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Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies

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ABSTRACT

Introduction: New medications for anaemia associated with chronic kidney disease (CKD) are desirable, owing to the limitations of erythropoiesis-stimulating agents (ESAs), the current standard of care. Molidustat is a novel hypoxia-inducible factor prolyl-hydroxylase inhibitor that stimulates erythropoietin production, predominately in the kidney. We report methodological details of three phase 3 trials, named **M**olidustat **I**mproves s**Y**mptoms of renal **A**nemia **B**y **I**ncreasing endogenous erythropoietin (MIYABI), designed primarily to investigate the efficacy of molidustat therapy in adults with renal anaemia and dialysis-dependent CKD.

Methods and analysis: MIYABI Haemodialysis-Correction (HD-C) is a single-arm trial (24-week treatment duration) in approximately 25 patients on haemodialysis, currently untreated with ESAs. MIYABI Peritoneal Dialysis (PD) is a single-arm trial (36-week treatment duration) in approximately 50 patients on peritoneal dialysis, treated or untreated with ESAs. MIYABI Haemodialysis-Maintenance (HD-M) is a randomised, active-controlled, double-blinded, double-dummy trial (52-week treatment duration) comparing molidustat with darbepoetin alfa in approximately 225 patients on haemodialysis, treated with ESAs. Molidustat (starting dose 75 mg/day) will be titrated 4-weekly to maintain haemoglobin in pre-determined target ranges. The primary objective is to evaluate the efficacy of molidustat, using the following measures: the rate of rise in haemoglobin (g/dL/week) at the first dose change up to week 8 (MIYABI HD-C); responder rate (MIYABI HD-C and MIYABI PD); non-inferiority to darbepoetin alfa with respect to mean haemoglobin level and change from baseline during weeks 33–36 (MIYABI HD-M). The secondary objectives are to assess safety, pharmacokinetics and pharmacodynamics. These trials will provide the first evaluations of molidustat therapy in patients receiving either peritoneal dialysis or currently untreated with ESAs on haemodialysis, and provide further evidence in patients treated with ESAs on haemodialysis.

Ethics and dissemination: The trials will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Trial registration numbers: NCT03351166, NCT03418168, NCT03543657

Keywords: Chronic kidney disease; dialysis; molidustat; renal anaemia

STRENGTHS AND LIMITATIONS OF THESE STUDIES

- The three phase 3 MIYABI trials in patients with renal anaemia on dialysis will comprise two open-label, single-arm studies (due to feasibility of recruitment) and one randomised, active-controlled, double-blinded, double-dummy, parallel-group study.
- In MIYABI HD-M, molidustat treatment will be compared with an ESA (darbepoetin alfa), the current standard of care for renal anaemia, in a double-blinded manner; the only other study that has investigated the effects of molidustat therapy in patients with renal anaemia on haemodialysis was an open-label phase 2b trial using epoetin as a comparator.
- The MIYABI HD-M trial will involve a larger patient population (n=150) receiving a 75 mg starting dose than in the phase 2b trial (n=44 of the 157 patients treated with molidustat received a 75 mg starting dose).
- Treatment durations will be longer (eg, 52 weeks in MIYABI HD-M) than in the phase 2b trial (16 weeks), although approximately one-third of the molidustat-treated patients in the phase 2b trial (n=57) continued treatment in an extension study for up to 36 months.
- The efficacy of molidustat therapy will be investigated for the first time in patients on peritoneal dialysis in MIYABI PD and in patients currently untreated with ESAs on haemodialysis in MIYABI HD-C.

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INTRODUCTION

Anaemia is a common and serious complication of chronic kidney disease (CKD),[1] which worsens as CKD progresses.[2-4] The main cause of anaemia associated with CKD (also known as renal anaemia) is erythropoietin (EPO) deficiency.[5]

Treatment with erythropoiesis-stimulating agents (ESAs) is the current standard of care for renal anaemia.[6] However, this approach has limitations. In 10–20% of patients, irrespective of dialysis status, ESAs are ineffective at raising haemoglobin (Hb) to prespecified levels.[7-9] ESAs may also cause several adverse events (AEs), including pure red cell aplasia,[10] development or worsening of hypertension,[11-13] thrombosis,[14] tumour progression in patients with various malignancies,[15 16] poor cardiovascular outcomes and death.[17 18] These AEs may be related to injecting high doses of ESAs to achieve Hb targets[14 17 19 20] and excessive increases in Hb levels.[21]

A new approach under investigation involves using small molecules to inhibit hypoxia-inducible factor prolyl-hydroxylases (HIF-PH), thereby inducing EPO production. In addition to addressing EPO deficiency, the main cause of renal anaemia, the therapeutic effect of HIF-PH inhibition may also be mediated by increasing the availability of iron for erythropoiesis, as indicated by reductions in hepcidin levels.[22-27] These findings are particularly notable, given that functional iron deficiency may contribute to the inadequate responses that 10–20% of patients experience during treatment with ESAs, even though these patients often receive intravenous iron supplementation.[5-9] HIF-PH inhibition may theoretically also have a downside, because HIF transcriptionally upregulates a large number of genes; although EPO gene upregulation is helpful in treating anaemia associated with CKD, vascular endothelial growth factor (VEGF) upregulation could potentially exacerbate undesirable conditions.[23] However, in clinical trials of HIF-PH inhibitors, no safety signals or changes in VEGF levels were reported.[25-27]

Molidustat, a novel, orally administered inhibitor of HIF-PH, induces circulating levels of EPO close to the normal physiological range, with high relative selectivity for the induction of EPO gene expression, predominately in the kidney.[22] Results from preclinical[22] and clinical studies[28] suggest that molidustat is a promising option for the treatment of EPO-sensitive

anaemia in patients with CKD. In preclinical studies, molidustat restored renal EPO production with minor induction of hepatic EPO. Molidustat increased plasma EPO and EPO mRNA in the kidney and prevented decline in haematocrit and corrected decreases in Hb level.[22] In a randomised, placebo-controlled, phase 1 study involving 59 healthy participants, single doses of molidustat (5–50 mg) elicited a dose-dependent increase in EPO and were well tolerated.[28] In three 16-week, randomised, phase 2b, dose-ranging studies, comprising one study with patients on haemodialysis and two studies with patients not on dialysis, more than 400 patients with CKD were enrolled. These studies demonstrated that, during treatment with flexible-dose molidustat, Hb levels could be corrected relative to placebo or maintained at levels comparable to those in patients who continued treatment with ESAs, with manageable side effects. Comparable results and no significant safety concerns were observed in extension studies up to 36 months (manuscripts for phase 2 studies of molidustat are currently under consideration for publication).

Based on the positive findings of the preclinical and phase 2b clinical studies, the **M**olidustat **I**mproves s**Y**mptoms of renal **A**nemia **B**y **I**ncreasing endogenous EPO (MIYABI) programme of five phase 3 trials has been designed to investigate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of molidustat further in patients with renal anaemia in Japan. Here, we report the methodological details of the three MIYABI trials in which molidustat therapy will be investigated in patients receiving dialysis. These trials will provide the first evaluations of molidustat therapy in patients on peritoneal dialysis and in patients currently untreated with ESAs on haemodialysis, as well as extending the evidence in patients treated with ESAs on haemodialysis.

METHODS AND PLANNED ANALYSES

Study designs, objectives and populations

Each of the three phase 3 trials is a multicentre study conducted in adults with renal anaemia and dialysis-dependent CKD in Japan. In each trial, the primary objective is to evaluate the efficacy of molidustat in the respective patient populations and, in the MIYABI Haemodialysis Maintenance (HD-M) trial, to show non-inferiority to darbepoetin alfa. The secondary objectives of each trial are to evaluate the safety, tolerability, PK and PD of molidustat during the treatment periods.

Trial designs are shown in figure 1 and table 1, and key inclusion criteria are also summarised in table 1. All inclusion and exclusion criteria are shown in table 2.

MIYABI Haemodialysis Correction (HD-C) is a single-arm study in patients on haemodialysis who are not currently treated with ESAs, with a 24-week treatment duration. Japanese guidelines for the clinical evaluation of medications for renal anaemia recommend demonstrating efficacy in the correction and maintenance of renal anaemia in patients on dialysis, as well as in patients not on dialysis.[29] However, the number of patients with renal anaemia on dialysis who do not receive ESAs is limited in Japan. A single-arm study design was chosen owing to the feasibility of patient recruitment.[30]

MIYABI Peritoneal Dialysis (PD) is a single-arm study in patients on peritoneal dialysis who are treated or not treated with ESAs, with a 36-week treatment duration. A single-arm study design was chosen owing to the limited number of peritoneal dialysis patients with renal anaemia in Japan.

MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group study comparing molidustat with darbepoetin alfa in patients on haemodialysis who are treated with ESAs. The study will have a treatment duration of 52 weeks. As most patients with renal anaemia on dialysis in Japan are treated with ESAs, it is feasible to recruit sufficient patients to perform a confirmatory, randomised, double-blinded trial of molidustat in this patient population. In MIYABI HD-M, eligible patients will be randomised in a ratio of 2:1 to the molidustat group or darbepoetin alfa group. Randomisation will be stratified by previous ESA dose group (low or high) and by medical history of thromboembolic events (yes or no for myocardial infarction, pulmonary thromboembolism, stroke [excluding haemorrhagic stroke] or acute limb ischaemia). Unblinding will be permitted in cases of emergency, such as occurrence of a suspected, unexpected, serious AE, when the investigator needs to know which drug has been allocated.

Each study will be overseen by a data monitoring committee consisting of independent clinical experts and an independent biostatistician supported by an independent statistical analysis centre, whose main responsibility will be to recommend a change, interruption or termination of the study (or all phase 3 studies) based on safety findings.

Treatments

Study treatments are summarised in table 1. In each study, a starting dose of 75 mg molidustat once daily (OD) will be titrated every 4 weeks using an interactive voice/web response system (IxRS), based on the patient's Hb response to the previous dose. Planned doses for the titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD. The dose of molidustat will be adjusted to correct and maintain Hb levels in the target ranges (≥10.0 to <12.0 g/dL in MIYABI HD-C and MIYABI HD-M; ≥11.0 to <13.0 g/dL in MIYABI PD).

For patients untreated with ESAs (all patients in MIYABI HD-C and some patients in MIYABI PD), a dose adaptation visit will occur at week 4 to avoid excessive elevation of Hb levels after the initiation of molidustat treatment. In both studies, dose titration at week 4 will be based on both the magnitude of the rise in Hb and the Hb level (supplementary table 1) and from week 8 according to the Hb level alone (supplementary table 2). For patients treated with ESAs (all patients in MIYABI HD-M and some patients in MIYABI PD), the dose will be titrated from week 4 according to Hb level (supplementary table 2).

In MIYABI HD-M, patients will receive molidustat or molidustat placebo orally and darbepoetin alfa or darbepoetin alfa placebo intravenously. Patients in the molidustat group will receive molidustat plus darbepoetin alfa placebo, while patients in the darbepoetin alfa group will receive darbepoetin alfa plus molidustat placebo. The starting dose of darbepoetin alfa or darbepoetin alfa placebo will be selected for each patient based on their previous ESA dosage. Patients treated with darbepoetin alfa at screening will continue this treatment or start treatment with darbepoetin alfa placebo at the previous dose and interval (ie, weekly or biweekly). Patients treated with an epoetin therapy at screening will be treated with darbepoetin alfa or darbepoetin alfa placebo at a starting dose and interval determined by their epoetin dosage at screening. Then, depending on the Hb level (supplementary table 2), doses of darbepoetin alfa and darbepoetin alfa placebo will be titrated at biweekly intervals from week 2, and doses of molidustat and molidustat placebo will be titrated from week 4 at 4-weekly intervals.

Iron, vitamin B12 and folate supplementation is permitted if required and will be administered according to Japanese guideline recommendations.[31]

Variables

All efficacy and safety variables, and associated definitions, are shown in table 3. The primary efficacy variables in MIYABI HD-C are the rate of rise in Hb level (g/dL/week) at the first dose change up to week 8 and responder rate. In all three studies, a responder is defined as a patient who meets all of the following criteria: (i) mean of the Hb levels during the evaluation period is in the target range; (ii) ≥50% of the Hb levels during the evaluation period are in the target range; (iii) no rescue treatment received up to the end of the evaluation period. In MIYABI PD, the primary efficacy variable will be the responder rate. In MIYABI HD-M, the primary efficacy variables will be mean Hb level during the evaluation period and its change from baseline. Secondary variables are shown in table 3. Exploratory variables will include measures of iron metabolism, VEGF levels and health-related quality of life assessments.

To investigate systemic exposure to molidustat and the relationship between molidustat exposure and response, sparse sampling for PK and EPO will be conducted. If possible, molidustat exposure parameters (eg, C_{max}, AUC) and the relationship between molidustat exposure and treatment effects will be evaluated using population approaches (eg, non-linear mixed effect modelling), including potential influence of relevant patient covariables.

Statistical analysis

All variables (including demographic and other baseline characteristics) will be analysed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by summary statistics (mean, standard deviation, minimum, median and maximum). Summary statistics will be presented for the original data as well as for the difference from baseline.

The primary analysis set for efficacy will be the full analysis set, which includes all patients assigned to treatment who have at least one baseline Hb level (ie, at least one Hb level before the first dose of the study drug).

In MIYABI HD-C, the primary efficacy variables (rate of rise in Hb and responder rate) and their two-sided 95% confidence intervals (CI) will be estimated using one-sample *t*-statistics and the Clopper–Pearson method, respectively. In MIYABI PD, the primary efficacy variable

(responder rate) and its two-sided 95% CI will be estimated using the Clopper–Pearson method. In MIYABI HD-M, the primary efficacy variables (mean Hb level and change in mean Hb level) will be analysed by sequentially testing two hypotheses. The primary objective of showing non-inferiority to darbepoetin alfa will be achieved if the following two hypotheses are confirmed. (i) In the molidustat treatment group, the mean Hb level during the evaluation period (weeks 30–36) remains within the target range (≥10.0 to <12.0 g/dL). The mean Hb level in the molidustat treatment group will be calculated using the mean Hb level per patient. If the lower limit of the two-sided 95% CI of the mean of the mean Hb level is greater than or equal to the lower limit of the target Hb level (ie, ≥10.0 g/dL) and if the upper limit of the two-sided 95% CI is less than the upper limit of the target Hb level (ie, <12.0 g/dL), it will be established that the mean Hb level is within the target range. Two-sided 95% CI will be estimated using one sample *t*-statistics. (ii) Molidustat is not inferior to darbepoetin alfa. The non-inferiority of molidustat to darbepoetin alfa will be established if the lower limit of the two-sided 95% CI for the difference (molidustat minus darbepoetin alfa) is above –1.0 g/dL with non-inferiority margin of 1.0 g/dL. This margin was chosen because a variation of approximately 1.0 g/dL is considered acceptable in Japanese clinical practice.[31] The difference in change between the treatment groups and its two-sided 95% CI will be estimated using an analysis of covariance (ANCOVA) model, including treatment group, previous ESA dose group (low/high) and previous thromboembolic events (yes/no) as fixed effects and baseline Hb level as a covariate.

