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ORIGINAL ARTICLE

Molidustat for anemia correction in Japanese patients undergoing hemodialysis: a single-arm, phase 3 study

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Abstract

Molidustat, an orally administered hypoxia-inducible factor prolyl-hydroxylase inhibitor, is under development for the treatment of anemia of CKD. This 24-week, phase 3, single-arm, multicenter study evaluated the efficacy and safety of molidustat in Japanese patients with renal anemia who were undergoing hemodialysis and who were not receiving an erythropoiesis-stimulating agent. Twenty-five patients received molidustat at a starting dose of 75 mg once daily, which was adjusted to maintain a Hb target of ≥10.0 to <12.0 g/dL. The mean rates of Hb increase from baseline and week 0 to the first dose change up to week 8 were −0.030 and 0.080 g/dL/week, respectively. By week 24, 89% of patients had a Hb level within target range. No adverse events of special interest were reported. Treatment with dose-titrated molidustat for 24 weeks was well tolerated in Japanese patients undergoing hemodialysis, and no new safety signal was observed. Clinicaltrials.gov identifier: NCT03351166.

KEYWORDS

anemia, chronic kidney disease, dialysis, erythropoiesis

1 | INTRODUCTION

Anemia is a common and serious complication of CKD [1, 2]. Untreated anemia in patients with CKD is associated with an increased risk of mortality, cardiovascular disease, cognitive impairment, and reduced quality of life [3]. The risk of anemia increases as glomerular filtration rate declines, primarily owing to reduced synthesis of erythropoietin (EPO) [4]. In Japan, the prevalence of anemia in patients undergoing hemodialysis has been reported as 13.8%–95%, compared with 10.4%–68.4% in those with CKD not undergoing dialysis [2].

Erythropoiesis-stimulating agents (ESAs) mimic the actions of endogenous EPO and are standard of care for patients with renal anemia; however, at high doses, ESAs are reported to be associated with an increased risk of cardiovascular adverse events (AEs) [2, 5–7]. The Japanese Society for Dialysis Therapy recommends that the Hb level in Japanese patients undergoing hemodialysis is maintained in the range 10–12 g/dL and that ESA doses should be reduced or discontinued if the Hb level exceeds 12 g/dL [8]. However, ESAs are ineffective in elevating Hb levels in 10%–20% of patients, largely owing to the presence of systemic inflammation and iron deficiency,

which inhibit the erythropoietic response [9]. Therefore, novel treatment strategies for renal anemia are required.

Molidustat is an orally administered inhibitor of hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) that induces EPO gene expression, predominantly in the kidney, thereby raising circulating levels of EPO in individuals with renal anemia to close to the normal physiological range [10]. Based on positive preclinical and clinical studies, the MolIdustat once dailY improves renal Anemia By Inducing EPO (MIYABI) program of five phase 3 clinical trials was designed to investigate the efficacy and safety of molidustat in Japanese patients with renal anemia, with and without dialysis and with and without prior treatment with ESAs [11, 12]. Here, we present the results of the MIYABI hemodialysis correction study (MIYABI HD-C), which was conducted to evaluate the efficacy and safety of molidustat for anemia correction in Japanese patients who were undergoing hemodialysis and not receiving ESAs [11].

2 | PATIENTS AND METHODS

2.1 | Study design

The design of the MIYABI HD-C study (NCT03351166) is shown in Figure 1 and has been previously described [11]. Briefly, this was a 24-week, phase 3, single-arm, multicenter study to evaluate the efficacy, safety, and tolerability of dose-titrated molidustat in Japanese patients with renal anemia who were undergoing hemodialysis and who were not receiving ESAs. A single-arm study design was chosen owing to the feasibility of patient recruitment; therefore, randomization and blinding were not performed.

Screening was carried out in the 12 weeks before the administration of study drug. Study visits took place weekly for the first 4 weeks of treatment (weeks 0–4), every 2 weeks until week 8, and every 4 weeks until week 20. During the evaluation period from week 21 to week 24, visits took place each week, followed by a 4-week follow-up period (Figure 1).

The study protocol was approved by the institutional review board and ethics committee at each participating center (Table S1). The study was conducted according to Good Clinical Practice guidance 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. AEs of special interest (i.e., death, myocardial infarction, unstable angina pectoris, stroke [ischemic, hemorrhagic, or undetermined], transient ischemic attack, pulmonary embolism, or acute limb ischemia) were monitored and outcomes adjudicated by the relevant independent committees (Table S2).

