysis maintenance, and HD-M: hemodialysis maintenance) [25]. The other 2 MIYABI trials were 24- and 36-week, single-arm studies for the evaluation of molidustat treatment in patients who were undergoing hemodialysis or peritoneal dialysis, respectively (HD-C: hemodialysis correction and PD: peritoneal dialysis correction and maintenance) [24, 26]. Here, we present the results from the MIYABI ND-C study (NCT03350321), which investigated the efficacy and safety of molidustat over a 52-week period in a Japanese population of patients with renal anemia, who were not undergoing dialysis and were not receiving ESA treatment.

**Materials and Methods**

**Study Design**

The design of the MIYABI ND-C study has been previously described (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000518071) [25]. In summary, this was a 52-week, randomized, open-label, active-control, paral-
Molidustat in ESA-Naive Japanese Patients Not on Dialysis

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Am J Nephrol

Molidustat in ESA-Naive Japanese

Women aged 20 years or older who: had CKD with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m² using the Matsuo et al. [27] formula; were not undergoing dialysis or were not expected to start undergoing dialysis during the study period; were not receiving ESAs and/or HIF-PHI inhibitors in the 8 weeks before randomization; and had mean central Hb levels based on the last 2 screening measurements, of ≥8.0 g/dL and <11.0 g/dL, with a difference between the 2 measurements (taken ≥2 days apart) of <1.2 g/dL.

Key exclusion criteria included a history of cardiovascular or cerebrovascular events in the 6 months before randomization, sustained and poorly controlled arterial hypertension (systolic blood pressure [SBP] ≥180 mmHg or diastolic blood pressure ≥110 mmHg) or hypotension (SBP <90 mmHg) at randomization stage, and presence of New York Heart Association Class III or IV congestive heart failure.

Treatments

Molidustat was administered orally once daily after breakfast at a starting dose of 25 mg (based on the PK/PD analysis of the phase 2 DIALOGUE studies) for the first 4 weeks of the study, and darbepoetin was injected subcutaneously every 2 weeks at a starting dose of 30 μg. Dosing for both treatments was adjusted in a stepwise manner, based on the Hb response to the previous dose, to correct or to maintain Hb levels in the target range of ≥11.0 g/dL and <13.0 g/dL, as detailed previously [25]. In the molidustat group, dose titration visits were scheduled every 4 weeks after the first 8 weeks of the treatment. In the darbepoetin group, titrations were initially scheduled every 2 weeks during the treatment period, but the frequency changed to every 4 weeks once Hb levels were stabilized within the target range. In addition to regular titration, a dose adaptation visit was scheduled at week 4 (visit 3) to prevent excessive elevation of Hb levels following treatment initiation with molidustat and darbepoetin, and doses were adjusted based on the local Hb level at randomization and the local Hb level at visit 3. In both treatment groups, doses were reduced to the next lowest available dose or suspended (in cases in which no lower dose was available) at any time if the rate of Hb increase was >1.0 g/dL per 2 weeks or >2.0 g/dL per 4 weeks. For patients with a medical history of thromboembolic events and with Hb levels exceeding 12 g/dL, doses of molidustat or darbepoetin could be reduced to the next lowest available dose or suspended, if no lower dose was available, at the investigator’s discretion.

Patients with iron, folate, and vitamin B12 deficiencies were treated prior to enrollment in the study and during the study period. All the supplements were administered at the investigator’s discretion following current guidelines to maintain appropriate levels of these parameters. During the treatment period, iron supplementation should be administered orally in principle, with the aim of targeting serum ferritin levels of ≥100 ng/mL or transferrin saturation of ≥20%, in line with JSDT guidelines [10]. Folate and vitamin B12 levels were measured only during the screening period, whereas iron metabolism parameters (total iron, ferritin, total iron binding capacity, transferrin saturation, and unsaturated iron binding capacity) were quantified during the screening period and at each study visit, excluding weeks 30 and 34.

During the study, rescue treatment to address low Hb levels (i.e., red blood cell [RBC] transfusion or any ESA treatment) could be administered at the discretion of the investigator or treating physician. However, it was not recommended for patients who had Hb levels of ≥8.0 g/dL.

Outcomes

The primary efficacy outcomes were the mean Hb level during the evaluation period and its change from baseline. The primary efficacy of molidustat was demonstrated if 2 conditions were met. First, the mean Hb level during the evaluation period for molidustat treatment had to be within the prespecified target range, with the lower and upper limits of the 2-sided 95% confidence interval (CI) being ≥11.0 g/dL and <13.0 g/dL, respectively. Second, molidustat had to be noninferior to darbepoetin based on the difference between treatments (molidustat-darbepoetin) in the change in mean Hb level during the evaluation period from baseline; noninferiority was established if the lower limit of the 2-sided 95% CI for the difference was above −1.0 g/dL, with a noninferiority margin of 1.0 g/dL. The 1.0 g/dL noninferiority margin used in this study was selected based on: (1) a variation of approximately 1.0 g/dL in Hb levels being accepted in routine clinical practice according to the 2015 JSDT for Renal Anemia in Chronic Kidney Disease guidelines [10] and (2) a Hb equivalence margin of 1.0 g/dL being used in another study evaluating the efficacy of darbepoetin for the treatment of renal anemia [28].