Determination of sample size

In MIYABI HD-C and MIYABI PD, the respective sample sizes of approximately 25 and 50 patients are determined based on feasibility.

In MIYABI HD-M, if 150 patients are randomised to the molidustat group and 75 patients to the darbepoetin alfa group, the power to establish that mean Hb levels are within target levels during the evaluation period is ≥98%. This sample size has >90% power to reject the null hypothesis that molidustat is inferior to darbepoetin alfa with a non-inferiority margin of 1.0 g/dL at a one-sided 2.5% significance level, assuming the expected difference between molidustat and darbepoetin alfa to be 0 g/dL and with a common standard deviation of 1.3–1.5 g/dL. In addition, assuming a dropout rate of approximately 30%, this

sample size should result in sufficient data to assess the long-term safety of molidustat therapy.

DISCUSSION

Renal anaemia due to EPO deficiency is a common and serious complication of CKD.[1] However, new approaches to the treatment of renal anaemia are needed, owing to safety issues and limitations with current treatments. Results from previous studies, including three phase 2b dose-ranging trials, suggest that molidustat is a promising option for the treatment of EPO-sensitive anaemia in patients with CKD.

At present, only one phase 2b trial assessing molidustat has been conducted in patients with renal anaemia who are on dialysis. It is anticipated that the three phase 3 trials described here will demonstrate the efficacy and safety of molidustat in patients with renal anaemia on dialysis, and that the trials will have the following strengths, relative to the one phase 2b trial conducted in patients on dialysis: (i) in MIYABI HD-M, molidustat treatment will be compared with an ESA (darbepoetin alfa), the current standard of care for renal anaemia, in a double-blinded manner, whereas an open-label design was used in the phase 2b trial, in which molidustat treatment was compared with another ESA (epoetin); (ii) a larger patient population in the MIYABI HD-M trial (n=150) receiving a starting dose of 75 mg molidustat OD than in the phase 2b trial (n=44 of the 157 patients treated with molidustat received a 75 mg starting dose); (iii) the treatment periods will be longer (eg, 52 weeks in MIYABI HD-M) than in the phase 2b trial (16 weeks), although about one-third of the molidustat-treated patients in the phase 2b trial (n=57) continued treatment in an extension study, with a duration of up to 36 months; (iv) molidustat therapy will be investigated for the first time in patients who are not treated with ESAs on haemodialysis in the MIYABI HD-C trial, and MIYABI HD-M will provide further evaluations of molidustat in patients treated with ESAs, whereas the phase 2b trial only included patients who switched from epoetin; (v) the efficacy of molidustat therapy will be investigated for the first time in patients on peritoneal dialysis in MIYABI PD, whereas only patients undergoing haemodialysis were included in the phase 2b trial.

In the three MIYABI trials in patients on dialysis, the efficacy of molidustat will primarily be assessed by investigating Hb levels, including changes from baseline and maintenance of prespecified Hb targets. However, several exploratory variables will be also investigated. These include assessments of VEGF levels and ophthalmological examinations, conducted to evaluate the theoretical risk of VEGF-mediated diabetic retinopathy,[23] and biomarkers of iron metabolism as, in addition to increasing renal EPO production, molidustat may increase the availability of iron for erythropoiesis.[22-24]

In summary, the three trials in patients on dialysis described here, together with two other trials in patients who are not receiving dialysis (the MIYABI ND-C and MIYABI ND-M randomised, open-label, active-controlled, parallel-group, multicentre trials), comprise the MIYABI phase 3 programme. This programme will investigate the efficacy and safety of molidustat in a broad clinical spectrum spanning approximately 600 patients with renal anaemia and CKD in Japan.

ETHICS AND DISSEMINATION

The studies will be conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP). Documented approval from appropriate independent ethics committees and institutional review boards has been obtained, according to GCP and local laws, regulations and organisations. Informed consent will be obtained from patients before entering the studies and may be withdrawn at any time. The studies have been registered on ClinicalTrials.gov (NCT03351166 [MIYABI HD-C], NCT03418168 [MIYABI PD], NCT03543657 [MIYABI HD-M]). Results will be disseminated through peer-reviewed publications and presentation(s).

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AUTHOR CONTRIBUTORS

TA, HY and TY contributed to designing these studies. TY contributed to developing the original study protocols. MT contributed to drafting the article and revising it. TA, HY, MT and KI critical revised the article for important intellectual content. YM contributed to developing the statistical analysis plan and assisted in the preparation of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately resolved.

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FIGURE LEGEND

Figure 1 Trial designs for (**A**) MIYABI HD-C, (**B**) MIYABI PD and (**C**) MIYABI HD-M. MIYABI HD-C and MIYABI PD are single-arm, multicentre trials. MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre trial. Haemoglobin levels and safety will be assessed at each study visit, conducted at the time points shown.

BL, baseline; EOF, end of follow-up; EOT, end of treatment; ESA, erythropoiesis-stimulating agent.

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TABLES

Table 1 Trial designs, patient populations and treatments

	MIYABI HD-C [NCT03351166]	MIYABI PD [NCT03418168]	MIYABI HD-M [NCT03543657]
Trial design	Single-arm, multicentre	Single-arm, multicentre	Randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre
Patient population	Men and women (aged ≥20 years, body weight >40 and ≤160 kg) with a diagnosis of renal anaemia		
Key inclusion criteria	Patients with ESKD on haemodialysis at least weekly for ≥2 weeks Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment Not treated with ESAs during the 8 weeks before study drug assignment Mean of the last two Hb levels between ≥8.0 and <10.0 g/dL	Patients with ESKD on peritoneal dialysis Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment Not treated or treated with ESAs during the 8 weeks before study drug assignment Mean of the last two Hb levels between ≥8.0 and <11.0 g/dL for ESA untreated and ≥10.0 and <13.0 g/dL for ESA treated	Patients with ESKD on haemodialysis at least weekly for ≥12 weeks Treated with the same ESA for ≥8 weeks before screening Mean of all Hb levels (at least two measurements) between ≥9.5 and <12.0 g/dL
Study treatments	A starting dose of 75 mg molidustat OD, titrated based on Hb response of the previous dose. Planned doses for	A starting dose of 75 mg molidustat OD, titrated based on Hb response of the previous dose. Planned doses for	Two groups: molidustat + darbepoetin alfa placebo, or molidustat placebo + darbepoetin alfa

	titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD Hb target range ≥10.0 to <12.0 g/dL	titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD Hb target range ≥11.0 to <13.0 g/dL	A starting dose of 75 mg molidustat or molidustat placebo OD, titrated based on Hb response of the previous dose Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD. Hb target range ≥10.0 to <12.0 g/dL A starting dose of darbepoetin alfa or darbepoetin alfa placebo will be decided in accordance with the previous ESA dosages and schedule of once a week or every 2 weeks per Japanese label
Treatment duration, weeks	24	36	52

ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor prolyl-hydroxylase; OD, once daily.

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Table 2 An overview of all inclusion and exclusion criteria

Inclusion criteria
All three trials had the following inclusion criteria • Written informed consent before performing any study-specific tests or procedures • Body weight (after dialysis) >40 and ≤160 kg at screening • Male or female ≥20 years of age at screening • At least one kidney • Serum folate level and serum vitamin B12 level above LLN at screening • Women of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form until 12 weeks after the last administration of the study drug. o Acceptable methods of contraception may include, but are not limited to, condoms (male or female) with or without a spermicidal agent; diaphragm or cervical cap with spermicide; intra-uterine device; hormone-based contraception. o Patients must agree to utilise two reliable and acceptable methods of contraception simultaneously. Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhoea with an appropriate clinical profile (eg, age-appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhoea with serum FSH levels >40 mIU/mL or have had surgical treatment such as bilateral tubal ligation, bilateral ovariectomy or hysterectomy. • Ability to understand and follow study-related instructions.
MIYABI HD-C had four additional inclusion criteria • Patients with ESKD on dialysis (including haemodiafiltration, haemodialysis and other modalities except for peritoneal dialysis) weekly or more than weekly for ≥2 weeks before study drug assignment • Mean screening Hb level ≥8.0 and <10.0 g/dL (at least two measurements must be taken ≥2 days apart, assessed by the central laboratory, and the difference between the two measurements must be <1.2 g/dL) with the last screening Hb measurement during the 14 days before study drug assignment • Not treated with any ESAs or HIF-PH inhibitors during the 8 weeks before study drug assignment. For patients 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 be >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol

- Ferritin ≥50 ng/mL at screening

MIYABI PD had five additional inclusion criteria

- Patients with ESKD on peritoneal dialysis before study drug assignment and not expected to start maintenance dialysis (eg, haemodialysis, haemodiafiltration) other than peritoneal dialysis during the study period
- Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment
- Patients who meet one of the following criteria

  A: Untreated with ESA at study drug assignment

  Mean screening Hb level ≥8.0 and <11.0 g/dL (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment

  B: Pre-treated with ESA at study drug assignment

  Mean screening Hb level ≥10.0 and <13.0 g/dL (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment
- Patients who meet one of the following criteria

  A: Untreated with ESA at study drug assignment

  - Patient with ESKD on peritoneal dialysis for ≥2 weeks before study drug assignment

  and

  - Not treated with ESA for the 8 weeks before study drug assignment

  or

  - Washed out from ESAs, when the mean Hb level (based on at least two measurements taken ≥2 days apart, assessed by the central laboratory) has decreased by ≥0.5 g/dL after the last ESA administration, AND the interval from the last ESA administration to study drug assignment should be >2 weeks for epoetin alfa/beta and >4 weeks for darbepoetin alfa or epoetin beta pegol

  B: Pre-treated with ESA at study drug assignment

  - Patient with ESKD on peritoneal dialysis for ≥12 weeks before study drug assignment

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- Treated with IV or SC ESA during the 8 weeks before study drug assignment
- Treated with 2- or 4-weekly dose of darbepoetin alfa, 4-weekly dose of epoetin beta pegol, OR 3 times per week, twice per week, weekly or biweekly dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before study drug assignment

- Patients who meet one of the following criteria
  A: Untreated with ESA at study drug assignment
  Ferritin ≥50 ng/mL at screening
  B: Pre-treated with ESA at study drug assignment
- Ferritin ≥100 ng/mL or transferrin saturation ≥20%

MIYABI HD-M had five additional inclusion criteria

- Patients with ESKD on dialysis (including haemodiafiltration, haemofiltration, haemodialysis and other modalities except for peritoneal dialysis) weekly or more than weekly for ≥12 weeks before randomisation
- Treated with the same ESA for ≥8 weeks before screening
- Treated with weekly or biweekly dose of darbepoetin alfa, monthly or biweekly dose of epoetin beta pegol, OR weekly, biweekly, twice or three times per week dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before randomisation
- Mean screening Hb level ≥9.5 and <12.0 g/dL before dialysis (based on at least two measurements taken ≥2 days apart, assessed by the central laboratory, AND the difference between the lowest level and highest level <1.2 g/dL), with the last screening Hb level measurement during the 14 days before randomisation
- Ferritin ≥100 ng/mL or transferrin saturation ≥20% at screening

Exclusion criteria

All three trials had the following exclusion criteria

- Any current condition leading to significant blood loss
- Active haemolysis or diagnosis of haemolytic syndrome
- Previous or concurrent myelodysplastic syndrome, multiple myeloma, marrow fibrosis or PRCA
- Previous or concurrent haemosiderosis or haemochromatosis
- Previous or concurrent hereditary haemoglobinopathies (eg, sickle-cell disease, beta thalassaemia, thalassaemia major)

- Previous or concurrent aplastic anaemia
- Previous or concurrent chronic lymphoproliferative diseases
- Proliferative choroidal or retinal disease, such as neovascular age-related macular degeneration or proliferative diabetic retinopathy requiring invasive treatment (eg, intraocular injections or laser photocoagulation) at screening
- Chronic inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease, which is determined to be the principal cause of the anaemia
- Known hypersensitivity to the study drugs (active substances or excipients of the preparations)
- Uncontrolled and symptomatic hyperparathyroidism
- Uncontrolled active infection at study drug assignment
- Previous or concurrent cancer except cervical carcinoma *in situ*, treated basal cell carcinoma, superficial bladder tumours (Ta, Tis and T1) or any cancer curatively treated >3 years before study drug assignment
- Previous or scheduled organ transplantation (being on a transplant waiting list does not exclude a patient)
- History of alcohol or drug abuse during the 2 years before study drug assignment
- RBC-containing transfusion for treatment of anaemia during the 8 weeks before study drug assignment
- Treatment with uridine-diphosphate-glucuronosyltransferase 1 family, polypeptide A1 inhibitors during the 7 days before study drug assignment:
    - antiretroviral drugs (eg, ritonavir, saquinavir, atazanavir, indinavir, lopinavir, nelfinavir)
    - tyrosine kinase inhibitors (eg, erlotinib, pazopanib, nilotinib, sorafenib, regorafenib)
    - tranilast
- Patients treated with immune- or myelosuppressive therapy during the 8 weeks before study drug assignment (eg, everolimus, sirolimus, rituximab, azathioprine, mycophenolate mofetil, mycophenolic acid, cyclosporine, methotrexate, tacrolimus, chemotherapeutic agents and other anticancer agents, and systemic steroids treatment [except inhaled steroids] for 7 days or more)
- Treated with the following therapies during the 8 weeks before study drug assignment: anabolic hormone, testosterone enanthate or mepitiostane
- History of cardiovascular or cerebrovascular events (eg, unstable angina, myocardial infarction, stroke, pulmonary thromboembolism and ALI) during the 6 months before study drug assignment
- Sustained, poorly controlled arterial hypertension (defined as systolic BP ≥180mmHg or diastolic BP ≥110mmHg) or hypotension (defined as

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systolic BP <90mmHg) at study drug assignment

- NYHAclass III or IV congestive heart failure
- Severe hepatic disorder (defined as ALT or AST >3 x the upper limit of normal, total bilirubin >2 mg/dL, or Child-Pugh B or C) at screening
- Previous use of molidustat
- A patient in need of surgery that may be expected to lead to significant blood loss
- Expected need for rescue treatment during the next 7 days after study drug assignment
- Active hepatitis, as assessed by the investigator
- Any medical condition that in the opinion of the investigator may pose a safety risk to a patient in this study, may confound safety or efficacy assessment or may interfere with study participation
- Previous assignment to study treatment during this study
- Previous (during the 30 days before study drug assignment) or concomitant participation in another clinical study with investigational medicinal product(s)
- Close affiliation with the investigational site, for example, a close relative of the investigator, dependent person (eg, employee or student at the investigational site)
- Pregnant or breastfeeding women

MIYABI PD had two additional exclusion criteria

- Previous or concurrent indications for removal of peritoneal dialysis catheter (eg, recurrent peritoneum inflammation, refractory tunnel infection)
- Concomitant use of maintenance dialysis (eg, haemodialysis, haemodiafiltration) other than peritoneal dialysis

ALI, acute limb ischaemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; FSH, follicle-stimulating hormone; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor propyl hydoxylase; IV, intravenous; LLN, lower limit of normal; NYHA, New York Heart Association; PRCA, pure red cell aplasia; RBC, red blood cell; SC, subcutaneous.