2.2 | Selection criteria

A complete list of patient eligibility criteria was provided by Akizawa et al. [11]. Briefly, men and women aged ≥20 years, who were undergoing hemodialysis at least once per week for ≥2 weeks before study drug assignment and had a Hb level of ≥8.0 to <10.0 g/dL and a ferritin level of ≥50 ng/mL, were eligible for inclusion. Patients who had not received ESAs or HIF-PH inhibitors during the 8 weeks before study drug assignment were also eligible. For those washed out from ESAs, the mean Hb level before dialysis (at least two measurements taken ≥2 days apart, assessed by the central laboratory) must have decreased by ≥0.5 g/dL after the last ESA administration, and the interval from the last ESA administration to study drug assignment should have been >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol (Figure 1).

Key exclusion criteria included previous or scheduled organ transplantation, aplasia or non-renal causes of anemia, any current condition leading to significant blood loss, active hemolysis, or hemolytic syndrome, and diagnosis of cardiovascular or cerebrovascular events within the 6 months before study drug assignment.

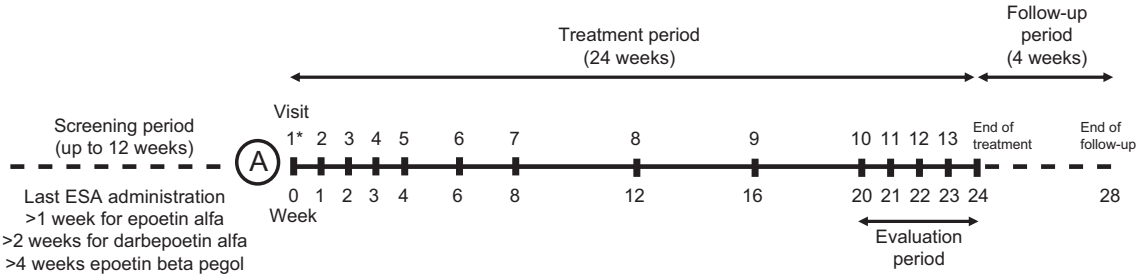

FIGURE 1 Study design. *Baseline visit. A, assignment; ESA, erythropoiesis-stimulating agent

2.3 | Treatments

Eligible patients were to receive molidustat 75 mg once daily for the first 4 weeks of the study. The dose was then titrated every 4 weeks until week 24 in order to achieve and maintain the Hb level within the target range of ≥10.0 to <12.0 g/dL, as described previously [11]. If the dose of molidustat had been changed during the first 4 weeks due to an excessive increase in Hb level, defined as increases of >1.0 g/dL per 2 weeks or >2.0 g/dL per 4 weeks, dose adaptation at week 4 was not performed.

Patients with iron, folate, or vitamin B12 deficiency were to be treated before study enrollment and during the study. Supplements were administered at the investigator's discretion, in line with current guidelines. During the treatment period, iron supplements were administered intravenously in order to achieve a serum ferritin level of ≥100 ng/mL or transferrin saturation ≥20%, in line with Japanese guidelines [13]. Rescue treatment, which was prespecified in the protocol and defined as red blood cell transfusion due to renal anemia or any ESA treatment started due to lack of efficacy as judged by the investigator, was administered at the investigator's discretion, for example, in patients with a Hb level < 8.0 g/dL. Red blood cell transfusions administered due to study procedures or to treat acute bleeding, were recorded but not considered as rescue treatment.

2.4 | Outcomes

The primary efficacy outcomes were the rate of increase in Hb level from baseline to the first molidustat dose change up to week 8, and the proportion of patients who responded to molidustat treatment. For the purposes of measuring Hb levels, "baseline" was defined as the mean of the last two Hb levels during the screening period and the Hb level at week 0 (baseline visit).

The rate of increase in Hb level from baseline to the first dose change up to week 8 was defined as the increase in Hb level from baseline to the first molidustat dose change up to week 8 divided by the duration of the starting dose (in weeks). If no dose change was performed up to week 8, then the Hb level at week 8 and the date of the week 8 visit were used to calculate the change in Hb level and the duration. An additional analysis was performed in which the change in Hb level was measured from week 0 (baseline visit).