Data were analyzed for subgroups defined by baseline characteristics. Mean Hb levels at each study visit and during the evaluation period were explored according to baseline eGFR (eGFR ≥30 mL/min/1.73 m², eGFR ≥15 and <30 mL/min/1.73 m², and eGFR <15 mL/min/1.73 m²) and according to baseline C-reactive protein (CRP) levels (CRP ≤0.3 mg/dL and CRP >0.3 mg/dL) as part of a post hoc analysis. Additionally, post hoc analyses of study drug dosages were also conducted in subgroups according to baseline eGFR and CRP levels. Secondary outcomes included the proportion of patients who had Hb levels below, within, and above the target range at each study visit and the responder rate for each treatment group, which was defined as the proportion of patients who met the following criteria: (1) the mean Hb level during the evaluation period was within the target range of ≥11.0 g/dL and <13.0 g/dL, (2) ≥50% of the Hb levels during the evaluation period were within the target range, and (3) rescue treatment was not received up to the end of the evaluation period. The proportion of patients who received at least 1 use of RBC transfusion, ESA, or...
HIF-PH inhibitor (regardless of the main indication) were also evaluated [25].

Safety outcomes included all treatment-emergent adverse events (TEAEs) observed during the 52 weeks of treatment, as assessed by the principal investigator and coded using the Medical Dictionary for Regulatory Activities version 22.0. A TEAE was predefined as any event that occurred between the first study drug intake and the date of the end of treatment visit/premature discontinuation visit plus 3 days, inclusive. The incidence of major adverse cardiovascular events (MACEs), adjudicated by an independent committee of specialists (online suppl. Table 2), was also investigated. MACEs were defined as cardiovascular death, myocardial infarction, unstable angina pectoris, ischemic stroke (ischemic stroke or ischemic stroke with hemorrhagic transformation), pulmonary thromboembolism, and acute limb ischemia. Measurements of clinically relevant laboratory parameters, including serum cholesterol, were also conducted as part of the safety evaluation. Parameters of iron treatment, iron metabolism, and renal function (including eGFR based on serum creatinine measurements) were investigated as exploratory variables [25].

**Statistical Analysis**

A target sample size of 75 patients per treatment arm was determined following the formal power calculation analysis and considering sufficiency of safety data, as previously detailed [25]. The full analysis set (FAS) and the safety analysis set (SAF) were the primary sets for analysis of efficacy and safety, respectively. The FAS included all randomized patients who had at least 1 baseline Hb level recorded before the first dose of molidustat or darbepoetin. The SAF was based on all randomized patients who received at least 1 dose of the study drug. Sensitivity analyses were conducted in the per protocol set (PPS), which included all patients from the FAS who had at least 2 central Hb levels collected at weeks 30 (visit 10), 32 (visit 11), 34 (visit 12), or 36 (visit 13)/premature discontinuation visit and who showed no validity findings that may have affected efficacy (findings after week 36 were not considered). Validity findings that may have affected efficacy included treatment compliance <80%, no treatment with the study drug, and violation of inclusion/exclusion criteria that may have impacted the evaluation of efficacy.

Baseline Hb level was calculated as the mean of the last 2 central Hb levels during the screening period and the central measurement at visit 1 (baseline visit). The mean Hb level during the evaluation period was calculated using the central Hb levels collected at each scheduled visit during this period (visits 10–13). If rescue treatment was started before week 36 (visit 13), 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. When <2 valid central Hb levels (measured at scheduled visits) were available during the evaluation period, imputation was conducted using Hb levels measured after baseline (visit 1) to ensure that at least 1 valid determination was available at any visit during the evaluation period. In the process of imputation, post-baseline Hb levels were used in the following priority order: (1) the local Hb level at the scheduled visit during the evaluation period; (2) the latest unscheduled central Hb level in the week prior to the evaluation period scheduled visit; and (3) the latest unscheduled local Hb level in the week prior to the evaluation period scheduled visit. If Hb levels were missing after the imputation, the last central or local Hb level measured after the first dose of study drug was used as the mean Hb level during the evaluation period.

Descriptive statistical analyses were presented for efficacy, safety, and exploratory variables. For molidustat, the mean of the mean Hb levels during the evaluation period and its 2-sided 95% CI were estimated using 1-sample t statistics. The least-squares (LS) mean difference between treatments (molidustat-darbepoetin) for the change in mean Hb level during the evaluation period from baseline and its 2-sided 95% CI were estimated using an analysis of covariance (ANCOVA) model. In the ANCOVA model, treatment group and prior thromboembolic events were included as fixed effects and baseline Hb levels as a covariate.