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Table 3 Efficacy and safety variables

	MIYABI HD-C	MIYABI PD	MIYABI HD-M
Primary efficacy variables specific to each trial	• Rate of rise in Hb level (g/dL/week) at the first dose change up to week 8* • Responder rate during the evaluation period (weeks 21–24)†	• Responder rate during the evaluation period (weeks 30–36)†	• Mean Hb level during the evaluation period (weeks 33–36) • Change in mean Hb level from baseline during the evaluation period
Secondary efficacy variables in all three trials	• Proportions of patients who meet the three response criteria during the evaluation period† • Hb level and change from baseline (measurement at each visit and mean during the evaluation period) • Proportion of patients whose mean Hb level is in, above or below the target range during the evaluation period • Proportion of patients whose Hb level is in, above or below the target range, respectively, at each visit • Proportion of patients whose maximum rise in Hb between each consecutive visit is >0.5 g/dL/week (defined as change in Hb level/duration between two visits [weeks])		
Secondary efficacy variables specific to each trial	• Rate of rise in Hb (g/dL/week) at the dose change up to week 4 • Cumulative proportion of patients who achieve the lower limit of the target Hb range at least once at each visit	• Rate of rise in Hb level (g/dL/week) at the dose changes up to weeks 4 and 8* • Change in mean Hb level from baseline during the evaluation period • Mean Hb level during the evaluation period	• Responder rate during the evaluation period†
Other efficacy variables in MIYABI HD-C and MIYABI HD-M (secondary variables	• Rate of rise in Hb level (g/dL/week) during each visit interval • Percentage of days in the target Hb range during the evaluation period and treatment period, respectively (defined as the number of days in the target range/number of days during the period × 100 [%])		

in MIYABI PD)	• Percentage of Hb levels in target range during the evaluation period and treatment period, respectively (defined as the number of measurements in the target range/number of measurements × 100 [%]) • Proportion of patients who received at least one rescue treatment (RBC transfusion, ESA treatment)
Safety variables in all three trials	• Adjudicated AEs‡ • AEs including serious AEs • Change in vital signs (pulse rate and blood pressure) • 12-lead electrocardiogram parameters • Observations of ophthalmological examination (fundus and anterior ocular segment examination and intraocular pressure measurement) • Laboratory examinations (including haematology, coagulation, clinical chemistry, electrolyte, HbA_{1c}, PTH and TSH levels)
Exploratory variables in all three trials	• Parameters of iron metabolism • EQ-5D-5L • Vascular endothelial growth factor

AEs, adverse events; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; ESA, erythropoiesis-stimulating agents; Hb, haemoglobin; HbA_{1c}, glycated haemoglobin; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; RBC, red blood cell.

*Rate of rise in Hb (g/dL/week) at the first dose change up to week 8 is defined as the change in Hb level from baseline to the first dose change of study drug up to week 8 divided by the duration of the starting dose (in weeks). If no dose change is performed up to week 8, then an Hb level at week 8 and the date of the week 8 visit will be used to calculate the change in Hb level and duration.

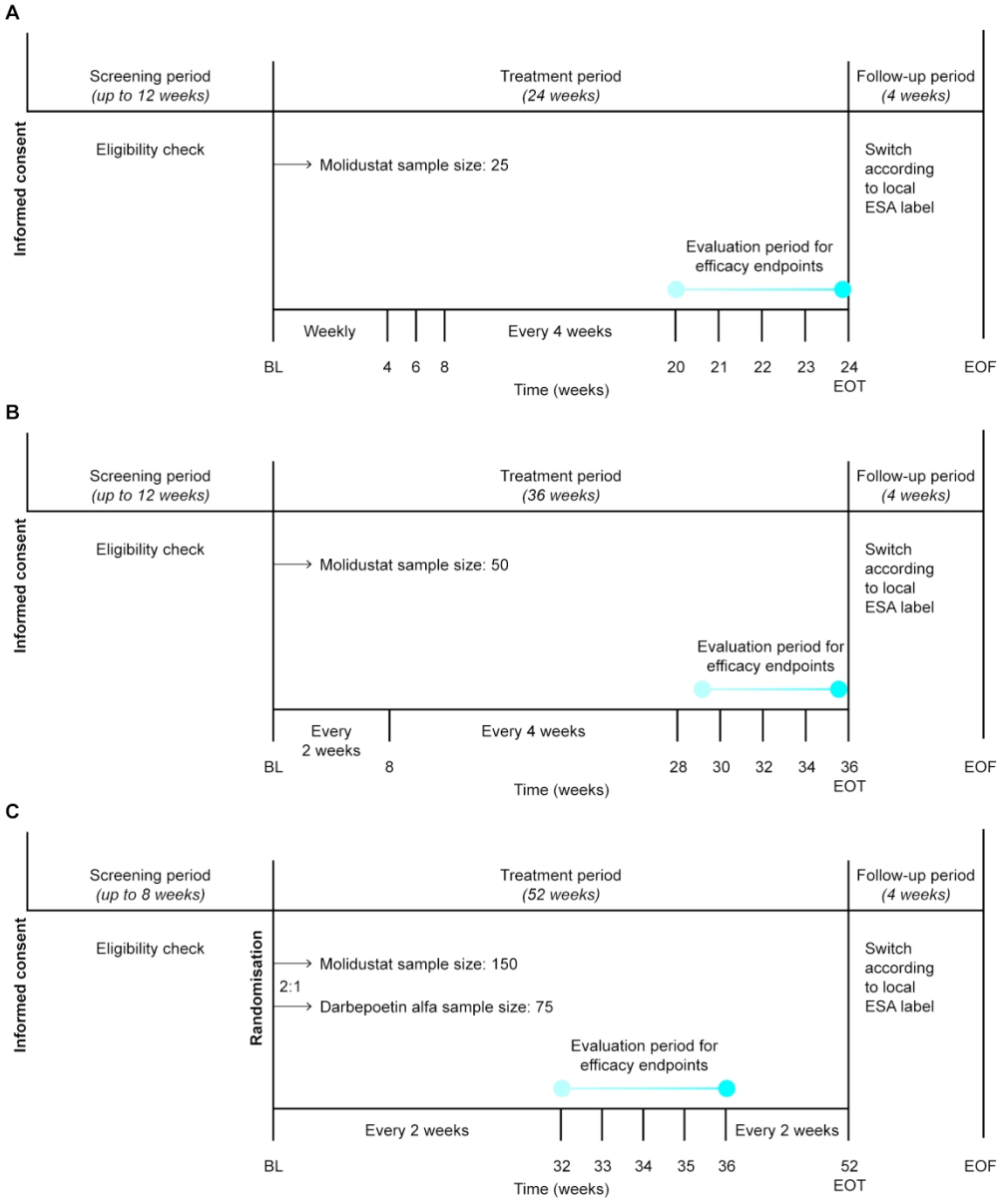
†A responder is defined as a patient who meets all of the following criteria:

(i) mean of the Hb levels during the evaluation period is in the target range

(ii) ≥50% of the Hb levels during the evaluation period are in the target range

(iii) no rescue treatment up to the end of the evaluation period.

‡Adjudicated AEs include death, myocardial infarction, unstable angina pectoris, stroke or transient ischaemic attack, pulmonary thromboembolism or acute limb ischaemia.



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SUPPLEMENTARY TABLES

Supplementary table 1 Dose titration for molidustat at week 4 for all patients in the MIYABI HD-C trial* and for patients not treated with ESA at study drug assignment in the MIYABI PD trial

Rise in Hb in the first 4 weeks (g/dL)	Hb level (g/dL) in MIYABI HD-C	Hb level (g/dL) in MIYABI PD	Titration step
<0.5	<9.5	<10.5	Increase to the next higher dose
	≥9.5	≥10.5	Maintain the same dose
≥0.5 and <1.0	Any value	Any value	
≥1.0 and ≤2.0	≤10.0	≤11.0	
	>10.0	>11.0	Decrease to the next lower dose
>2.0	Any value	Any value	

*All patients in MIYABI HD-C will not be treated with ESAs at study drug assignment or during the trial.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

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Supplementary table 2 Dose titration from week 8 in MIYABI HD-C, from week 4 or 8 in MIYABI PD*, and from week 2 or 4 in MIYABI HD-M†

Hb level (g/dL) in MIYABI HD-C and MIYABI HD-M	Hb level (g/dL) in MIYABI PD	Titration step
<10.0	<11.0	Increase to the next higher dose
≥10.0 and <12.0	≥11.0 and <12.5	Maintain the same dose
≥12.0 and <13.0	≥12.5 and <13.0	Decrease to the next dose
≥13.0	≥13.0	Suspend a dose until the next scheduled visit

*In MIYABI PD, patients treated with ESAs at study drug assignment will start this dose-titration schedule for molidustat at week 4, whereas patients not treated with ESAs at study drug assignment will start this dose titration schedule for molidustat at week 8.

†In MIYABI HD-M, doses of darbepoetin alfa or darbepoetin alfa placebo will be titrated from week 2, whereas doses of molidustat will be titrated from week 4.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

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Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies

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Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies

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ABSTRACT

Introduction: New medications for anaemia associated with chronic kidney disease (CKD) are desirable, owing to the limitations of erythropoiesis-stimulating agents (ESAs), the current standard of care. Molidustat is a novel hypoxia-inducible factor prolyl-hydroxylase inhibitor that stimulates erythropoietin production, predominately in the kidney. We report methodological details of three phase 3 trials, named **M**olidustat **I**mproves s**Y**mptoms of renal **A**nemia **B**y **I**ncreasing endogenous erythropoietin (MIYABI), designed primarily to investigate the efficacy of molidustat therapy in adults with renal anaemia and dialysis-dependent CKD.

Methods and analysis: MIYABI Haemodialysis-Correction (HD-C) is a single-arm trial (24-week treatment duration) in approximately 25 patients on haemodialysis, currently untreated with ESAs. MIYABI Peritoneal Dialysis (PD) is a single-arm trial (36-week treatment duration) in approximately 50 patients on peritoneal dialysis, treated or untreated with ESAs. MIYABI Haemodialysis-Maintenance (HD-M) is a randomised, active-controlled, double-blinded, double-dummy trial (52-week treatment duration) comparing molidustat with darbepoetin alfa in approximately 225 patients on haemodialysis, treated with ESAs. Molidustat (starting dose 75 mg/day) will be titrated 4-weekly to maintain haemoglobin in pre-determined target ranges. The primary objective is to evaluate the efficacy of molidustat, using the following measures: the rate of rise in haemoglobin (g/dL/week) at the first dose change up to week 8 (MIYABI HD-C); responder rate (MIYABI HD-C and MIYABI PD); mean haemoglobin level during weeks 33–36 and non-inferiority to darbepoetin alfa shown by change in mean haemoglobin level from baseline (MIYABI HD-M). The secondary objectives are to assess safety, pharmacokinetics and pharmacodynamics. These trials will provide the first evaluations of molidustat therapy in patients receiving either peritoneal dialysis or currently untreated with ESAs on haemodialysis, and provide further evidence in patients treated with ESAs on haemodialysis.

Ethics and dissemination: The trials will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Trial registration numbers: NCT03351166, NCT03418168, NCT03543657

Keywords: Chronic kidney disease; dialysis; molidustat; renal anaemia

STRENGTHS AND LIMITATIONS OF THESE STUDIES

- The three phase 3 MIYABI trials in patients with renal anaemia on dialysis will comprise two open-label, single-arm studies (due to feasibility of recruitment) and one randomised, active-controlled, double-blinded, double-dummy, parallel-group study.
- In MIYABI HD-M, molidustat treatment will be compared with an ESA (darbepoetin alfa), the current standard of care for renal anaemia, in a double-blinded manner; the only other study that has investigated the effects of molidustat therapy in patients with renal anaemia on haemodialysis was an open-label phase 2b trial using epoetin as a comparator.
- The MIYABI HD-M trial will involve a larger patient population (n=150) receiving a 75 mg starting dose than in the phase 2b trial (n=44 of the 157 patients treated with molidustat received a 75 mg starting dose).
- Treatment durations will be longer (eg, 52 weeks in MIYABI HD-M) than in the phase 2b trial (16 weeks), although approximately one-third of the molidustat-treated patients in the phase 2b trial (n=57) continued treatment in an extension study for up to 36 months.
- The efficacy of molidustat therapy will be investigated for the first time in patients on peritoneal dialysis in MIYABI PD and in patients currently untreated with ESAs on haemodialysis in MIYABI HD-C.

INTRODUCTION

Anaemia is a common and serious complication of chronic kidney disease (CKD),[1] which worsens as CKD progresses.[2-4] The main cause of anaemia associated with CKD (also known as renal anaemia) is erythropoietin (EPO) deficiency.[5]

Treatment with erythropoiesis-stimulating agents (ESAs) is the current standard of care for renal anaemia.[6] However, this approach has limitations. In 10–20% of patients, irrespective of dialysis status, ESAs are ineffective at raising haemoglobin (Hb) to prespecified levels.[7-9] ESAs may also cause several adverse events (AEs), including development or worsening of hypertension,[10-12] rare cases of antibody-mediated pure red cell aplasia,[13] poor cardiovascular outcomes and death.[14-16] In patients with cancer and anaemia, ESA use is associated with increased risk of thrombosis.[17] These AEs may be related to injecting high doses of ESAs to achieve Hb targets[15 17-19] and excessive increases in Hb levels.[20]

A new approach under investigation involves using small molecules to inhibit hypoxia-inducible factor prolyl-hydroxylases (HIF-PH), thereby inducing EPO production. In addition to addressing EPO deficiency, the main cause of renal anaemia, the therapeutic effect of HIF-PH inhibition may also be mediated by increasing the availability of iron for erythropoiesis, as indicated by reductions in hepcidin levels.[21-26] These findings are particularly notable, given that functional iron deficiency may contribute to the inadequate responses that 10–20% of patients experience during treatment with ESAs, even though these patients often receive intravenous iron supplementation.[5-9] HIF-PH inhibition may theoretically also have a downside, because HIF transcriptionally upregulates a large number of genes; although EPO gene upregulation is helpful in treating anaemia associated with CKD, vascular endothelial growth factor (VEGF) upregulation could result in neoplasia and diabetic retinopathy.[22] However, in clinical trials of HIF-PH inhibitors, no safety signals or changes in VEGF levels were reported.[24-26]

Molidustat, a novel, orally administered inhibitor of HIF-PH, induces circulating levels of EPO close to the normal physiological range, with high relative selectivity for the induction of EPO gene expression, predominately in the kidney.[21] Results from preclinical[21] and clinical studies[27] suggest that molidustat is a promising option for the treatment of EPO-sensitive anaemia in patients with CKD. In preclinical studies, molidustat restored renal EPO

production with minor induction of hepatic EPO. Molidustat increased plasma EPO and EPO mRNA in the kidney and prevented decline in haematocrit and corrected decreases in Hb level.[21] In a randomised, placebo-controlled, phase 1 study involving 59 healthy participants, single doses of molidustat (5–50 mg) elicited a dose-dependent increase in EPO and were well tolerated.[27] In three 16-week, randomised, phase 2b, dose-ranging studies, comprising one study with patients on haemodialysis and two studies with patients not on dialysis, more than 400 patients with CKD were enrolled. These studies demonstrated that, during treatment with flexible-dose molidustat, Hb levels could be corrected relative to placebo or maintained at levels comparable to those in patients who continued treatment with ESAs, with manageable side effects.[28] Comparable results and no significant safety concerns were observed in extension studies up to 36 months (unpublished data).