Patients who met all of the following criteria were deemed to have responded to treatment: (1) mean Hb level during the evaluation period within the target range; (2) ≥50% of Hb level measurements during the evaluation period within the target range; and (3) no rescue treatment received up to the end of the evaluation period.

Secondary efficacy variables included rate of increase in Hb level at the first dose change up to week 4 and proportion of patients who met each criterion for response to treatment. Secondary efficacy, safety, and exploratory outcomes have been described in detail previously [11].

2.5 | Statistical analysis

The target sample size of approximately 25 treated patients was based on feasibility considerations; no formal sample size calculation was performed.

Analyses of efficacy and safety were performed in the full analysis set and safety analysis set, respectively. The full analysis set comprised all patients assigned to treatment who had at least one baseline Hb level before the first dose of molidustat. The safety analysis set included all patients who received at least one dose of molidustat.

All variables were analyzed descriptively. For the primary efficacy analysis, two-sided 95% CIs were estimated using one-sample *t*-statistics for the mean rate of increase in Hb and by the Clopper–Pearson exact method for the proportion of responders.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Overall, 32 patients were enrolled, of whom 2 withdrew before treatment assignment and 5 did not pass screening. Of the five patients who did not pass screening, two had Hb levels outside of the range ≥8.0 to <10.0 g/dL, two had medical conditions, which, at the opinion of the investigator, may pose a safety risk to the patient, may confound safety/efficacy assessment or may interfere with study participation and one patient had medical conditions and received ESAs or HIF-PH inhibitors during the 8 weeks before study drug assignment (i.e., did not meet inclusion criteria for those washed out from ESAs). Therefore, 25 Japanese patients undergoing hemodialysis received molidustat and 18 completed the study (Figure 2). Of the seven patients who prematurely discontinued treatment and did not complete the study, five required rescue treatment and discontinued study treatment during the first 8 weeks of the treatment period, and two experienced an adverse event. Demographic and baseline characteristics are shown in Table 1. The mean Hb level was reduced by 0.366 g/dL/week during the screening period (Table 1).

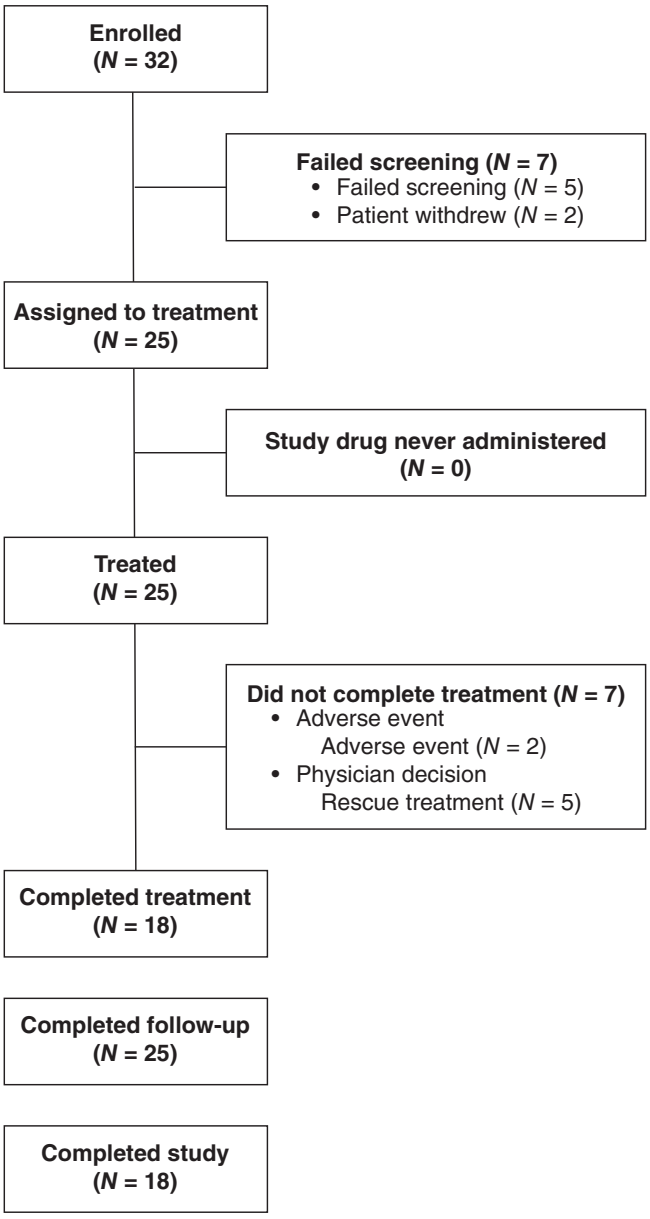

FIGURE 2 Patient disposition

3.2 | Efficacy

3.2.1 | Hb level

The primary and key secondary efficacy outcome data are shown in Tables 2 and 3, respectively.