### Results

**Patient Disposition and Baseline Characteristics**

Following screening, 162 patients were randomized to receive molidustat (n = 82) or darbepoetin (n = 80) (online suppl. Fig. 2). All randomized patients received the assigned study drug except for 1 in the darbepoetin group. In total, 135 patients completed treatment up to week 36 (63 [76.8%] for molidustat and 72 [90.0%] for darbepoetin), and 118 patients completed treatment up to week 52 (53 [64.6%] for molidustat and 65 [81.3%] for darbepoetin). The primary reasons for study drug discontinuation are detailed in online suppl. Tables 3 and 4.

Demographic and baseline characteristics were generally well balanced between treatment groups, with numerical differences observed for eGFR, main cause of CKD (such as diabetic nephropathy and nephrosclerosis), SBP, CKD duration, and CKD stages G3a, G3b, and G4 (Table 1). Mean (standard deviation [SD]) Hb level at baseline was 9.84 (0.64) g/dL for molidustat and 10.00 (0.61) g/dL for darbepoetin. Additionally, most patients (146/162, 90.1%) had no prior thromboembolic events (Table 1; online suppl. Table 5).

**Efficacy Outcomes**

The mean (95% CI) Hb level during the evaluation period was 11.28 (11.07, 11.50) g/dL for molidustat and 11.70 (11.50, 11.90) g/dL for darbepoetin; both were within the prespecified target range of ≥11.0 g/dL and <13.0 g/dL (Fig. 1a). The LS mean change in mean Hb level during the evaluation period from baseline was 1.32 g/dL and 1.69 g/dL for the molidustat and darbepoetin groups, respectively. Based on the prespecified noninferiority margin of 1.0 g/dL, molidustat was noninferior to darbepoetin, with a LS mean difference (95% CI) between treatments (molidustat-darbepoetin) of −0.38 (−0.67, −0.08) g/dL. In all the subgroup analyses according to baseline characteristics, the LS mean difference (molidustat-dar-
bepoetin) in the change in mean Hb level was above −1.0 g/dL (online suppl. Fig. 3). Primary efficacy outcomes were also explored in the PPS (online suppl. Table 6).

The mean Hb levels at each study visit in the FAS remained within the prespecified target range from week 12 for molidustat and from week 8 for darbepoetin (Fig. 1a). The proportion of patients with Hb levels below, within, and above the prespecified target range (≥11.0 g/dL and <13.0 g/dL) at each study visit for both treatments are presented in Figure 2. During the evaluation period, 68.3% of patients in the molidustat group and 85.0% of those in the darbepoetin group had Hb levels within the prespecified target range (Fig. 2). For molidustat, the mean Hb levels also remained within the target range from week 16 when stratified according to baseline eGFR subgroups, with the exception of weeks 34 and 40 in the subgroup with eGFR <15 mL/min/1.73 m², for which mean Hb levels were <11.0 g/dL (Fig. 1b). For darbepoetin, the mean Hb levels were within the prespecified target range from week 8 in all the eGFR subgroups (Fig. 1c).