Based on the positive findings of the preclinical and phase 2b clinical studies, the **M**olidustat **I**mproves s**Y**mptoms of renal **A**nemia **B**y **I**ncreasing endogenous EPO (MIYABI) programme of five phase 3 trials has been designed to investigate molidustat therapy further in patients with renal anaemia in Japan. Here, we report the methodological details of the three MIYABI trials in which the efficacy (up to 36 weeks), safety, pharmacokinetics and pharmacodynamics (up to 52 weeks) of molidustat therapy will be investigated in patients receiving dialysis. These three trials will provide the first evaluations of molidustat therapy in patients on peritoneal dialysis and in patients currently untreated with ESAs on haemodialysis, as well as extending the evidence in patients treated with ESAs on haemodialysis.

METHODS AND PLANNED ANALYSES

Study designs, objectives and populations

Each of the three phase 3 trials is a multicentre study conducted in adults aged 20 years or older with renal anaemia and dialysis-dependent CKD in Japan. In each trial, the primary objective is to evaluate the efficacy of molidustat in the respective patient populations and, in the MIYABI Haemodialysis Maintenance (HD-M) trial, to show non-inferiority to darbepoetin alfa. The secondary objectives of each trial are to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of molidustat during the treatment periods. The three trials commenced in the first half of 2018 and have finished recruiting.

Patient eligibility was assessed during screening periods lasting up to 12 weeks in the MIYABI Haemodialysis Correction (HD-C) and MIYABI Peritoneal Dialysis (PD) studies and up to 8 weeks in MIYABI HD-M. To be eligible, the mean of at least two Hb measurements (both taken before dialysis, at least 2 days apart, with the last measurement taken within 14 days before study drug assignment, and with a difference of less than 1.2 g/dL between the lowest and highest values) was required to lie within pre-specified levels (table 1). The main inclusion criteria are summarised in table 1. All inclusion and exclusion criteria are shown in supplementary table 1.

MIYABI HD-C is a single-arm study in patients on haemodialysis who are not currently treated with ESAs, with a 24-week treatment duration (figure 1 and table 1). Japanese guidelines for the clinical evaluation of medications for renal anaemia recommend demonstrating efficacy in the correction and maintenance of renal anaemia in patients on dialysis, as well as in patients not on dialysis.[29] However, the number of patients with renal anaemia on dialysis who do not receive ESAs is limited in Japan. A single-arm study design was chosen for MIYABI HD-C owing to the feasibility of patient recruitment.[30]

MIYABI PD is a single-arm study in patients on peritoneal dialysis who are treated or not treated with ESAs, with a 36-week treatment duration (figure 1 and table 1). A single-arm study design was chosen for MIYABI PD owing to the limited number of peritoneal dialysis patients with renal anaemia in Japan.

MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group study comparing molidustat with darbepoetin alfa in patients on haemodialysis who are treated with ESAs (figure 1 and table 1). The study has a treatment duration of 52 weeks. As most patients with renal anaemia on dialysis in Japan are treated with ESAs, it is feasible to recruit sufficient patients to perform a confirmatory, randomised, double-blinded trial of molidustat in this patient population. Therefore, in MIYABI HD-M, eligible patients will be randomised in a ratio of 2:1 to the molidustat group or darbepoetin alfa group. Allocation to treatment arms will be achieved using an interactive voice/web response system (IxRS) at the first (baseline) visit. Randomisation will be stratified by previous ESA dose group (low or high) and by medical history of thromboembolic events (yes or no for myocardial infarction, pulmonary thromboembolism, stroke [excluding haemorrhagic

stroke] or acute limb ischaemia). All investigators and patients in MIYABI HD-M will be blinded to treatment allocation. In cases of emergency, such as occurrence of a suspected, unexpected, serious AE, when the investigator needs to know which drug has been allocated, unblinding will occur by entering the emergency key code for the relevant patient into the IxRS.

Each study is being overseen by a data monitoring committee consisting of independent clinical experts and an independent biostatistician supported by an independent statistical analysis centre, whose main responsibility is to recommend a change, interruption or termination of the study (or all phase 3 studies) based on safety findings.

Treatments

Study treatments are summarised in table 1. In each study, a starting dose of 75 mg molidustat once daily (OD) will be titrated every 4 weeks using the IxRS, based on the patient's Hb response to the previous dose. In each study, planned doses for the titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD. The dose of molidustat will be adjusted to correct and maintain Hb levels in the target ranges of ≥10.0 to <12.0 g/dL in MIYABI HD-C and MIYABI HD-M and ≥11.0 to <13.0 g/dL in MIYABI PD.

For patients untreated with ESAs (all patients in MIYABI HD-C and some patients in MIYABI PD, but no patients in MIYABI HD-M), a dose adaptation visit will occur at week 4 to avoid excessive elevation of Hb levels after the initiation of molidustat treatment. In MIYABI HD-C and MIYABI PD, dose titration at week 4 will be based on both the magnitude of the rise in Hb and the Hb level (supplementary table 2) and from week 8 according to the Hb level alone (supplementary table 3). For patients treated with ESAs (all patients in MIYABI HD-M and some patients in MIYABI PD, but no patients in MIYABI HD-C), the dose will be titrated from week 4 according to Hb level (supplementary table 3).

In MIYABI HD-M, patients will receive molidustat or molidustat placebo orally and darbepoetin alfa or darbepoetin alfa placebo intravenously. Patients in the molidustat group will receive molidustat plus darbepoetin alfa placebo, while patients in the darbepoetin alfa group will receive darbepoetin alfa plus molidustat placebo. The starting dose of darbepoetin alfa or darbepoetin alfa placebo will be selected for each patient based on their

previous ESA dosage. Patients treated with darbepoetin alfa at screening will continue this treatment or start treatment with darbepoetin alfa placebo at the previous dose and interval (ie, weekly or biweekly). Patients treated with an epoetin therapy at screening will be treated with darbepoetin alfa or darbepoetin alfa placebo at a starting dose and interval determined by their epoetin dosage at screening. Then, depending on the Hb level (supplementary table 3), doses of darbepoetin alfa and darbepoetin alfa placebo will be titrated at biweekly intervals from week 2, and doses of molidustat and molidustat placebo will be titrated from week 4 at 4-weekly intervals.

In each study, iron, vitamin B12 and folate supplementation is permitted if required and will be administered according to Japanese guideline recommendations.[31] Iron supplementation will be administered to reach a target serum ferritin level of at least 100 ng/mL or transferrin saturation of at least 20%.

Variables

All efficacy and safety variables, and associated definitions, are shown in table 2. The primary efficacy variables in MIYABI HD-C are the rate of rise in Hb level (g/dL/week) at the first dose change up to week 8 and responder rate. In MIYABI PD, the primary efficacy variable will be the responder rate. In MIYABI HD-M, the primary efficacy variables will be mean Hb level during the evaluation period and its change from baseline. In all three studies, a responder is defined as a patient who meets all of the following criteria: (i) mean of the Hb levels during the evaluation period is in the target range; (ii) ≥50% of the Hb levels during the evaluation period are in the target range; (iii) no rescue treatment received up to the end of the evaluation period. Secondary variables for the three trials are shown in table 2. In each study, exploratory variables will include measures of iron metabolism, VEGF levels and health-related quality of life assessments.

In each study, to investigate systemic exposure to molidustat and the relationship between molidustat exposure and response, sparse sampling from all patients will be conducted for pharmacokinetics and pharmacodynamics. If possible, molidustat exposure parameters (eg, C_{max}, AUC) and the relationship between molidustat exposure and treatment effects will be evaluated using population approaches (eg, non-linear mixed effect modelling), including potential influence of relevant patient covariables.

Statistical analysis

All variables (including demographic and other baseline characteristics) will be analysed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by summary statistics (mean, standard deviation, minimum, median and maximum). Summary statistics will be presented for the original data as well as for the difference from baseline.

In each study, the primary analysis set for efficacy will be the full analysis set, which includes all patients assigned to treatment who have at least one baseline Hb level (ie, at least one Hb level before the first dose of the study drug).

In MIYABI HD-C, the primary efficacy variables (rate of rise in Hb and responder rate) and their two-sided 95% confidence intervals (CI) will be estimated using one-sample *t*-statistics and the Clopper–Pearson method, respectively. In MIYABI PD, the primary efficacy variable (responder rate) and its two-sided 95% CI will be estimated using the Clopper–Pearson method. In MIYABI HD-M, the primary efficacy variables (mean Hb level and change in mean Hb level) will be analysed by sequentially testing two hypotheses. In MIYABI HD-M, the primary objective will be achieved if the following two hypotheses are confirmed. (i) In the molidustat treatment group, the mean Hb level during the evaluation period (weeks 33–36) remains within the target range (≥10.0 to <12.0 g/dL). The mean Hb level in the molidustat treatment group will be calculated using the mean Hb level per patient. If the lower limit of the two-sided 95% CI of the mean of the mean Hb level is greater than or equal to the lower limit of the target Hb level (ie, ≥10.0 g/dL) and if the upper limit of the two-sided 95% CI is less than the upper limit of the target Hb level (ie, <12.0 g/dL), it will be established that the mean Hb level is within the target range. Two-sided 95% CI will be estimated using one sample *t*-statistics. (ii) Molidustat is not inferior to darbepoetin alfa. The non-inferiority of molidustat to darbepoetin alfa will be established if the lower limit of the two-sided 95% CI for the difference (molidustat minus darbepoetin alfa) is above –1.0 g/dL with non-inferiority margin of 1.0 g/dL. This margin was chosen because a variation of approximately 1.0 g/dL is considered acceptable in Japanese clinical practice.[31] In MIYABI HD-M, the difference in change between the treatment groups and its two-sided 95% CI will be estimated using an analysis of covariance (ANCOVA) model, including treatment group,

previous ESA dose group (low/high) and previous thromboembolic events (yes/no) as fixed effects and baseline Hb level as a covariate.

Determination of sample size

In MIYABI HD-C and MIYABI PD, the respective sample sizes of approximately 25 and 50 patients are determined based on feasibility.

In MIYABI HD-M, the sample size of 150 patients in the molidustat group and 75 patients in the darbepoetin alfa group should result in sufficient data to assess the long-term safety of molidustat therapy, assuming a dropout rate of approximately 30%. If 150 patients are randomised to the molidustat group, the power to establish that mean Hb levels are within target levels during the evaluation period is ≥98%, assuming a standard deviation of 1.3–1.5g/dL from the previous phase 2b studies. This sample size has >90% power to reject the null hypothesis that molidustat is inferior to darbepoetin alfa with a non-inferiority margin of 1.0 g/dL at a one-sided 2.5% significance level, assuming the expected difference between molidustat and darbepoetin alfa to be 0 g/dL and with a common standard deviation of 1.3–1.5 g/dL.

Patient and public involvement

Patients are not involved in the design and conduct of the studies.

DISCUSSION

Renal anaemia due to EPO deficiency is a common and serious complication of CKD.[1] However, new approaches to the treatment of renal anaemia are needed, owing to safety issues and limitations with current treatments. Results from previous studies, including three phase 2b dose-ranging trials, suggest that molidustat is a promising option for the treatment of EPO-sensitive anaemia in patients with CKD.

At present, only one phase 2b trial assessing molidustat has been conducted in patients with renal anaemia who are on dialysis. It is anticipated that the three phase 3 trials described here will demonstrate the efficacy and safety of molidustat in patients with renal anaemia on dialysis, and that the trials will have the following strengths, relative to the one phase 2b trial conducted in patients on dialysis: (i) in MIYABI HD-M, molidustat treatment will be compared with an ESA (darbepoetin alfa), the current standard of care for renal anaemia, in

a double-blinded manner, whereas an open-label design was used in the phase 2b trial, in which molidustat treatment was compared with another ESA (epoetin); (ii) a larger patient population in the MIYABI HD-M trial (n=150) receiving a starting dose of 75 mg molidustat OD than in the phase 2b trial (n=44 of the 157 patients treated with molidustat received a 75 mg starting dose); (iii) the treatment periods will be longer (eg, 52 weeks in MIYABI HD-M) than in the phase 2b trial (16 weeks), although about one-third of the molidustat-treated patients in the phase 2b trial (n=57) continued treatment in an extension study, with a duration of up to 36 months; (iv) molidustat therapy will be investigated for the first time in patients who are not treated with ESAs on haemodialysis in the MIYABI HD-C trial, and MIYABI HD-M will provide further evaluations of molidustat in patients treated with ESAs, whereas the phase 2b trial only included patients who switched from epoetin; (v) the efficacy of molidustat therapy will be investigated for the first time in patients on peritoneal dialysis in MIYABI PD, whereas only patients undergoing haemodialysis were included in the phase 2b trial.

Approximately 600 patients are planned to be involved in the five studies in the phase 3 MIYABI programme; three studies in patients on dialysis and two studies in patients not on dialysis. While safety assessments will be conducted for all patients in the MIYABI programme, including assessments of vital signs and 12-lead electrocardiogram parameters, the sample size is insufficient to determine the risk of cardiovascular events. The MIYABI HD-C and MIYABI PD studies will also be limited to investigating molidustat therapy in the absence of a comparator and with small sample sizes (approximately 25 and 50, respectively), owing to the feasibility of patient recruitment (in Japan, limited numbers of patients with renal anaemia are on dialysis while not receiving ESAs or are on peritoneal dialysis), although molidustat will be compared with the current standard of care (darbepoetin alfa) as a maintenance treatment in a study powered to assess efficacy and safety in 150 patients on dialysis.