The mean rate of increase in Hb level from baseline (defined as the mean of the last two Hb levels during the screening period and the Hb level at week 0 [baseline visit]) to the first dose change up to week 8 was −0.030 (95% CI −0.1683, 0.1079) g/dL/week. The mean rate of increase from week 0 to the first dose change up to week 8 was 0.080 (95% CI −0.0527, 0.2129) g/dL/week. The proportion of responders during the evaluation period was 56.0% (95% CI 34.9, 75.6) (Table 2).

The mean baseline Hb level (defined as the mean of the last two Hb levels during the screening period and the Hb level at week 0 [baseline visit]) was 9.21 g/dL and the increase in Hb level from baseline to the evaluation period was 1.15 g/dL (Table 3). The mean and SD of the increase from baseline Hb level during the course of the study are shown in Figure 3 and changes in measured Hb levels during the screening period and throughout the study are shown in Figure S1. The proportion of patients with at least one Hb level increase of >0.5 g/dL/week since the previous visit was 36.0% (9/25 patients) during the treatment period; when assessed over time, the proportion was highest at week 3 (16.7%).

Overall, 15/25 (60.0%), 2/25 (8.0%), and 8/25 patients (32.0%) had mean Hb levels during the evaluation period that were within, above, and below the target range (≥10.0 to <12.0 g/dL), respectively. The proportion of patients with a Hb level within the target range increased over time until week 16, plateaued around 67%–78% from week 16 to week 23, and was 89% by week 24 (Figure 4).

3.2.2 | Treatments and dose modifications

Overall, 68% of patients continued treatment until the evaluation period; the treatment duration was ≥140 days in 76.0% of patients. Seven patients prematurely discontinued molidustat treatment. Of these, five patients discontinued molidustat owing to a need for rescue treatment and two patients discontinued owing to AEs.

The proportion of patients receiving each molidustat dose at each study visit is shown in Figure 5. The most common maximum molidustat dose was 75 mg (13/25 patients), followed by 100 and 150 mg (both 5/25 patients); however, 2 patients received maximum doses of 200 mg. Dose adjustments were required in 21 patients, of whom 5 required dose reductions owing to excessive increases in Hb level.

3.2.3 | Rescue treatment

Overall, 5/25 patients (20.0%) received rescue treatment with an ESA and discontinued molidustat during the first 8 weeks of the treatment period; of these, 3 patients (60.0%) had received an ESA in the 8 weeks before molidustat initiation (Table S3).

3.3 | Safety

Of the 25 patients, 21 (84.0%) experienced at least one AE; most AEs were mild (64.0%) or moderate (16.0%)