### Table 1. Summary of demographic and baseline characteristics in the FAS

| Parameter                                      | Molidustat (n = 82) | Darbepoetin (n = 80) | Total (N = 162) |
|------------------------------------------------|---------------------|---------------------|-----------------|
| Men, n (%)                                     | 50 (61.0)           | 50 (62.5)           | 100 (61.7)      |
| Age, mean (SD), years                         | 72.1 (9.3)          | 71.2 (10.1)         | 71.7 (9.6)      |
| Weight, mean (SD), kg                         | 61.10 (10.00)       | 60.48 (10.40)       | 60.80 (10.17)   |
| Hb, mean (SD), g/dL                           | 9.84 (0.64)         | 10.00 (0.61)        | 9.92 (0.63)     |
| eGFR, mean (SD), mL/min/1.73 m²                | 19.0 (8.5)          | 22.1 (12.0)         | 20.5 (10.5)     |
| Ferritin, mean (SD), ng/mL                     | 118.9 (97.4)        | 137.9 (113.9)       | 128.3 (106.0)   |
| Transferrin saturation, mean (SD), %           | 28.5 (8.5)          | 29.9 (9.7)          | 29.2 (9.1)      |
| Vitamin B12, mean (SD), pmol/L                 | 291.4 (141.2)       | 304.7 (185.0)       | 298.0 (163.8)   |
| Folate, mean (SD), nmol/L                      | 32.4 (103.9)        | 46.1 (190.0)        | 39.2 (152.3)    |
| Serum CRP, mean (SD), mg/dL                    | 0.317 (0.630)       | 0.148 (0.241)       | 0.234 (0.485)   |
| HbA1c, mean (SD), %                            | 6.02 (0.62)         | 6.00 (0.75)         | 6.01 (0.68)     |
| LDL cholesterol, mean (SD), mg/dL              | 99.6 (29.2)         | 100.5 (31.2)        | 100.1 (30.1)    |
| HDL cholesterol, mean (SD), mg/dL              | 50.8 (16.3)         | 51.7 (16.6)         | 51.2 (16.4)     |
| Triglycerides, mean (SD), mg/dL                | 144.8 (90.6)        | 152.8 (121.8)       | 148.7 (106.9)   |
| Smoking history, n (%)                         | 33 (40.2)           | 35 (43.8)           | 68 (42.0)       |
| Former                                         | 10 (12.2)           | 7 (8.8)             | 17 (10.5)       |
| Current                                        |                     |                     |                 |
| CKD stage based on eGFR, n (%)                 |                     |                     |                 |
| G3a (≥45 and <60 mL/min/1.73 m²)               | 1 (1.2)             | 5 (6.3)             | 6 (3.7)         |
| G3b (≥30 and <45 mL/min/1.73 m²)               | 9 (11.0)            | 14 (17.5)           | 23 (14.2)       |
| G4 (≥15 and <30 mL/min/1.73 m²)                | 43 (52.4)           | 34 (42.5)           | 77 (47.5)       |
| G5 (<15 mL/min/1.73 m²)                        | 29 (35.4)           | 27 (33.8)           | 56 (34.6)       |
| Main cause of CKD, n (%)                       |                     |                     |                 |
| Chronic glomerulonephritis                     | 19 (23.2)           | 19 (23.8)           | 38 (23.5)       |
| Diabetic nephropathy                           | 34 (41.5)           | 22 (27.5)           | 56 (34.6)       |
| Nephrosclerosis                                | 17 (20.7)           | 28 (35.0)           | 45 (27.8)       |
| Polycystic kidney disease                      | 5 (6.1)             | 3 (3.8)             | 8 (4.9)         |
| Others                                         | 7 (8.5)             | 8 (10.0)            | 15 (9.3)        |
| CKD duration, mean (SD), years                 | 7.369 (7.823)       | 8.564 (10.604)      | 7.959 (9.291)   |
| Prior thromboembolic events, n (%)             | 8 (9.8)             | 8 (10.0)            | 16 (9.9)        |
| SBP, mean (SD), mmHg                           | 138.2 (17.0)        | 133.3 (15.8)        | 135.8 (16.6)    |
| DBP, mean (SD), mmHg                           | 71.6 (13.2)         | 69.1 (10.2)         | 70.3 (11.9)     |

Calculated percentages are subject to rounding. CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

a Baseline Hb level was defined as the mean of the last 2 central Hb levels during the screening period and central Hb level at visit 1 (baseline visit). b eGFR was calculated using serum creatinine and the formulas from Matsuo et al. [27].
Fig. 1. Mean (SD) Hb levels at each study visit in the FAS: for each treatment (including overall mean during the evaluation period and at the end of follow-up) (a); and by baseline eGFR subgroup for molidustat (b) and darbepoetin (c). Dashed lines indicate the limits of the target range (≥11.0 g/dL and <13.0 g/dL). Baseline Hb level was defined as the mean of the last 2 central Hb levels during the screening period and central Hb level at visit 1 (baseline visit). BL, baseline; eGFR, estimated glomerular filtration rate; EOF, end of follow-up; FAS, full analysis set; Hb, hemoglobin; SD, standard deviation.
Regarding the effect of inflammation, mean Hb levels in both baseline CRP subgroups remained within the pre-specified target range from weeks 12 and 16 for molidustat and darbepoetin, respectively (online suppl. Fig. 4). For darbepoetin, mean Hb levels up to week 20 were moderately lower for patients in the subgroup with CRP levels >0.3 mg/dL compared with those in the subgroup with CRP levels ≤0.3 mg/dL. Mean Hb levels for molidustat were overall similar between patients in both CRP subgroups up to week 28. During the evaluation period,
molidustat showed numerically lower mean Hb levels in the subgroup with CRP levels >0.3 mg/dL than in the subgroup with CRP levels ≤0.3 mg/dL (online suppl. Fig. 4a). In contrast, in the darbepoetin group mean Hb levels during the evaluation period appeared to be overall higher in patients with CRP levels >0.3 mg/dL than in those with CRP levels ≤0.3 mg/dL (online suppl. Fig. 4b).