In the three MIYABI trials in patients on dialysis, the efficacy of molidustat will primarily be assessed by investigating Hb levels, including changes from baseline and maintenance of prespecified Hb targets. However, several exploratory variables will be also investigated. These include assessments of VEGF levels and ophthalmological examinations, conducted to

evaluate the theoretical risk of VEGF-mediated diabetic retinopathy,[22] and biomarkers of iron metabolism as, in addition to increasing EPO production predominately in the kidney, molidustat may increase the availability of iron for erythropoiesis.[21-23]

In summary, the three trials in patients on dialysis described here, together with two other trials in patients who are not receiving dialysis (the MIYABI ND-C and MIYABI ND-M randomised, open-label, active-controlled, parallel-group, multicentre trials), comprise the MIYABI phase 3 programme. This programme will investigate the efficacy and safety of molidustat in a broad clinical spectrum spanning approximately 600 patients with renal anaemia and CKD in Japan.

ETHICS AND DISSEMINATION

The studies are being conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP). Documented approval from appropriate independent ethics committees and institutional review boards has been obtained, according to GCP and local laws, regulations and organisations. Informed consent was obtained from patients before entering the studies and may be withdrawn at any time.

The studies have been registered on ClinicalTrials.gov (NCT03351166 [MIYABI HD-C], NCT03418168 [MIYABI PD], NCT03543657 [MIYABI HD-M]). Results will be disseminated through peer-reviewed publication(s).

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AUTHOR CONTRIBUTORS

TA, HY and TY contributed to designing these studies. TY contributed to developing the original study protocols. MT contributed to drafting the article and revising it. TA, HY, MT and KI critical revised the article for important intellectual content. YM contributed to developing the statistical analysis plan and assisted in the preparation of the manuscript. All

authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately resolved.

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COMPETING INTERESTS MT, YM, KI and TY are employees of Bayer Yakuhin Ltd. TA received consulting and lecture fees from Bayer Yakuhin Ltd during the conduct of the study. TA also received consulting, lecture or manuscript fees outside the submitted work from Astellas, GlaxoSmithKline, JT Pharmaceuticals, Kissei Pharmaceutical Co. Ltd, Kyowa Hakko Kirin, Nipro Corporation, Fuso Pharmaceutical Industries Ltd, and Ono Pharmaceutical Co. Ltd, and lecture fees from Bayer Yakuhin, Chugai Pharmaceutical Co. Ltd, Kyowa Hakko Kirin, and Torii Pharmaceutical Co. Ltd. HY received consulting fees from Bayer Yakuhin Ltd during the conduct of the study.

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FIGURE LEGEND

Figure 1 Trial designs for (**A**) MIYABI HD-C, (**B**) MIYABI PD and (**C**) MIYABI HD-M. MIYABI HD-C and MIYABI PD are single-arm, multicentre trials. MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre trial. Haemoglobin levels and safety will be assessed at each study visit, conducted at the time points shown.

BL, baseline; EOF, end of follow-up; EOT, end of treatment; ESA, erythropoiesis-stimulating agent.

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TABLES

Table 1 Trial designs, patient populations and treatments

	MIYABI HD-C [NCT03351166]	MIYABI PD [NCT03418168]	MIYABI HD-M [NCT03543657]
Trial design	Single-arm, multicentre	Single-arm, multicentre	Randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre
Patient population	Men and women (aged ≥20 years, body weight >40 and ≤160 kg) with a diagnosis of renal anaemia		
Key inclusion criteria	Patients with ESKD on haemodialysis at least weekly for ≥2 weeks	Patients with ESKD on peritoneal dialysis	Patients with ESKD on haemodialysis at least weekly for ≥12 weeks
	Mean of the last two Hb levels between ≥8.0 and <10.0 g/dL	Mean of the last two Hb levels between ≥8.0 and <11.0 g/dL for ESA untreated and ≥10.0 and <13.0 g/dL for ESA treated	Mean of all Hb levels (at least two measurements) between ≥9.5 and <12.0 g/dL
	Not treated with ESAs during the 8 weeks before study drug assignment	Not treated or treated with ESAs during the 8 weeks before study drug assignment*	Treated with the same ESA for ≥8 weeks before randomisation (weekly or biweekly dose of darbepoetin alfa, monthly or biweekly dose of epoetin beta pegol, OR weekly, biweekly, twice or three times per week dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before randomisation)*

	Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment	Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment	
Study treatments	A starting dose of 75 mg molidustat OD, titrated based on Hb response of the previous dose. Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD Hb target range ≥10.0 to <12.0 g/dL	A starting dose of 75 mg molidustat OD, titrated based on Hb response of the previous dose. Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD Hb target range ≥11.0 to <13.0 g/dL	Two groups: molidustat + darbepoetin alfa placebo, or molidustat placebo + darbepoetin alfa A starting dose of 75 mg molidustat or molidustat placebo OD, titrated based on Hb response of the previous dose Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD. Hb target range ≥10.0 to <12.0 g/dL A starting dose of darbepoetin alfa or darbepoetin alfa placebo will be decided in accordance with the previous ESA dosages and schedule of once a week or every 2 weeks per Japanese label
Treatment duration, weeks	24	36	52

ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor prolyl-hydroxylase; OD, once daily.

*For patients 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 be >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol.

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Table 2 Efficacy and safety variables

	MIYABI HD-C	MIYABI PD	MIYABI HD-M
Primary efficacy variables specific to each trial	• Rate of rise in Hb level (g/dL/week) at the first dose change up to week 8* • Responder rate during the evaluation period (weeks 21–24)†	• Responder rate during the evaluation period (weeks 30–36)†	• Mean Hb level during the evaluation period (weeks 33–36) • Change in mean Hb level from baseline during the evaluation period
Secondary efficacy variables in all three trials	• Proportions of patients who meet the three response criteria during the evaluation period† • Hb level and change from baseline (measurement at each visit and mean during the evaluation period) • Proportion of patients whose mean Hb level is in, above or below the target range during the evaluation period • Proportion of patients whose Hb level is in, above or below the target range, respectively, at each visit • Proportion of patients whose maximum rise in Hb between each consecutive visit is >0.5 g/dL/week (defined as change in Hb level/duration between two visits [weeks])		
Secondary efficacy variables specific to each trial	• Rate of rise in Hb (g/dL/week) at the dose change up to week 4 • Cumulative proportion of patients who achieve the lower limit of the target Hb range at least once at each visit	• Rate of rise in Hb level (g/dL/week) at the dose changes up to weeks 4 and 8* • Change in mean Hb level from baseline during the evaluation period • Mean Hb level during the evaluation period	• Responder rate during the evaluation period†
Other efficacy variables in MIYABI HD-C and MIYABI HD-M (secondary variables in MIYABI PD)	• Rate of rise in Hb level (g/dL/week) during each visit interval • Percentage of days in the target Hb range during the evaluation period and treatment period, respectively (defined as the number of days in the target range/number of days during the period × 100 [%]) • Percentage of Hb levels in target range during the evaluation period and treatment period, respectively (defined as the		

	number of measurements in the target range/number of measurements × 100 [%]) • Proportion of patients who received at least one rescue treatment (RBC transfusion, ESA treatment)
Safety variables in all three trials	• Adjudicated AEs‡ • AEs including serious AEs • Change in vital signs (pulse rate and blood pressure) • 12-lead electrocardiogram parameters • Observations of ophthalmological examination (fundus and anterior ocular segment examination and intraocular pressure measurement) • Laboratory examinations (including haematology, coagulation, clinical chemistry, electrolyte, HbA_{1c}, PTH and TSH levels)
Exploratory variables in all three trials	• Parameters of iron metabolism • EQ-5D-5L • Vascular endothelial growth factor

AEs, adverse events; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; ESA, erythropoiesis-stimulating agents; Hb, haemoglobin; HbA_{1c}, glycated haemoglobin; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; RBC, red blood cell.

*Rate of rise in Hb (g/dL/week) at the first dose change up to week 8 is defined as the change in Hb level from baseline to the first dose change of study drug up to week 8 divided by the duration of the starting dose (in weeks). If no dose change is performed up to week 8, then an Hb level at week 8 and the date of the week 8 visit will be used to calculate the change in Hb level and duration.

†A responder is defined as a patient who meets all of the following criteria:

(i) mean of the Hb levels during the evaluation period is in the target range

(ii) ≥50% of the Hb levels during the evaluation period are in the target range

(iii) no rescue treatment up to the end of the evaluation period.

‡Adjudicated AEs include death, myocardial infarction, unstable angina pectoris, stroke or transient ischaemic attack, pulmonary thromboembolism or acute limb ischaemia.

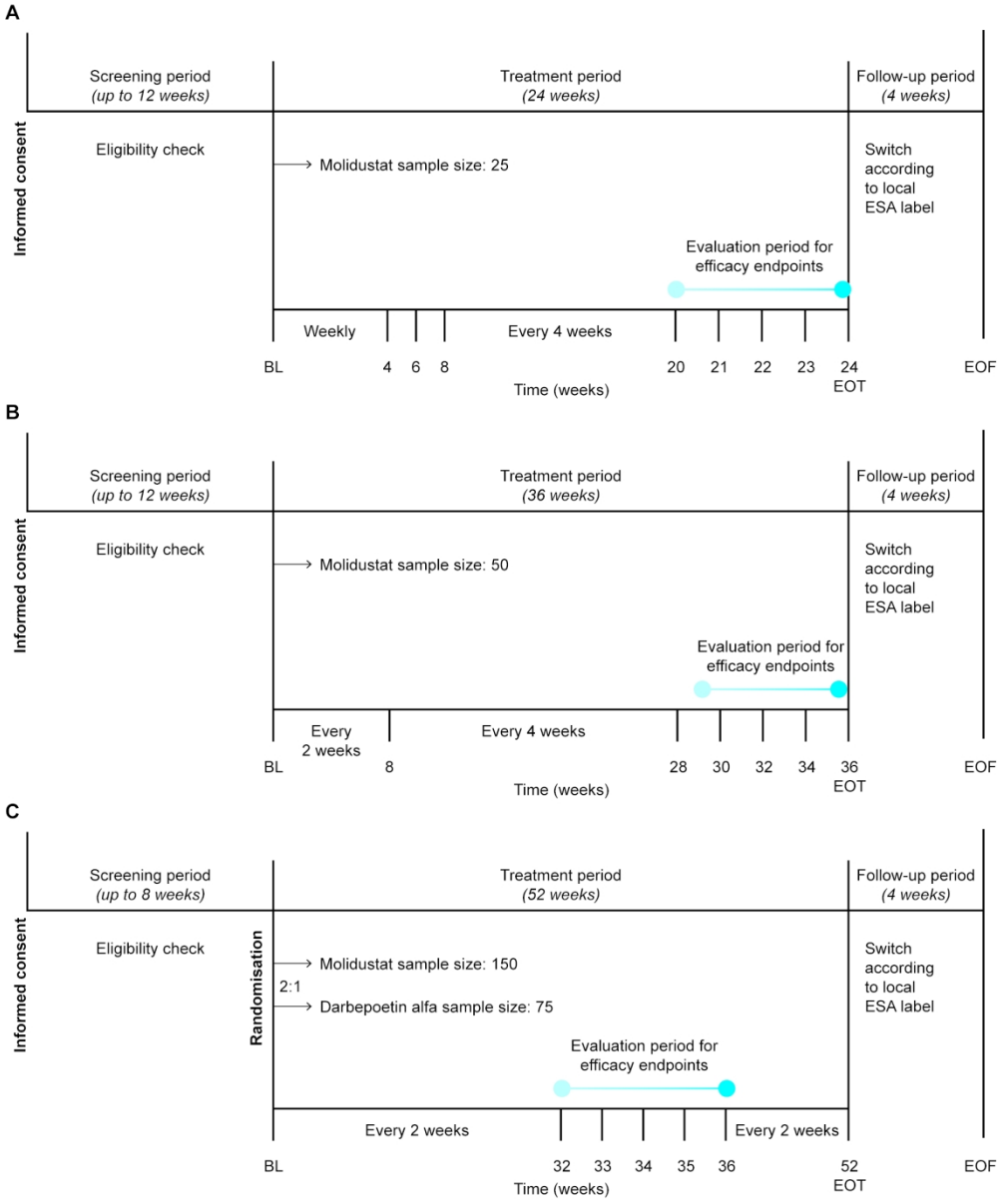

Figure 1 Trial designs for (A) MIYABI HD-C, (B) MIYABI PD and (C) MIYABI HD-M. MIYABI HD-C and MIYABI PD are single-arm, multicentre trials. MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre trial. Haemoglobin levels and safety will be assessed at each study visit, conducted at the time points shown.
BL, baseline; EOF, end of follow-up; EOT, end of treatment; ESA, erythropoiesis-stimulating agent.

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SUPPLEMENTARY TABLES

Supplementary table 1 An overview of all inclusion and exclusion criteria

Inclusion criteria
All three trials had the following inclusion criteria • Written informed consent before performing any study-specific tests or procedures • Body weight (after dialysis) >40 and ≤160 kg at screening • Male or female ≥20 years of age at screening • At least one kidney • Serum folate level and serum vitamin B12 level above LLN at screening • Women of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form until 12 weeks after the last administration of the study drug. o Acceptable methods of contraception may include, but are not limited to, condoms (male or female) with or without a spermicidal agent; diaphragm or cervical cap with spermicide; intra-uterine device; hormone-based contraception. o Patients must agree to utilise two reliable and acceptable methods of contraception simultaneously. Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhoea with an appropriate clinical profile (eg, age-appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhoea with serum FSH levels >40 mIU/mL or have had surgical treatment such as bilateral tubal ligation, bilateral ovariectomy or hysterectomy. • Ability to understand and follow study-related instructions.
MIYABI HD-C had four additional inclusion criteria • Patients with ESKD on dialysis (including haemodiafiltration, haemodialysis and other modalities except for peritoneal dialysis) weekly or more than weekly for ≥2 weeks before study drug assignment • Mean screening Hb level ≥8.0 and <10.0 g/dL (at least two measurements must be taken ≥2 days apart, assessed by the central laboratory; the

difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment

- Not treated with any ESAs or HIF-PH inhibitors during the 8 weeks before study drug assignment. For patients 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 be >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol
- Ferritin ≥50 ng/mL at screening

MIYABI PD had five additional inclusion criteria

- Patients with ESKD on peritoneal dialysis before study drug assignment and not expected to start maintenance dialysis (eg, haemodialysis, haemodiafiltration) other than peritoneal dialysis during the study period
- Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment
- Patients who meet one of the following criteria

  A: Untreated with ESA at study drug assignment

  Mean screening Hb level ≥8.0 and <11.0 g/dL (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment

  B: Pre-treated with ESA at study drug assignment

  Mean screening Hb level ≥10.0 and <13.0 g/dL (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment
- Patients who meet one of the following criteria

  A: Untreated with ESA at study drug assignment

  - Patient with ESKD on peritoneal dialysis for ≥2 weeks before study drug assignment

  and

  - Not treated with ESA for the 8 weeks before study drug assignment

  or

  - Washed out from ESAs, when the mean Hb level (based on at least two measurements taken ≥2 days apart, assessed by the central

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laboratory) has decreased by ≥0.5 g/dL after the last ESA administration, AND the interval from the last ESA administration to study drug assignment should be >2 weeks for epoetin alfa/beta and >4 weeks for darbepoetin alfa or epoetin beta pegol