TABLE 1 Patient demography and baseline characteristics

Parameter	Full analysis set ($N = 25$)
Sex, *N* (%)	
Male	15 (60.0)
Female	10 (40.0)
Age (years)	
Mean (SD)	65.9 (10.3)
Median (range)	67.0 (45–86)
Weight (kg)	
Mean (SD)	59.32 (11.59)
Median (range)	58.5 (40.6–79.4)
Height (cm)	
Mean (SD)	161.73 (10.78)
Median (range)	161.2 (140.8–180.0)
BMI (kg/m^2)	
Mean (SD)	22.58 (3.33)
Median (range)	22.2 (17.4–29.2)
Baseline[a] Hb level (g/dL)	
Mean (SD)	9.21 (0.55)
Median (range)	9.4 (7.8–9.8)
Week 0 (baseline visit) Hb level (g/dL)	
Mean (SD)	8.79 (0.68)
Median (range)	9.0 (7.3–10.0)
Change in Hb level during screening (g/dL/week)	
Mean (SD)	−0.366 (0.192)
Median (range)	−0.338 (−0.85 to −0.05)
Prior thromboembolic event, *N* (%)	3 (12.0)
Use of ESAs in the 8 weeks before molidustat initiation, *N* (%)	
Yes	16 (64.0)
No	9 (36.0)
Last ESA before molidustat initiation, *N* (%)	
Darbepoetin alfa	11 (44.0)
Methoxy polyethylene glycol-epoetin beta	2 (8.0)
Epoetin alfa or beta	11 (44.0)
Last ESA dose before molidustat initiation[b] (IU/week/kg)	
Mean (SD)	50.7 (36.9)
Median (range)	39.9 (0–164)
Main cause of CKD, *N* (%)	
Diabetic nephropathy	9 (36.0)
Other	13 (52.0)
IgA nephropathy	2 (8.0)
Chronic glomerulonephritis	7 (28.0)
Nephrosclerosis	2 (8.0)
Polycystic kidney disease	2 (8.0)
Unknown	3 (12.0)
Duration of dialysis (years)	
Mean (SD)	7.36 (8.35)
Median (range)	3.945 (0.07–35.17)
TSAT (%)	
Mean (SD)	43.6 (14.2)
Median (range)	43.3 (23–89)
Hepcidin (ng/mL)	
Mean (SD)	117.5 (41.5)
Median (range)	122.5 (45–224)
Ferritin (ng/mL)	
Mean (SD)	206.9 (99.9)
Median (range)	197 (71–524)
Vitamin B12 (pM/L)	
Mean (SD)	430.9 (261.9)
Median (range)	324.6 (142–1011)
Folate (nM/L)	
Mean (SD)	180.8 (674.6)
Median (range)	16.1 (9–3354)

Abbreviations: ESA, erythropoiesis-stimulating agent; TSAT, transferrin saturation.

[a]Baseline Hb levels were defined as the mean of the last two Hb levels during the screening period and the Hb level at week 0 (baseline visit).

[b]The last ESA dose was calculated as follows: for darbepoetin, dose in μg × 200; for epoetin beta pegol, dose in μg × 100; for epoetin alfa or beta, dose in IU × 1.

TABLE 2 Primary efficacy outcomes

Parameter	Full analysis set ($N = 25$)
Rate of increase in Hb level from baseline[a] to the first dose change up to week 8, mean (95% CI) (g/dL/week)	−0.030 (−0.1683, 0.1079)
Proportion of responders, *N* (% [95% CI])	14 (56.0 [34.9, 75.6])

[a]Baseline Hb levels were defined as the mean of the last two Hb levels during the screening period and the Hb level at week 0 (baseline visit).

in intensity (Table 4). The most commonly reported AEs were nasopharyngitis (12.0%), conjunctivitis, contusion, thermal burn, arthralgia, and insomnia (all 8.0%) (Table S4).

AEs related to procedures required by the protocol were reported in two patients (8.0%): anemia and

TABLE 3 Secondary and other efficacy outcomes

Parameter	Full analysis set ($N = 25$)
Secondary efficacy outcomes[a]	
Rate of increase in Hb level from baseline to the first dose change up to week 4, mean (95% CI) (g/dL/week)	−0.030 (−0.1668, 0.1074)
Patients meeting responder criteria, *N* (% [95% CI])	
Criterion 1	14 (56.0 [34.9, 75.6])
Criterion 2	16 (64.0 [42.5, 82.0])
Criterion 3	20 (80.0 [59.3, 93.2])
Cumulative proportion of patients whose Hb level reached the lower limit of the target range, *N* (%)	
Week 0	0
End of follow-up	21 (84.0)
Hb level, mean (95% CI) (g/dL)	
Baseline	9.21 (8.99, 9.44)
Evaluation period	10.36 (9.72, 11.01)
Change from baseline to evaluation period	1.15 (0.53, 1.76)
Proportion of patients with an increase in Hb level > 0.5 g/dL/week since the previous scheduled visit, *N* (%)	
Treatment period	9 (36.0)
Other efficacy variables[a]	
Change in Hb level between consecutive visits, mean (g/dL/week)	
Highest (between baseline and week 1)	−0.323
Lowest (between week 2 and week 3)	0.185
Change in Hb level from baseline to week 8, mean (95% CI) (g/dL/week)	0.091 (0.0284, 0.1541)
Proportion of days within target Hb range, mean (SD) (%)	
Treatment period	39.03 (29.81)
Evaluation period	54.65 (42.51)
Patients with Hb level ≥ 13.0 g/dL, *n* (%)	
Week 0	0
Treatment period	3 (12.0)
End of follow-up	L0
Patients with Hb level < 8.0 g/dL, *n* (%)	
Week 0	1 (4.0)
Treatment period	5 (20.0)
End of follow-up	1 (4.0)
Other efficacy variables measured based on change in Hb level from week 0 (baseline visit)	
Rate of increase in Hb level from week 0 to the first dose change up to week 4, mean (95% CI) (g/dL/week)	0.094 (−0.0383, 0.2265)
Hb level, mean (95% CI) (g/dL)	
Week 0	8.79 (8.51, 9.07)
Evaluation period	10.36 (9.72, 11.01)
Change from week 0 to evaluation period	1.57 (0.95, 2.19)
Proportion of patients with an increase in Hb level > 0.5 g/dL/week since the previous scheduled visit, *n* (%)	
Treatment period	12 (48.0)
Week 1	5 (20.0)
Change in Hb level between consecutive visits, mean (g/dL/week)	
Highest (between week 21 and week 22)	−0.178
Lowest (between week 2 and week 3)	0.185
Change in Hb level from week 0 to week 8, mean (95% CI) (g/dL/week)	0.143 (0.0779, 0.2084)