The responder rate during the evaluation period was 59.8% in the molidustat group and 82.5% in the darbepoetin group, and the point estimate (95% CI) of the treatment difference (molidustat-darbepoetin) was −21.3% (−34.9, −7.7) (online suppl. Table 7). Analysis of the responder rate using the PPS is shown in online suppl. Table 8. After randomization and before the end of the evaluation period (week 36), the proportion of patients who received any ESA, HIF-PH inhibitor, or RBC transfusion (regardless of the main indication) was 2.4% (2/82) in the molidustat group and 3.8% (3/80) in the darbepoetin group. RBC transfusion was administered as a rescue treatment in 1 patient in each treatment group. Adverse event (AE) was the main reason for RBC transfusion in 1 additional patient in the darbepoetin group. ESA treatment was administered due to initiation of maintenance dialysis (1 patient in each treatment group) and after RBC transfusion (1 patient in the darbepoetin group). On or after the end of the evaluation period and before the end of the treatment period (week 52), 1 patient in the molidustat group received ESA treatment due to an AE. No patients required treatment with HIF-PH inhibitor or RBC transfusion.

**Exploratory Outcomes**

Over the 52-week treatment period, oral iron treatment (excluding iron treatment, which was not intended to supply iron) was administered to 50.0% (41/82) of patients in the molidustat group and 40.5% (32/79) of those in the darbepoetin group. Intravenous iron treatment was administered to 4 patients in each treatment group. The mean (SD) of the mean dosage of oral iron intended to supply iron deficiency during the treatment period was 48.98 (41.81) mg/day in the molidustat group and 40.1 (3.9–143.6) mg/day, respectively, for molidustat and darbepoetin. Dose adjustments up to week 18.32 (12.87) μg/week and 15.0 (2.4–63.5) μg/week, respectively, for darbepoetin. Up to week 52, treatment terminated before the end of the treatment period for 35.4% (29/82) of patients in the molidustat group and 18.8% (15/80) in the darbepoetin group (online suppl. Table 4).

After 52 weeks of treatment, mean (SD) and median (range) actual dosages were 46.30 (30.64) mg/day and 40.1 (3.9–143.6) mg/day, respectively, for molidustat and darbepoetin. Mean Hb levels showed a very minor decrease over time (online suppl. Fig. 5). Additionally, in both treatment groups, mean eGFR showed a very minor decrease over time (online suppl. Fig. 6).

**Exposure to Treatments**

Over the course of the study, mean (SD) and median treatment duration were 291.3 (109.0) days and 363.0 days, respectively, in the molidustat group and 335.4 (66.8) days and 364.0 days, respectively, in the darbepoetin group. The minimum and maximum durations of exposure were 4 days and 371 days, respectively, for molidustat and 14 days and 367 days, respectively, for darbepoetin. Up to week 52, treatment terminated before the end of the treatment period for 35.4% (29/82) of patients in the molidustat group and 18.8% (15/80) in the darbepoetin group (online suppl. Table 4).

After 52 weeks of treatment, mean (SD) and median (range) actual dosages were 46.30 (30.64) mg/day and 40.1 (3.9–143.6) mg/day, respectively, for molidustat and darbepoetin. Dose adjustments up to week 52 were required in 80 patients in the molidustat group and 76 patients in the darbepoetin group.

A post hoc analysis explored the mean dosage by visit for molidustat and darbepoetin according to baseline eGFR (online suppl. Fig. 7) and CRP (online suppl. Fig. 8) subgroups. For molidustat, the mean actual dosage for the patients in the eGFR <15 mL/min/1.73 m² subgroup was 46.71 (30.64) mg/day (range) actual dosages were 46.30 (30.64) mg/day and 40.1 (3.9–143.6) mg/day, respectively, for molidustat and darbepoetin. Dose adjustments up to week 52 were required in 80 patients in the molidustat group and 76 patients in the darbepoetin group.

A post hoc analysis explored the mean dosage by visit for molidustat and darbepoetin according to baseline eGFR (online suppl. Fig. 7) and CRP (online suppl. Fig. 8) subgroups. For molidustat, the mean actual dosage for the patients in the eGFR <15 mL/min/1.73 m² subgroup appeared to be numerically higher from week 4 (visit 3) compared with the other 2 eGFR subgroups (online suppl. Fig. 7a). Regarding CRP levels, a trend toward higher mean dosages of darbepoetin during the study period was observed in patients with CRP levels >0.3 mg/dL compared with those with CRP levels ≤0.3 mg/dL (online suppl. Fig. 8b). Such trend was not observed in the molidustat group (online suppl. Fig. 8a).

**Safety**

During the study, 93.9% of patients (77/82) in the molidustat group and 93.7% (74/79) in the darbepoetin group experienced at least 1 TEAE (Table 2). Most TEAEs were mild (54.9% for molidustat and 63.3% for darbepoetin) or moderate (22.0% for molidustat and 22.8% for darbepoetin) in intensity. Severe TEAEs were also observed in 17.1% of patients for molidustat and 7.6% for darbepoetin. The most common TEAEs were nasopharyngitis (31.7% for molidustat and 26.6% for darbepoetin) and worsening of CKD (19.5% for molidustat and 11.4% for darbepoetin) (Table 2). Serious TEAEs were reported in 35.4% (29/82) and 34.2% (27/79) of patients in the moli-
In total, there were 3 deaths in the molidustat group and 1 in the darbepoetin group. For molidustat, the AEs with outcome of death were completed suicide (in 1 patient), septic shock (in 1 patient), and interstitial lung disease, disseminated intravascular coagulation, and cerebral infarction (all in the same patient). Two AEs with outcome of death in the molidustat group (completed suicide and interstitial lung disease) and none in the darbepoetin group were considered TEAEs (Table 2).