B: Pre-treated with ESA at study drug assignment

- Patient with ESKD on peritoneal dialysis for ≥12 weeks before study drug assignment
- Treated with IV or SC ESA during the 8 weeks before study drug assignment
- Treated with 2- or 4-weekly dose of darbepoetin alfa, 4-weekly dose of epoetin beta pegol, OR 3 times per week, twice per week, weekly or biweekly dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before study drug assignment

- Patients who meet one of the following criteria

A: Untreated with ESA at study drug assignment

Ferritin ≥50 ng/mL at screening

B: Pre-treated with ESA at study drug assignment

- Ferritin ≥100 ng/mL or transferrin saturation ≥20%

MIYABI HD-M had five additional inclusion criteria

- Patients with ESKD on dialysis (including haemodiafiltration, haemofiltration, haemodialysis and other modalities except for peritoneal dialysis) weekly or more than weekly for ≥12 weeks before randomisation
- Treated with the same ESA for ≥8 weeks before screening
- Treated with weekly or biweekly dose of darbepoetin alfa, monthly or biweekly dose of epoetin beta pegol, OR weekly, biweekly, twice or three times per week dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before randomisation
- Mean screening Hb level ≥9.5 and <12.0 g/dL before dialysis (based on at least two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the lowest level and highest level <1.2 g/dL), with the last screening Hb level measurement during the 14 days before randomisation
- Ferritin ≥100 ng/mL or transferrin saturation ≥20% at screening

Exclusion criteria

All three trials had the following exclusion criteria

- Any current condition leading to significant blood loss

- Active haemolysis or diagnosis of haemolytic syndrome
- Previous or concurrent myelodysplastic syndrome, multiple myeloma, marrow fibrosis or PRCA
- Previous or concurrent haemosiderosis or haemochromatosis
- Previous or concurrent hereditary haemoglobinopathies (eg, sickle-cell disease, beta thalassaemia, thalassaemia major)
- Previous or concurrent aplastic anaemia
- Previous or concurrent chronic lymphoproliferative diseases
- Proliferative choroidal or retinal disease, such as neovascular age-related macular degeneration or proliferative diabetic retinopathy requiring invasive treatment (eg, intraocular injections or laser photocoagulation) at screening
- Chronic inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease, which is determined to be the principal cause of the anaemia
- Known hypersensitivity to the study drugs (active substances or excipients of the preparations)
- Uncontrolled and symptomatic hyperparathyroidism
- Uncontrolled active infection at study drug assignment
- Previous or concurrent cancer except cervical carcinoma *in situ*, treated basal cell carcinoma, superficial bladder tumours (Ta, Tis and T1) or any cancer curatively treated >3 years before study drug assignment
- Previous or scheduled organ transplantation (being on a transplant waiting list does not exclude a patient)
- History of alcohol or drug abuse during the 2 years before study drug assignment
- RBC-containing transfusion for treatment of anaemia during the 8 weeks before study drug assignment
- Treatment with uridine-diphosphate-glucuronosyltransferase 1 family, polypeptide A1 inhibitors during the 7 days before study drug assignment:
    - antiretroviral drugs (eg, ritonavir, saquinavir, atazanavir, indinavir, lopinavir, nelfinavir)
    - tyrosine kinase inhibitors (eg, erlotinib, pazopanib, nilotinib, sorafenib, regorafenib)
    - tranilast
- Patients treated with immune- or myelosuppressive therapy during the 8 weeks before study drug assignment (eg, everolimus, sirolimus, rituximab, azathioprine, mycophenolate mofetil, mycophenolic acid, cyclosporine, methotrexate, tacrolimus, chemotherapeutic agents and other anticancer agents, and systemic steroids treatment [except inhaled steroids] for 7 days or more)
- Treated with the following therapies during the 8 weeks before study drug assignment: anabolic hormone, testosterone enanthate or

mepitiostane

- History of cardiovascular or cerebrovascular events (eg, unstable angina, myocardial infarction, stroke, pulmonary thromboembolism and ALI) during the 6 months before study drug assignment
- Sustained, poorly controlled arterial hypertension (defined as systolic BP ≥180mmHg or diastolic BP ≥110mmHg) or hypotension (defined as systolic BP <90mmHg) at study drug assignment
- NYHAclass III or IV congestive heart failure
- Severe hepatic disorder (defined as ALT or AST >3 x the upper limit of normal, total bilirubin >2 mg/dL, or Child-Pugh B or C) at screening
- Previous use of molidustat
- A patient in need of surgery that may be expected to lead to significant blood loss
- Expected need for rescue treatment during the next 7 days after study drug assignment
- Active hepatitis, as assessed by the investigator
- Any medical condition that in the opinion of the investigator may pose a safety risk to a patient in this study, may confound safety or efficacy assessment or may interfere with study participation
- Previous assignment to study treatment during this study
- Previous (during the 30 days before study drug assignment) or concomitant participation in another clinical study with investigational medicinal product(s)
- Close affiliation with the investigational site, for example, a close relative of the investigator, dependent person (eg, employee or student at the investigational site)
- Pregnant or breastfeeding women

MIYABI PD had two additional exclusion criteria

- Previous or concurrent indications for removal of peritoneal dialysis catheter (eg, recurrent peritoneum inflammation, refractory tunnel infection)
- Concomitant use of maintenance dialysis (eg, haemodialysis, haemodiafiltration) other than peritoneal dialysis

ALI, acute limb ischaemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; FSH, follicle-stimulating hormone; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor prolyl hydoxylase; IV, intravenous; LLN, lower limit of normal; NYHA, New York Heart Association; PRCA, pure red cell aplasia; RBC, red blood cell; SC, subcutaneous.

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Supplementary table 2 Dose titration for molidustat at week 4 for all patients in the MIYABI HD-C trial* and for patients not treated with ESA at study drug assignment in the MIYABI PD trial

Rise in Hb in the first 4 weeks (g/dL)	Hb level (g/dL) in MIYABI HD-C	Hb level (g/dL) in MIYABI PD	Titration step
<0.5	<9.5	<10.5	Increase to the next higher dose
	≥9.5	≥10.5	Maintain the same dose
≥0.5 and <1.0	Any value	Any value	
≥1.0 and ≤2.0	≤10.0	≤11.0	
	>10.0	>11.0	Decrease to the next lower dose
>2.0	Any value	Any value	

*All patients in MIYABI HD-C will not be treated with ESAs at study drug assignment or during the trial.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

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Supplementary table 3 Dose titration from week 8 in MIYABI HD-C, from week 4 or 8 in MIYABI PD*, and from week 2 or 4 in MIYABI HD-M†

Hb level (g/dL) in MIYABI HD-C and MIYABI HD-M	**Hb level (g/dL) in MIYABI PD**	**Titration step**
<10.0	<11.0	Increase to the next higher dose
≥10.0 and <12.0	≥11.0 and <12.5	Maintain the same dose
≥12.0 and <13.0	≥12.5 and <13.0	Decrease to the next dose
≥13.0	≥13.0	Suspend a dose until the next scheduled visit

*In MIYABI PD, patients treated with ESAs at study drug assignment will start this dose-titration schedule for molidustat at week 4, whereas patients not treated with ESAs at study drug assignment will start this dose titration schedule for molidustat at week 8.

†In MIYABI HD-M, doses of darbepoetin alfa or darbepoetin alfa placebo will be titrated from week 2, whereas doses of molidustat will be titrated from week 4.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies

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Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies

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ABSTRACT

Introduction: New medications for anaemia associated with chronic kidney disease (CKD) are desirable, owing to the limitations of erythropoiesis-stimulating agents (ESAs), the current standard of care. Molidustat is a novel hypoxia-inducible factor prolyl-hydroxylase inhibitor that stimulates erythropoietin production, predominately in the kidney. We report methodological details of three phase 3 trials, named **M**ol**I**dustat once dail**Y** improves renal **A**nemia **B**y **I**nducing erythropoietin (MIYABI), designed primarily to investigate the efficacy of molidustat therapy in adults with renal anaemia and dialysis-dependent CKD.

Methods and analysis: MIYABI Haemodialysis-Correction (HD-C) is a single-arm trial (24-week treatment duration) in approximately 25 patients on haemodialysis, currently untreated with ESAs. MIYABI Peritoneal Dialysis (PD) is a single-arm trial (36-week treatment duration) in approximately 50 patients on peritoneal dialysis, treated or untreated with ESAs. MIYABI Haemodialysis-Maintenance (HD-M) is a randomised, active-controlled, double-blinded, double-dummy trial (52-week treatment duration) comparing molidustat with darbepoetin alfa in approximately 225 patients on haemodialysis, treated with ESAs. Molidustat (starting dose 75 mg/day) will be titrated 4-weekly to maintain haemoglobin in pre-determined target ranges. The primary objective is to evaluate the efficacy of molidustat, using the following measures: the rate of rise in haemoglobin (g/dL/week) at the first dose change up to week 8 (MIYABI HD-C); responder rate (MIYABI HD-C and MIYABI PD); mean haemoglobin level during weeks 33–36 and non-inferiority to darbepoetin alfa shown by change in mean haemoglobin level from baseline (MIYABI HD-M). The secondary objectives are to assess safety, pharmacokinetics and pharmacodynamics. These trials will provide the first evaluations of molidustat therapy in patients receiving either peritoneal dialysis or currently untreated with ESAs on haemodialysis, and provide further evidence in patients treated with ESAs on haemodialysis.

Ethics and dissemination: The protocols were approved by ethics committees at all participating sites. The trials will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Trial registration numbers: NCT03351166, NCT03418168, NCT03543657

Keywords: Chronic kidney disease; dialysis; molidustat; renal anaemia

STRENGTHS AND LIMITATIONS OF THESE STUDIES

- Due to recruitment feasibility limitations, MIYABI HD-C and MIYABI-PD are single arm, open-label studies.
- In MIYABI HD-M, a randomised, double-blind study, molidustat treatment will be directly compared with an ESA (darbepoetin alfa), the current standard of care for renal anaemia, and will build on the results of a previous open-label phase 2b trial in patients on haemodialysis.
- The MIYABI HD-M trial will involve a larger patient population (n=150) receiving a 75 mg starting dose than in the phase 2b trial.
- Treatment durations will be longer (eg, 52 weeks in MIYABI HD-M) than in the phase 2b trial (16 weeks), although some molidustat-treated patients in the phase 2b trial (n=57) continued treatment in an extension study for up to 36 months.
- These are the first studies to directly investigate the efficacy of molidustat therapy in patients on peritoneal dialysis and in patients currently untreated with ESAs on haemodialysis.

INTRODUCTION

Anaemia is a common and serious complication of chronic kidney disease (CKD),[1] which worsens as CKD progresses.[2-4] The main cause of anaemia associated with CKD (also known as renal anaemia) is erythropoietin (EPO) deficiency.[5]

Treatment with erythropoiesis-stimulating agents (ESAs) is the current standard of care for renal anaemia.[6] However, this approach has limitations. In 10–20% of patients, irrespective of dialysis status, ESAs are ineffective at raising haemoglobin (Hb) to prespecified levels.[7-9] ESAs may also cause several adverse events (AEs), including development or worsening of hypertension,[10-12] rare cases of antibody-mediated pure red cell aplasia,[13] poor cardiovascular outcomes and death.[14-16] In patients with cancer and anaemia, ESA use is associated with increased risk of thrombosis.[17] These AEs may be related to injecting high doses of ESAs to achieve Hb targets[15 17-19] and excessive increases in Hb levels.[20]

A new approach under investigation involves using small molecules to inhibit hypoxia-inducible factor prolyl-hydroxylases (HIF-PH), thereby inducing EPO production. In addition to addressing EPO deficiency, the main cause of renal anaemia, the therapeutic effect of HIF-PH inhibition may also be mediated by increasing the availability of iron for erythropoiesis, as indicated by reductions in hepcidin levels.[21-26] These findings are particularly notable, given that functional iron deficiency may contribute to the inadequate responses that 10–20% of patients experience during treatment with ESAs, even though these patients often receive intravenous iron supplementation.[5-9] HIF-PH inhibition may theoretically also have a downside, because HIF transcriptionally upregulates a large number of genes; although EPO gene upregulation is helpful in treating anaemia associated with CKD, vascular endothelial growth factor (VEGF) upregulation could result in neoplasia and diabetic retinopathy.[22] However, in clinical trials of HIF-PH inhibitors, no safety signals or changes in VEGF levels were reported.[24-26]

Molidustat, a novel, orally administered inhibitor of HIF-PH, induces circulating levels of EPO close to the normal physiological range, with high relative selectivity for the induction of EPO gene expression, predominately in the kidney.[21] Results from preclinical[21] and clinical studies[27] suggest that molidustat is a promising option for the treatment of EPO-sensitive anaemia in patients with CKD. In preclinical studies, molidustat restored renal EPO

production with minor induction of hepatic EPO. Molidustat increased plasma EPO and EPO mRNA in the kidney and prevented decline in haematocrit and corrected decreases in Hb level.[21] In a randomised, placebo-controlled, phase 1 study involving 59 healthy participants, single doses of molidustat (5–50 mg) elicited a dose-dependent increase in EPO and were well tolerated.[27] In three 16-week, randomised, phase 2b, dose-ranging studies, comprising one study with patients on haemodialysis and two studies with patients not on dialysis, more than 400 patients with CKD were enrolled. These studies demonstrated that, during treatment with flexible-dose molidustat, Hb levels could be corrected relative to placebo or maintained at levels comparable to those in patients who continued treatment with ESAs, with manageable side effects.[28] Comparable results and no significant safety concerns were observed in extension studies up to 36 months (unpublished data).

Based on the positive findings of the preclinical and phase 2b clinical studies, the **M**ol**I**dustat once dail**Y** improves renal **A**nemia **B**y **I**nducing EPO (MIYABI) programme of five phase 3 trials has been designed to investigate molidustat therapy further in patients with renal anaemia in Japan. Here, we report the methodological details of the three MIYABI trials in which the efficacy (up to 36 weeks), safety, pharmacokinetics and pharmacodynamics (up to 52 weeks) of molidustat therapy will be investigated in patients receiving dialysis. These three trials will provide the first evaluations of molidustat therapy in patients on peritoneal dialysis and in patients currently untreated with ESAs on haemodialysis, as well as extending the evidence in patients treated with ESAs on haemodialysis.