[a]Changes in Hb levels were measured from baseline, which was defined as the mean of the last two Hb levels during the screening period and the Hb level at week 0 (baseline visit).

somnolence (both 4.0%). No deaths were reported during the study. AEs resulting in discontinuation of the study drug were reported in three patients (12.0%): anemia, shunt occlusion, and metastatic gastric cancer in one patient (4.0%) each. No AEs resulting in dose interruption or AEs of special interest after administration of the study drug were reported.

Five patients (20.0%) experienced at least one ocular AE including eye disorders in four patients (asthenopia, blepharitis, conjunctival hyperemia, and retinal hemorrhage) and eye infections in two patients (conjunctivitis) (Table S4). Of the five ocular AEs, four were mild and one was moderate in intensity. No clinically meaningful changes from baseline were observed in vital signs or electrocardiogram parameters (data not shown).

4 | DISCUSSION

This single-arm phase 3 study is the only study to examine the efficacy, safety, and tolerability of molidustat in Japanese patients with renal anemia (Hb level of ≥8.0 to <10.0 g/dL) who were undergoing dialysis and not receiving ESAs. Over the 24-week treatment period, molidustat treatment increased the Hb level to within the target range in the majority of patients. The mean rate of increase in Hb level from baseline (i.e., the mean of the last two Hb levels during

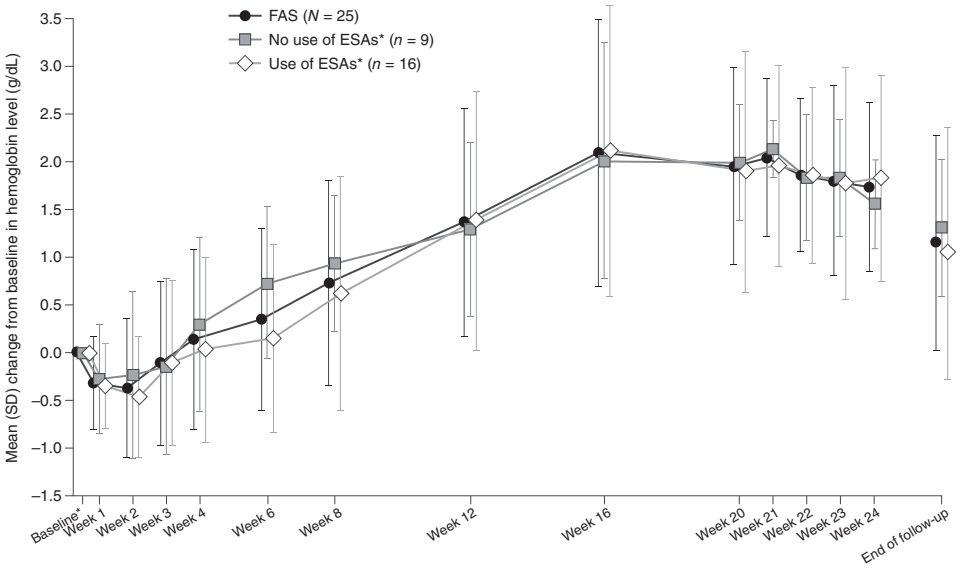

FIGURE 3 Mean change from baseline in Hb level by visit. *Baseline Hb levels were defined as the mean of the last two Hb levels during the screening period and the Hb level at week 0 (baseline visit). **Within the 8 weeks before molidustat initiation. FAS, full analysis set