Table 2. TEAEs reported up to week 52 in the SAF

| Category                                                   | Molidustat (n = 82) | Darbepoetin (n = 79) | Total (N = 161) |
|-------------------------------------------------------------|---------------------|----------------------|-----------------|
| Any TEAE, n (%)                                            | 77 (93.9)           | 74 (93.7)            | 151 (93.8)      |
| Mild                                                        | 45 (54.9)           | 50 (63.3)            | 95 (59.0)       |
| Moderate                                                   | 18 (22.0)           | 18 (22.8)            | 36 (22.4)       |
| Severe                                                      | 14 (17.1)           | 6 (7.6)              | 20 (12.4)       |
| Any serious TEAE, n (%)                                     | 29 (35.4)           | 27 (34.2)            | 56 (34.8)       |
| Any TEAE leading to death, n (%)                           | 2 (2.4)             | 0                    | 2 (1.2)         |

TEAEs reported in ≥5% of the patients from any treatment group:

- **Eye disorders, n (%)**
  - Cataract 1 (1.2) 6 (7.6) 7 (4.3)
  - Gastrointestinal disorders, n (%)
    - Constipation 10 (12.2) 8 (10.1) 18 (11.2)
    - Dental caries 1 (1.2) 4 (5.1) 5 (3.1)
    - Diarrhea 8 (9.8) 3 (3.8) 11 (6.8)
    - Nausea 6 (7.3) 4 (5.1) 10 (6.2)
    - Stomatitis 1 (1.2) 4 (5.1) 5 (3.1)

- **General disorders and administration site conditions, n (%)**
  - Pyrexia 1 (1.2) 5 (6.3) 6 (3.7)

- **Infections and infestations, n (%)**
  - Bronchitis 5 (6.1) 3 (3.8) 8 (5.0)
  - Nasopharyngitis 26 (31.7) 21 (26.6) 47 (29.2)
  - Pneumonia 6 (7.3) 2 (2.5) 8 (5.0)

- **Injury, poisoning, and procedural complications, n (%)**
  - Contusion 10 (12.2) 3 (3.8) 13 (8.1)

- **Metabolism and nutrition disorders, n (%)**
  - Hyperkalemia 10 (12.2) 9 (11.4) 19 (11.8)

- **Musculoskeletal and connective tissue disorders, n (%)**
  - Back pain 8 (9.8) 3 (3.8) 11 (6.8)
  - Muscle spasms 2 (2.4) 5 (6.3) 7 (4.3)

- **Renal and urinary disorders, n (%)**
  - CKD worsening a 16 (19.5) 9 (11.4) 25 (15.5)

- **Respiratory, thoracic, and mediastinal disorders, n (%)**
  - Cough 2 (2.4) 4 (5.1) 6 (3.7)

- **Skin and subcutaneous tissue disorders, n (%)**
  - Eczema 3 (3.7) 4 (5.1) 7 (4.3)

- **Surgical and medical procedures, n (%)**
  - Arteriovenous fistula operation 3 (3.7) 5 (6.3) 8 (5.0)

- **Vascular disorders, n (%)**
  - Hypertension 8 (9.8) 4 (5.1) 12 (7.5)

Calculated percentages are subject to rounding. CKD, chronic kidney disease; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event. a Primary SOC term from Medical Dictionary for Regulatory Activities version 22.0. A patient was counted only once within each preferred term or any primary SOC. b The term “CKD worsening” in the TEAE table is a collection of a variety of reported terms in the Medical Dictionary for Regulatory Activities. 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. The study protocol defined that the worsening of kidney function as a natural course of CKD should not be recorded as an adverse event, and therefore, these events were not recorded as TEAEs.
Adjudicated and confirmed MACEs that occurred after the start of the study drug were reported in 7.3% of patients treated with molidustat (6/82) and none of those treated with darbepoetin (online suppl. Table 9). One cardiovascular death (owing to interstitial lung disease, disseminated intravascular coagulation, and cerebral infarction) and 1 undetermined death (owing to septic shock) were observed in the molidustat group. None of the 6 MACEs identified in the molidustat group were considered to be related to the study drug by the investigators. Serum cholesterol levels at each study visit remained stable compared with baseline levels (online suppl. Fig. 9).