METHODS AND PLANNED ANALYSES

Study designs, objectives and populations

Each of the three phase 3 trials is a multicentre study conducted in adults aged 20 years or older with renal anaemia and dialysis-dependent CKD in Japan. In each trial, the primary objective is to evaluate the efficacy of molidustat in the respective patient populations and, in the MIYABI Haemodialysis Maintenance (HD-M) trial, to show non-inferiority to darbepoetin alfa. The secondary objectives of each trial are to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of molidustat during the treatment periods. The three trials commenced in the first half of 2018 and have finished recruiting. The planned end dates for MIYABI HD-C, MIYABI PD, and MIYABI HD-M are November 2018,

August 2019 and December 2019, respectively. Patient eligibility was assessed during screening periods lasting up to 12 weeks in the MIYABI Haemodialysis Correction (HD-C) and MIYABI Peritoneal Dialysis (PD) studies and up to 8 weeks in MIYABI HD-M. To be eligible, the mean of at least two Hb measurements (both taken before dialysis, at least 2 days apart, with the last measurement taken within 14 days before study drug assignment, and with a difference of less than 1.2 g/dL between the lowest and highest values) was required to lie within pre-specified levels (table 1). The main inclusion criteria are summarised in table 1. All inclusion and exclusion criteria are shown in supplementary table 1.

MIYABI HD-C is a single-arm study in patients on haemodialysis who are not currently treated with ESAs, with a 24-week treatment duration (figure 1 and table 1). Japanese guidelines for the clinical evaluation of medications for renal anaemia recommend demonstrating efficacy in the correction and maintenance of renal anaemia in patients on dialysis, as well as in patients not on dialysis.[29] However, the number of patients with renal anaemia on dialysis who do not receive ESAs is limited in Japan. A single-arm study design was chosen for MIYABI HD-C owing to the feasibility of patient recruitment.[30]

MIYABI PD is a single-arm study in patients on peritoneal dialysis who are treated or not treated with ESAs, with a 36-week treatment duration (figure 1 and table 1). A single-arm study design was chosen for MIYABI PD owing to the limited number of peritoneal dialysis patients with renal anaemia in Japan.

MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group study comparing molidustat with darbepoetin alfa in patients on haemodialysis who are treated with ESAs (figure 1 and table 1). The study has a treatment duration of 52 weeks. As most patients with renal anaemia on dialysis in Japan are treated with ESAs, it is feasible to recruit sufficient patients to perform a confirmatory, randomised, double-blinded trial of molidustat in this patient population. Therefore, in MIYABI HD-M, eligible patients will be randomised in a ratio of 2:1 to the molidustat group or darbepoetin alfa group. Allocation to treatment arms will be achieved using an interactive voice/web response system (IxRS) at the first (baseline) visit. Randomisation will be stratified by previous ESA dose group (low or high) and by medical history of thromboembolic events (yes or no for myocardial infarction, pulmonary thromboembolism, stroke [excluding haemorrhagic

stroke] or acute limb ischaemia). All investigators and patients in MIYABI HD-M will be blinded to treatment allocation. In cases of emergency, such as occurrence of a suspected, unexpected, serious AE, when the investigator needs to know which drug has been allocated, unblinding will occur by entering the emergency key code for the relevant patient into the IxRS.

Each study is being overseen by a data monitoring committee consisting of independent clinical experts and an independent biostatistician supported by an independent statistical analysis centre, whose main responsibility is to recommend a change, interruption or termination of the study (or all phase 3 studies) based on safety findings.

Treatments

Study treatments are summarised in table 1. In each study, a starting dose of 75 mg molidustat once daily (OD) will be titrated every 4 weeks using the IxRS, based on the patient's Hb response to the previous dose. In each study, planned doses for the titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD. The dose of molidustat will be adjusted to correct and maintain Hb levels in the target ranges of ≥10.0 to <12.0 g/dL in MIYABI HD-C and MIYABI HD-M and ≥11.0 to <13.0 g/dL in MIYABI PD, as per Japanese guideline recommendations.[31]

For patients untreated with ESAs (all patients in MIYABI HD-C and some patients in MIYABI PD, but no patients in MIYABI HD-M), a dose adaptation visit will occur at week 4 to avoid excessive elevation of Hb levels after the initiation of molidustat treatment. In MIYABI HD-C and MIYABI PD, dose titration at week 4 will be based on both the magnitude of the rise in Hb and the Hb level (supplementary table 2) and from week 8 according to the Hb level alone (supplementary table 3). For patients treated with ESAs (all patients in MIYABI HD-M and some patients in MIYABI PD, but no patients in MIYABI HD-C), the dose will be titrated from week 4 according to Hb level (supplementary table 3).

In MIYABI HD-M, patients will receive molidustat or molidustat placebo orally and darbepoetin alfa or darbepoetin alfa placebo intravenously. Patients in the molidustat group will receive molidustat plus darbepoetin alfa placebo, while patients in the darbepoetin alfa group will receive darbepoetin alfa plus molidustat placebo. The starting dose of

darbepoetin alfa or darbepoetin alfa placebo will be selected for each patient based on their previous ESA dosage. Patients treated with darbepoetin alfa at screening will continue this treatment or start treatment with darbepoetin alfa placebo at the previous dose and interval (ie, weekly or biweekly). Patients treated with an epoetin therapy at screening will be treated with darbepoetin alfa or darbepoetin alfa placebo at a starting dose and interval determined by their epoetin dosage at screening. Then, depending on the Hb level (supplementary table 3), doses of darbepoetin alfa and darbepoetin alfa placebo will be titrated at biweekly intervals from week 2, and doses of molidustat and molidustat placebo will be titrated from week 4 at 4-weekly intervals.

In each study, iron, vitamin B12 and folate supplementation is permitted if required and will be administered according to Japanese guideline recommendations.[31] Iron supplementation will be administered to reach a target serum ferritin level of at least 100 ng/mL or transferrin saturation of at least 20%.

Variables

All efficacy and safety variables, and associated definitions, are shown in table 2. The primary efficacy variables in MIYABI HD-C are the rate of rise in Hb level (g/dL/week) at the first dose change up to week 8 and responder rate. In MIYABI PD, the primary efficacy variable will be the responder rate. In MIYABI HD-M, the primary efficacy variables will be mean Hb level during the evaluation period and its change from baseline. In all three studies, a responder is defined as a patient who meets all of the following criteria: (i) mean of the Hb levels during the evaluation period is in the target range; (ii) ≥50% of the Hb levels during the evaluation period are in the target range; (iii) no rescue treatment received up to the end of the evaluation period. Secondary variables for the three trials are shown in table 2. In each study, exploratory variables will include measures of iron metabolism, VEGF levels and assessment of health-related quality of life using the EuroQol 5-dimension 5-level questionnaire.

In each study, to investigate systemic exposure to molidustat and the relationship between molidustat exposure and response, sparse sampling from all patients will be conducted for pharmacokinetics and pharmacodynamics. If possible, molidustat exposure parameters (eg, C_{max}, AUC) and the relationship between molidustat exposure and treatment effects will be

evaluated using population approaches (eg, non-linear mixed effect modelling), including potential influence of relevant patient covariables.

Statistical analysis

All variables (including demographic and other baseline characteristics) will be analysed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by summary statistics (mean, standard deviation, minimum, median and maximum). Summary statistics will be presented for the original data as well as for the difference from baseline.

In each study, the primary analysis set for efficacy will be the full analysis set, which includes all patients assigned to treatment who have at least one baseline Hb level (ie, at least one Hb level before the first dose of the study drug).

In MIYABI HD-C, the primary efficacy variables (rate of rise in Hb and responder rate) and their two-sided 95% confidence intervals (CI) will be estimated using one-sample *t*-statistics and the Clopper–Pearson method, respectively. In MIYABI PD, the primary efficacy variable (responder rate) and its two-sided 95% CI will be estimated using the Clopper–Pearson method. In MIYABI HD-M, the primary efficacy variables (mean Hb level and change in mean Hb level) will be analysed by sequentially testing two hypotheses. In MIYABI HD-M, the primary objective will be achieved if the following two hypotheses are confirmed. (i) In the molidustat treatment group, the mean Hb level during the evaluation period (weeks 33–36) remains within the target range (≥10.0 to <12.0 g/dL). The mean Hb level in the molidustat treatment group will be calculated using the mean Hb level per patient. If the lower limit of the two-sided 95% CI of the mean of the mean Hb level is greater than or equal to the lower limit of the target Hb level (ie, ≥10.0 g/dL) and if the upper limit of the two-sided 95% CI is less than the upper limit of the target Hb level (ie, <12.0 g/dL), it will be established that the mean Hb level is within the target range. Two-sided 95% CI will be estimated using one sample *t*-statistics. (ii) Molidustat is not inferior to darbepoetin alfa. The non-inferiority of molidustat to darbepoetin alfa will be established if the lower limit of the two-sided 95% CI for the difference (molidustat minus darbepoetin alfa) is above –1.0 g/dL with non-inferiority margin of 1.0 g/dL. This margin was chosen because a variation of approximately 1.0 g/dL is considered acceptable in Japanese clinical practice.[31] In MIYABI HD-M, the

difference in change between the treatment groups and its two-sided 95% CI will be estimated using an analysis of covariance (ANCOVA) model, including treatment group, previous ESA dose group (low/high) and previous thromboembolic events (yes/no) as fixed effects and baseline Hb level as a covariate.

Determination of sample size

In MIYABI HD-C and MIYABI PD, the respective sample sizes of approximately 25 and 50 patients are determined based on feasibility.

In MIYABI HD-M, the sample size of 150 patients in the molidustat group and 75 patients in the darbepoetin alfa group should result in sufficient data to assess the long-term safety of molidustat therapy, assuming a dropout rate of approximately 30%. If 150 patients are randomised to the molidustat group, the power to establish that mean Hb levels are within target levels during the evaluation period is ≥98%, assuming a standard deviation of 1.3–1.5g/dL from the previous phase 2b studies. This sample size has >90% power to reject the null hypothesis that molidustat is inferior to darbepoetin alfa with a non-inferiority margin of 1.0 g/dL at a one-sided 2.5% significance level, assuming the expected difference between molidustat and darbepoetin alfa to be 0 g/dL and with a common standard deviation of 1.3–1.5 g/dL.

Patient and public involvement

Patients are not involved in the design and conduct of the studies.

DISCUSSION

Renal anaemia due to EPO deficiency is a common and serious complication of CKD.[1] However, new approaches to the treatment of renal anaemia are needed, owing to safety issues and limitations with current treatments. Results from previous studies, including three phase 2b dose-ranging trials, suggest that molidustat is a promising option for the treatment of EPO-sensitive anaemia in patients with CKD.

At present, only one phase 2b trial assessing molidustat has been conducted in patients with renal anaemia who are on dialysis. It is anticipated that the three phase 3 trials described here will demonstrate the efficacy and safety of molidustat in patients with renal anaemia on dialysis, and that the trials will have the following strengths, relative to the one phase 2b

trial conducted in patients on dialysis: (i) in MIYABI HD-M, molidustat treatment will be compared with an ESA (darbepoetin alfa), the current standard of care for renal anaemia, in a double-blinded manner, whereas an open-label design was used in the phase 2b trial, in which molidustat treatment was compared with another ESA (epoetin); (ii) a larger patient population in the MIYABI HD-M trial (n=150) receiving a starting dose of 75 mg molidustat OD than in the phase 2b trial (n=44 of the 157 patients treated with molidustat received a 75 mg starting dose); (iii) the treatment periods will be longer (eg, 52 weeks in MIYABI HD-M) than in the phase 2b trial (16 weeks), although about one-third of the molidustat-treated patients in the phase 2b trial (n=57) continued treatment in an extension study, with a duration of up to 36 months; (iv) molidustat therapy will be investigated for the first time in patients who are not treated with ESAs on haemodialysis in the MIYABI HD-C trial, and MIYABI HD-M will provide further evaluations of molidustat in patients treated with ESAs, whereas the phase 2b trial only included patients who switched from epoetin; (v) the efficacy of molidustat therapy will be investigated for the first time in patients on peritoneal dialysis in MIYABI PD, whereas only patients undergoing haemodialysis were included in the phase 2b trial.

Approximately 600 patients are planned to be involved in the five studies in the phase 3 MIYABI programme; three studies in patients on dialysis and two studies in patients not on dialysis. While safety assessments will be conducted for all patients in the MIYABI programme, including assessments of vital signs and 12-lead electrocardiogram parameters, the sample size is insufficient to determine the risk of cardiovascular events. The MIYABI HD-C and MIYABI PD studies will also be limited to investigating molidustat therapy in the absence of a comparator and with small sample sizes (approximately 25 and 50, respectively), owing to the feasibility of patient recruitment (in Japan, limited numbers of patients with renal anaemia are on dialysis while not receiving ESAs or are on peritoneal dialysis), although molidustat will be compared with the current standard of care (darbepoetin alfa) as a maintenance treatment in a study powered to assess efficacy and safety in 150 patients on dialysis.

In the three MIYABI trials in patients on dialysis, the efficacy of molidustat will primarily be assessed by investigating Hb levels, including changes from baseline and maintenance of

prespecified Hb targets. However, several exploratory variables will be also investigated. These include assessments of VEGF levels and ophthalmological examinations, conducted to evaluate the theoretical risk of VEGF-mediated diabetic retinopathy,[22] and biomarkers of iron metabolism as, in addition to increasing EPO production predominately in the kidney, molidustat may increase the availability of iron for erythropoiesis.[21-23]

In summary, the three trials in patients on dialysis described here, together with two other trials in patients who are not receiving dialysis (the MIYABI ND-C and MIYABI ND-M randomised, open-label, active-controlled, parallel-group, multicentre trials), comprise the MIYABI phase 3 programme. The design and rationale of MIYABI ND-C and MIYABI ND-M are published in a companion article.[32] This programme will investigate the efficacy and safety of molidustat in a broad clinical spectrum spanning approximately 600 patients with renal anaemia and CKD in Japan.

ETHICS AND DISSEMINATION

The studies are being conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP). Documented approval from appropriate independent ethics committees and institutional review boards has been obtained, according to GCP and local laws, regulations and organisations. The MIYABI HD-C study has been approved by the institutional review board of All Tohoku Clinical Trial Review and Audit Organization (application number: 20171204) and another 20 sites. The MIYABI PD study has been approved by the institutional review board of Kyushu University Hospital (application number: 20180221) and another 26 sites. The MIYABI HD-M study has been approved by the institutional review board of Ibaraki Prefectural Central Hospital (application number: 20180524), Asahikawa-Kosei General Hospital (20180806) and another 51 sites. Informed consent was obtained from patients before entering the studies and may be withdrawn at any time.

The studies have been registered on ClinicalTrials.gov (NCT03351166 [MIYABI HD-C], NCT03418168 [MIYABI PD], NCT03543657 [MIYABI HD-M]). Results will be disseminated through peer-reviewed publication(s).

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AUTHOR CONTRIBUTORS

TA, HY and TY contributed to designing these studies. TY contributed to developing the original study protocols. MT contributed to drafting the article and revising it. TA, HY, MT and KI critical revised the article for important intellectual content. YM contributed to developing the statistical analysis plan and assisted in the preparation of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately resolved.