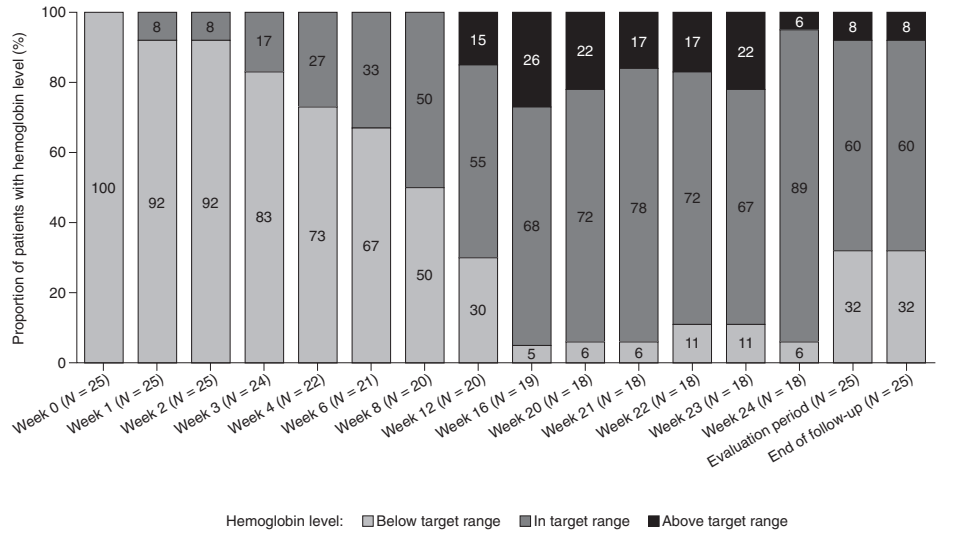

FIGURE 4 Proportion of patients with Hb level in, above, or below the target range (≥10.0 to <12.0 g/dL)