Discussion

The MIYABI ND-C study, 1 of the phase 3 randomized-controlled trials of the comprehensive MIYABI program, was designed to evaluate the efficacy and safety of molidustat over a 52-week period in the treatment of renal anemia in Japanese patients who were not undergoing dialysis and were not receiving ESA treatment [24, 25]. In this 52-week, randomized, open-label, active-control, parallel-group, multicenter, phase 3 study, molidustat demonstrated similar efficacy and tolerability to darbepoetin. MIYABI ND-C is the first clinical trial to demonstrate that molidustat was noninferior to darbepoetin with respect to correcting and maintaining mean Hb levels within the prespecified target range in this patient population. Furthermore, during the 52 weeks of treatment, molidustat was generally well tolerated and showed a similar incidence of TEAEs to darbepoetin.

During the evaluation period, molidustat maintained the mean Hb levels within the target range of ≥11.0 g/dL and <13.0 g/dL. Mean Hb levels for molidustat at each study visit were also within the prespecified target range from weeks 12 to 52. Moreover, molidustat was noninferior to darbepoetin as defined in this study. However, the proportion of patients with Hb levels outside the target range during the evaluation period was higher with molidustat than with darbepoetin. Furthermore, Hb concentrations in the molidustat group tended to be generally lower than those in the darbepoetin group. Although in phase 2 studies molidustat has been shown to increase Hb levels in a dose-dependent manner, it cannot be extrapolated that an increase in molidustat dosages would have resulted in an increase in Hb levels to those observed for darbepoetin, without affecting the safety profile of molidustat [23]. Although intention-to-treat analyses are the standard in clinical trials, the PPS analyses may also provide a clue to explain the differences observed between treatment groups in responder rate and in mean Hb level during the evaluation period. Indeed, according to the PPS analyses, these differences may have been due to differences in discontinuation rates between both groups.

Subgroup analyses according to baseline characteristics, including eGFR and CRP levels, were also conducted to investigate their effect on dosage and Hb levels during the treatment period. Patients with baseline eGFR <15 mL/min/1.73 m² in the molidustat group appeared to require higher dosages than those with eGFR levels in the other 2 predefined subgroups. The reduction in the number and the activity of renal EPO-producing cells as renal function declines could be one of the underlying reasons for this trend in dosages observed in the molidustat group. The numerically higher levels of pro-inflammatory markers such as CRP, hepcidin, and ferritin that were observed in the eGFR <15 mL/min/1.73 m² subgroup compared with the other 2 subgroups (online suppl. Table 10) may have also contributed to the increased dosages of molidustat required to achieve the prespecified Hb levels in patients with the lowest renal function. The baseline inflammatory status did not appear to have a significant effect in the mean Hb levels and the actual dosage of molidustat during the study period. Although higher dosages of darbepoetin appeared to be required in the subgroup of patients with the highest CRP levels, this trend was not observed for molidustat. In both treatment groups, higher concentration of hepcidin (inflammatory marker) and lower transferrin saturation percentage and total iron concentration were observed in patients in the subgroup with CRP levels >0.3 mg/dL compared with those who had CRP levels ≤0.3 mg/dL. Importantly, in this trial patients who had chronic inflammatory diseases were excluded, and additional investigation will be required to evaluate the effect that inflammation may have on the treatment of this specific population with molidustat. Overall, owing to the small size of the subgroups and the high variability in the data, further investigation will be required to reach meaningful conclusions for the subgroup analyses.

Safety outcomes in the MIYABI ND-C study in terms of overall incidence of TEAEs and serious TEAEs were consistent with the results from the long-term phase 2b
DIALOGUE 3 study evaluating treatment with molidustat and darbepoetin for ≤36 months in patients not undergoing dialysis [22]. During the 52 weeks of treatment, the proportions of patients presenting with at least 1 TEAE in the molidustat group were similar to that observed for darbepoetin. Although the proportion of severe TEAEs was higher for molidustat than for darbepoetin, the incidence of serious TEAEs was similar in both groups. Regarding AEs of special interest, the incidence of MACEs was notably higher for molidustat compared with darbepoetin. Interestingly, despite the differences in MACEs between the 2 treatment groups in the present study, the incidence of cardiovascular death was lower than that reported in a Japanese cohort of patients with CKD [29]. The imbalance observed between the 2 treatment groups for some baseline characteristics (such as CRP, SBP, eGFR, diabetic nephropathy, and CKD stage) may have affected the safety outcomes and may have played a role in the numerical difference in deaths and dropouts between the molidustat and darbepoetin groups.