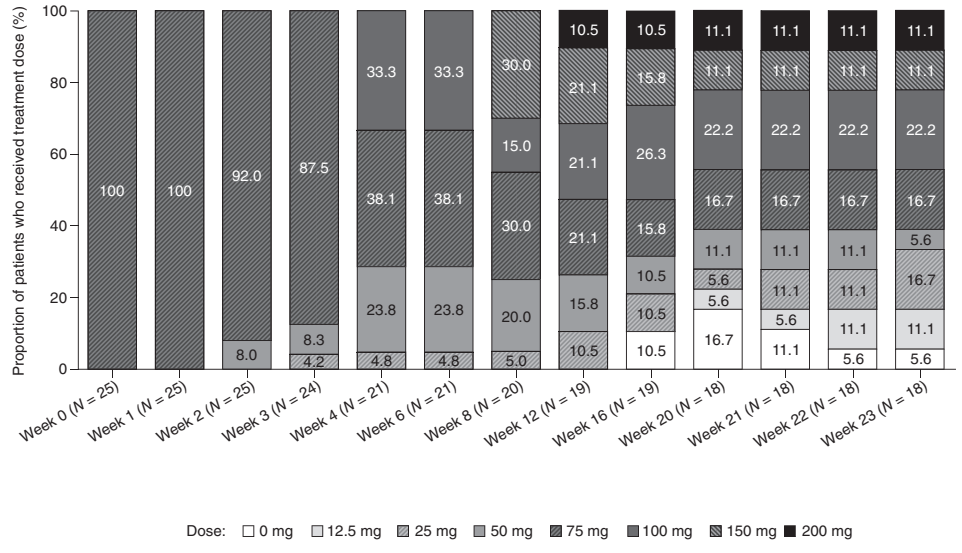

FIGURE 5 Proportion of patients receiving each dose of molidustat

TABLE 4 Adverse events

AEs, *N* (%)	Safety analysis set (*N* = 25)
Any AE	21 (84.0)
Mild	16 (64.0)
Moderate	4 (16.0)
Severe	1 (4.0)
Any study drug-related AE	0
Any AE related to study procedures	2 (8.0)
Anemia	1 (4.0)
Somnolence	1 (4.0)
Any AE resulting in molidustat discontinuation	3 (12.0)
Anemia	1 (4.0)
Shunt occlusion	1 (4.0)
Metastatic gastric cancer	1 (4.0)
Any AE resulting in dose interruption	0
Any SAE	3 (12.0)
Pneumonia	1 (4.0)
Shunt occlusion[a]	1 (4.0)
Subclavian vein thrombosis[a]	1 (4.0)
Metastatic gastric cancer	1 (4.0)
Any study drug-related SAE	0
Any SAE resulting in molidustat discontinuation	2 (8.0)
Shunt occlusion	1 (4.0)
Metastatic gastric cancer	1 (4.0)
Any AE leading to death	0
Any ocular AE	5 (20.0)
Mild	4 (16.0)
Moderate	1 (4.0)
Severe	0

Abbreviations: AE, adverse event; SAE, serious adverse event.
[a]Shunt occlusion and subclavian vein thrombosis were reported in the same patient.

the screening period and the Hb level at week 0) at the first dose change up to week 8 was −0.030 g/dL/week. Additional analyses based on change in Hb level from week 0 (baseline visit) were therefore performed, which showed a rate of increase in mean Hb level of 0.080 g/dL/week from week 0 to the first dose change up to week 8. The proportion of responders was 56.0%, and 60.0% of patients who received molidustat reached the target Hb range during the evaluation period. Molidustat was well tolerated and no AEs of special interest were reported.

Molidustat was initiated at 75 mg once daily and doses adjusted based on results from phase 2 dose-finding studies; the validity of the starting dose was further confirmed by population pharmacokinetic/pharmacodynamic analyses (data not shown) [14]. In this study, the most common maximum dose was 75 mg in 52.0% of patients, followed by 100 and 150 mg, both in 20.0% of patients, and 200 mg in 8.0% of patients. Further investigation will be required to understand the inter-patient variability in responses to molidustat.

The onset of effect of molidustat was 6–8 weeks or longer, which is consistent with the results of phase 1 and 2 studies conducted in White and Asian patients [14, 15]. Although five patients in the present study required rescue treatment, efficacy was observed in patients who did not prematurely discontinue study treatment.

There are limitations of this study, which should be noted. First, there was an unexpected reduction in the mean Hb level during the screening period. Hb levels during this period were originally assumed to be stable and therefore the baseline Hb level was originally defined as the mean of the last two Hb levels during the screening period and the Hb level at week 0. However, owing to the observed reduction in mean Hb level during screening, the inclusion of the last two Hb levels during screening in the definition of baseline Hb level was deemed inappropriate for evaluation. Additional analyses to evaluate changes from week 0 were therefore performed. The results suggest that the original method of measurement from baseline underestimated the effect of molidustat on increases in Hb levels. Second, the study sample size was small. Third, owing to the feasibility of patient recruitment, the study was conducted using an open-label design, which may have introduced bias related to knowledge of treatment assignment. To mitigate these limitations, the results from this study should be further studied in real-world clinical trials.

5 | CONCLUSIONS

Overall, 24 weeks of treatment with dose-titrated molidustat was well tolerated in Japanese patients undergoing hemodialysis, and no new safety signal was observed.

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CONFLICT OF INTEREST

Tadao Akizawa 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, GlaxoSmithKline, JT Pharmaceuticals, Kissei Pharmaceutical Co. Ltd, Kyowa Kirin, Nipro Corporation, Fuso Pharmaceutical Industries Ltd, Torii Pharmaceutical Co. Ltd, Sanwa Chemical Co. Ltd, Ono Pharmaceutical Co. Ltd, Otsuka Pharmaceutical Co. Ltd, and Chugai Pharmaceutical Co. Ltd. Hiroyasu Yamamoto received consulting and lecture fees from Bayer Yakuhin Ltd during the conduct of the study. Kiyoshi Nobori, Yoshimi Matsuda, Yasuhiro Hayashi and Takanori Hayasaki are employees of Bayer Yakuhin Ltd, which provided funding for the study.

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, timepoint, 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 United States and European Union 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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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