Likewise, the imbalance in baseline characteristics—including CRP, SBP, eGFR, and main cause of CKD—could partially explain the higher incidence of MACEs in the molidustat group than in the darbepoetin group. Nevertheless, the imbalance for some of these characteristics was modest and the extent of their clinical relevance in this context remains unclear. In addition to the putative effect of the imbalance in baseline characteristics between the 2 groups, concomitant medication may have also contributed to an increased risk of cardiovascular events in some of the patients who experienced MACEs in the molidustat group. In line with the results in this trial, higher incidence of MACEs was also observed for the licensed HIF-PH inhibitor vadadustat compared with darbepoetin in a study in patients with CKD not undergoing dialysis [30]. Conversely, vadadustat demonstrated noninferiority to darbepoetin in MACEs safety outcomes in patients with CKD undergoing dialysis [31]. In the present study, none of the MACEs were considered to be related to molidustat. However, following the learnings from the clinical use of ESAs, time and additional investigation will be needed to clarify the exact causal relationship between HIF-PH inhibitors and MACEs. Altogether, careful monitoring of HIF-PH inhibitors is warranted, and a combined analysis of data from the MIYABI program as well as post-marketing surveillance will be required as initial steps to elucidate the role of molidustat in the risk of MACEs.

For AEs related to renal function, the incidence of CKD worsening was higher with molidustat than with darbepoetin, despite molidustat having no apparent effect on eGFR levels throughout the 52 weeks of treatment. A potential reason for this difference could be the higher proportion of patients who had diabetic nephropathy as main cause of CKD in the molidustat group compared with the darbepoetin group, but this could not be confirmed. Of note, a trend toward increased incidence of CKD worsening among patients receiving highest dosages of molidustat and darbepoetin before or at the time of onset of this AE was observed in the study (online suppl. Table 12). Moreover, in this study, the proportion of contusions and falls identified as TEAEs was also higher for molidustat compared with darbepoetin; however, none of these TEAEs were judged to be related with molidustat treatment and no apparent relationship was identified between their incidence and the Hb level at the time of onset of the events (online suppl. Table 13).

Although ESAs are the standard of care for renal anemia, increased risk of cardiovascular events has been associated with the use of high doses of ESAs, which are more likely to be required by patients with ESA hyporesponsiveness [11–14, 19]. As a result, research has been conducted to find alternative treatments. HIF-PH inhibitors, such as molidustat, predominantly induce EPO production in the kidneys and correct EPO concentrations to a physiological level by mimicking the response to hypoxia [20]. Molidustat can stimulate EPO production in human-induced pluripotent stem hepatoblast-like cells, and in preclinical studies, treatment with molidustat also stimulated hepatic EPO mRNA expression in a gentamicin-induced renal anemia model in rats and in renal EPO knockout mice [20, 21]; however, its contribution to hepatic EPO production in patients with CKD remains unclear. The use of an orally administered drug such as molidustat may also improve treatment adherence compared with injectable treatments such as darbepoetin. Currently, the Japanese Society of Nephrology and the Asian Pacific Society of Nephrology recommend a limited clinical use of HIF-PH inhibitors in patients with any history of thrombotic events and a cautious use in patients with cardiovascular disease, acknowledging the role of hypoxia and HIF target genes in modulating coagulation, fibrinolysis, and thrombus resolution [32]. Altogether, based on the incidence of MACEs observed in this study, it is not possible to conclude that molidustat has an improved cardiovascular safety profile compared with ESAs.

In this phase 3 trial, the use of the standard treatment darbepoetin as an active control represents a strength of the study design. Nevertheless, the MIYABI ND-C study
has several limitations that are worth noting. The open-label design of the study may have introduced bias and partially confounded the safety outcomes of the trial, which may have also contributed to the higher number of dropouts for molidustat compared with darbepoetin; however, it was preferred over a blind approach owing to the advantages for evaluating exploratory quality-of-life outcomes. The imbalance in baseline characteristics between treatment groups may have also affected efficacy and safety outcomes in the trial. Although using a non-inferiority margin of 1.0 g/dL, instead of a narrower 1 (i.e., 0.75 g/dL), may represent a potential limitation for the interpretation of the efficacy results, this margin was chosen according to the JSDT guidelines and in line with the range of variation in Hb levels accepted in routine clinical practice [10, 33]. Additionally, patients with recent history of cardiovascular or cerebrovascular events were excluded from the trial, which impacts the representativity of these results for extrapolation to the real-world CKD population. Other limitations of the trial include the inconclusive results from the subgroup analyses, owing to the small number of patients in each arm of the trial.

Overall, the MIYABI ND-C study demonstrated that 52-week treatment with molidustat corrected and maintained Hb levels within the prespecified target range, with noninferiority to darbepoetin. Molidustat appeared to be generally well tolerated compared with darbepoetin; however, further investigation will be required to fully evaluate its impact on the risk of cardiovascular events.

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Statement of Ethics

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines from the International Council for Harmonisation (ICH). The study protocol and its amendments were reviewed and approved by the Institutional Review Board or Independent Ethics Committee of each study center (online suppl. Table 14). An informed consent form explaining the procedures and potential hazards of the study was voluntarily signed by each participant before entering the study.

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 United States, as necessary, for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the European Union and United States regulatory agencies on or after January 1, 2014.

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