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COMPETING INTERESTS MT, YM, KI and TY are employees of Bayer Yakuhin Ltd. TA received consulting and lecture fees from Bayer Yakuhin Ltd during the conduct of the study. TA also received consulting, lecture or manuscript fees outside the submitted work from Astellas, GlaxoSmithKline, JT Pharmaceuticals, Kissei Pharmaceutical Co. Ltd, Kyowa Hakko Kirin, Nipro Corporation, Fuso Pharmaceutical Industries Ltd, and Ono Pharmaceutical Co. Ltd, and lecture fees from Bayer Yakuhin, Chugai Pharmaceutical Co. Ltd, Kyowa Hakko Kirin, and Torii Pharmaceutical Co. Ltd. HY received consulting fees from Bayer Yakuhin Ltd during the conduct of the study.

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FIGURE LEGEND

Figure 1 Trial designs for (**A**) MIYABI HD-C, (**B**) MIYABI PD and (**C**) MIYABI HD-M. MIYABI HD-C and MIYABI PD are single-arm, multicentre trials. MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre trial. Haemoglobin levels and safety will be assessed at each study visit, conducted at the time points shown.

BL, baseline; EOF, end of follow-up; EOT, end of treatment; ESA, erythropoiesis-stimulating agent.

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TABLES

Table 1 Trial designs, patient populations and treatments

	MIYABI HD-C [NCT03351166]	MIYABI PD [NCT03418168]	MIYABI HD-M [NCT03543657]
Trial design	Single-arm, multicentre	Single-arm, multicentre	Randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre
Patient population	Men and women (aged ≥20 years, body weight >40 and ≤160 kg) with a diagnosis of renal anaemia		
Key inclusion criteria	Patients with ESKD on haemodialysis at least weekly for ≥2 weeks	Patients with ESKD on peritoneal dialysis	Patients with ESKD on haemodialysis at least weekly for ≥12 weeks
	Mean of the last two Hb levels between ≥8.0 and <10.0 g/dL	Mean of the last two Hb levels between ≥8.0 and <11.0 g/dL for ESA untreated and ≥10.0 and <13.0 g/dL for ESA treated	Mean of all Hb levels (at least two measurements) between ≥9.5 and <12.0 g/dL
	Not treated with ESAs during the 8 weeks before study drug assignment	Not treated or treated with ESAs during the 8 weeks before study drug assignment*	Treated with the same ESA for ≥8 weeks before randomisation (weekly or biweekly dose of darbepoetin alfa, monthly or biweekly dose of epoetin beta pegol, OR weekly, biweekly, twice or three times per week dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before randomisation)*

	Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment	Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment	
Study treatments	A starting dose of 75 mg molidustat OD, titrated based on Hb response of the previous dose. Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD Hb target range ≥10.0 to <12.0 g/dL	A starting dose of 75 mg molidustat OD, titrated based on Hb response of the previous dose. Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD Hb target range ≥11.0 to <13.0 g/dL	Two groups: molidustat + darbepoetin alfa placebo, or molidustat placebo + darbepoetin alfa A starting dose of 75 mg molidustat or molidustat placebo OD, titrated based on Hb response of the previous dose Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD. Hb target range ≥10.0 to <12.0 g/dL A starting dose of darbepoetin alfa or darbepoetin alfa placebo will be decided in accordance with the previous ESA dosages and schedule of once a week or every 2 weeks per Japanese label
Treatment duration, weeks	24	36	52

ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor prolyl-hydroxylase; OD, once daily.

*For patients 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 be >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol.

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Table 2 Efficacy and safety variables

	MIYABI HD-C	MIYABI PD	MIYABI HD-M
Primary efficacy variables specific to each trial	• Rate of rise in Hb level (g/dL/week) at the first dose change up to week 8* • Responder rate during the evaluation period (weeks 21–24)†	• Responder rate during the evaluation period (weeks 30–36)†	• Mean Hb level during the evaluation period (weeks 33–36) • Change in mean Hb level from baseline during the evaluation period
Secondary efficacy variables in all three trials	• Proportions of patients who meet the three response criteria during the evaluation period† • Hb level and change from baseline (measurement at each visit and mean during the evaluation period) • Proportion of patients whose mean Hb level is in, above or below the target range during the evaluation period • Proportion of patients whose Hb level is in, above or below the target range, respectively, at each visit • Proportion of patients whose maximum rise in Hb between each consecutive visit is >0.5 g/dL/week (defined as change in Hb level/duration between two visits [weeks])		
Secondary efficacy variables specific to each trial	• Rate of rise in Hb (g/dL/week) at the dose change up to week 4 • Cumulative proportion of patients who achieve the lower limit of the target Hb range at least once at each visit	• Rate of rise in Hb level (g/dL/week) at the dose changes up to weeks 4 and 8* • Change in mean Hb level from baseline during the evaluation period • Mean Hb level during the evaluation period	• Responder rate during the evaluation period†
Other efficacy variables in MIYABI HD-C and MIYABI HD-M (secondary variables	• Rate of rise in Hb level (g/dL/week) during each visit interval • Percentage of days in the target Hb range during the evaluation period and treatment period, respectively (defined as the number of days in the target range/number of days during the period × 100 [%])		

in MIYABI PD)	• Percentage of Hb levels in target range during the evaluation period and treatment period, respectively (defined as the number of measurements in the target range/number of measurements × 100 [%]) • Proportion of patients who received at least one rescue treatment (RBC transfusion, ESA treatment)
Safety variables in all three trials	• Adjudicated AEs‡ • AEs including serious AEs • Change in vital signs (pulse rate and blood pressure) • 12-lead electrocardiogram parameters • Observations of ophthalmological examination (fundus and anterior ocular segment examination and intraocular pressure measurement) • Laboratory examinations (including haematology, coagulation, clinical chemistry, electrolyte, HbA_{1c}, PTH and TSH levels)
Exploratory variables in all three trials	• Parameters of iron metabolism • EQ-5D-5L • Vascular endothelial growth factor

AEs, adverse events; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; ESA, erythropoiesis-stimulating agents; Hb, haemoglobin; HbA_{1c}, glycated haemoglobin; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; RBC, red blood cell.

*Rate of rise in Hb (g/dL/week) at the first dose change up to week 8 is defined as the change in Hb level from baseline to the first dose change of study drug up to week 8 divided by the duration of the starting dose (in weeks). If no dose change is performed up to week 8, then an Hb level at week 8 and the date of the week 8 visit will be used to calculate the change in Hb level and duration.

†A responder is defined as a patient who meets all of the following criteria:

(i) mean of the Hb levels during the evaluation period is in the target range

(ii) ≥50% of the Hb levels during the evaluation period are in the target range

(iii) no rescue treatment up to the end of the evaluation period.

‡Adjudicated AEs include death, myocardial infarction, unstable angina pectoris, stroke or transient ischaemic attack, pulmonary thromboembolism or acute limb ischaemia.

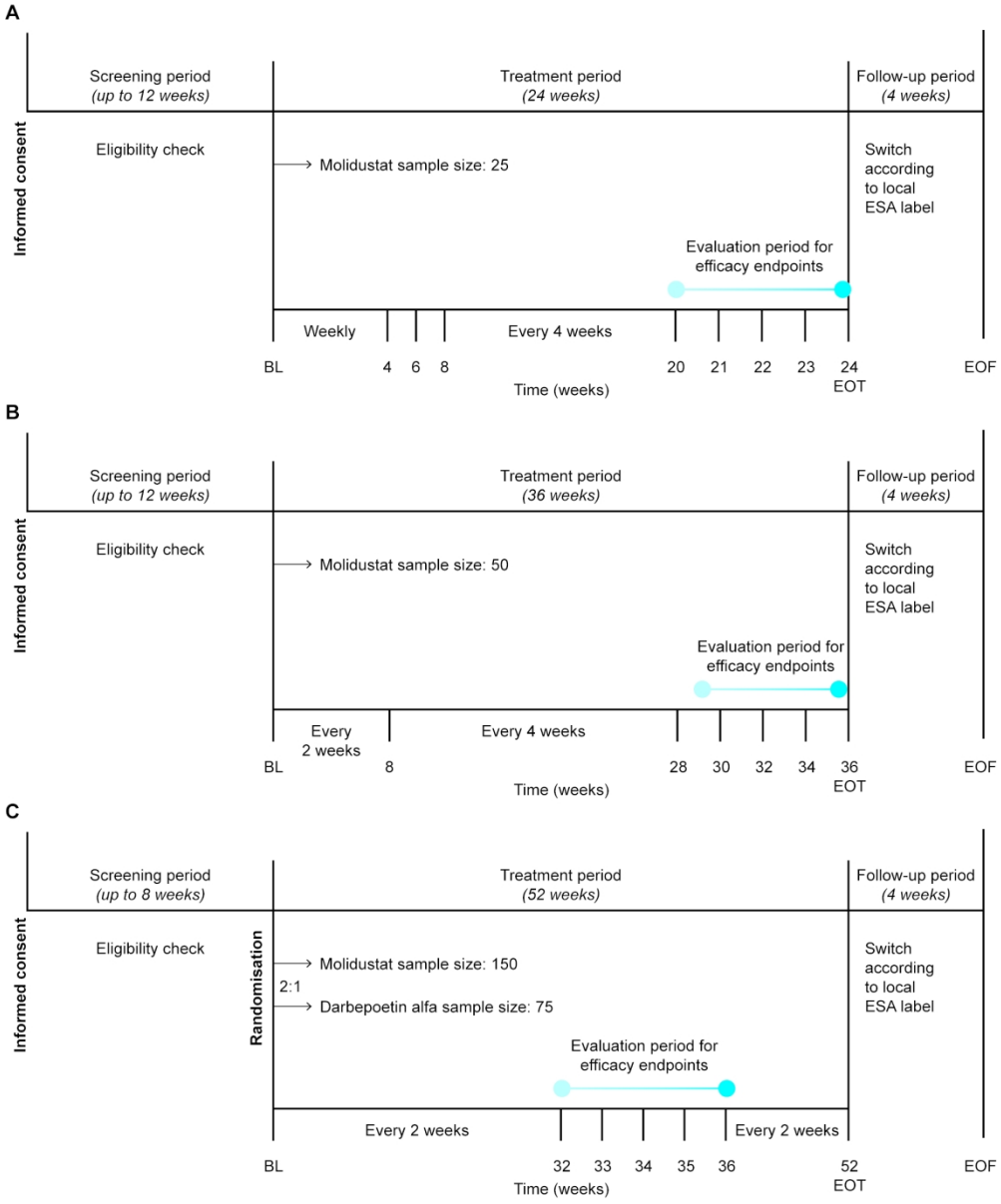

Figure 1 Trial designs for (A) MIYABI HD-C, (B) MIYABI PD and (C) MIYABI HD-M. MIYABI HD-C and MIYABI PD are single-arm, multicentre trials. MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre trial. Haemoglobin levels and safety will be assessed at each study visit, conducted at the time points shown.
BL, baseline; EOF, end of follow-up; EOT, end of treatment; ESA, erythropoiesis-stimulating agent.

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SUPPLEMENTARY TABLES

Supplementary table 1 An overview of all inclusion and exclusion criteria

Inclusion criteria
All three trials had the following inclusion criteria • Written informed consent before performing any study-specific tests or procedures • Body weight (after dialysis) >40 and ≤160 kg at screening • Male or female ≥20 years of age at screening • At least one kidney • Serum folate level and serum vitamin B12 level above LLN at screening • Women of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form until 12 weeks after the last administration of the study drug. o Acceptable methods of contraception may include, but are not limited to, condoms (male or female) with or without a spermicidal agent; diaphragm or cervical cap with spermicide; intra-uterine device; hormone-based contraception. o Patients must agree to utilise two reliable and acceptable methods of contraception simultaneously. Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhoea with an appropriate clinical profile (eg, age-appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhoea with serum FSH levels >40 mIU/mL or have had surgical treatment such as bilateral tubal ligation, bilateral ovariectomy or hysterectomy. • Ability to understand and follow study-related instructions.
MIYABI HD-C had four additional inclusion criteria • Patients with ESKD on dialysis (including haemodiafiltration, haemodialysis and other modalities except for peritoneal dialysis) weekly or more than weekly for ≥2 weeks before study drug assignment • Mean screening Hb level ≥8.0 and <10.0 g/dL (at least two measurements must be taken ≥2 days apart, assessed by the central laboratory; the

difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment

- Not treated with any ESAs or HIF-PH inhibitors during the 8 weeks before study drug assignment. For patients 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 be >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol
- Ferritin ≥50 ng/mL at screening

MIYABI PD had five additional inclusion criteria

- Patients with ESKD on peritoneal dialysis before study drug assignment and not expected to start maintenance dialysis (eg, haemodialysis, haemodiafiltration) other than peritoneal dialysis during the study period
- Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment
- Patients who meet one of the following criteria

  A: Untreated with ESA at study drug assignment

  Mean screening Hb level ≥8.0 and <11.0 g/dL (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment

  B: Pre-treated with ESA at study drug assignment

  Mean screening Hb level ≥10.0 and <13.0 g/dL (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment
- Patients who meet one of the following criteria

  A: Untreated with ESA at study drug assignment

  - Patient with ESKD on peritoneal dialysis for ≥2 weeks before study drug assignment

  and

  - Not treated with ESA for the 8 weeks before study drug assignment

  or

  - Washed out from ESAs, when the mean Hb level (based on at least two measurements taken ≥2 days apart, assessed by the central

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laboratory) has decreased by ≥0.5 g/dL after the last ESA administration, AND the interval from the last ESA administration to study drug assignment should be >2 weeks for epoetin alfa/beta and >4 weeks for darbepoetin alfa or epoetin beta pegol

B: Pre-treated with ESA at study drug assignment

- Patient with ESKD on peritoneal dialysis for ≥12 weeks before study drug assignment
- Treated with IV or SC ESA during the 8 weeks before study drug assignment
- Treated with 2- or 4-weekly dose of darbepoetin alfa, 4-weekly dose of epoetin beta pegol, OR 3 times per week, twice per week, weekly or biweekly dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before study drug assignment

- Patients who meet one of the following criteria

A: Untreated with ESA at study drug assignment

Ferritin ≥50 ng/mL at screening

B: Pre-treated with ESA at study drug assignment

- Ferritin ≥100 ng/mL or transferrin saturation ≥20%

MIYABI HD-M had five additional inclusion criteria

- Patients with ESKD on dialysis (including haemodiafiltration, haemofiltration, haemodialysis and other modalities except for peritoneal dialysis) weekly or more than weekly for ≥12 weeks before randomisation
- Treated with the same ESA for ≥8 weeks before screening
- Treated with weekly or biweekly dose of darbepoetin alfa, monthly or biweekly dose of epoetin beta pegol, OR weekly, biweekly, twice or three times per week dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before randomisation
- Mean screening Hb level ≥9.5 and <12.0 g/dL before dialysis (based on at least two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the lowest level and highest level <1.2 g/dL), with the last screening Hb level measurement during the 14 days before randomisation
- Ferritin ≥100 ng/mL or transferrin saturation ≥20% at screening

Exclusion criteria

All three trials had the following exclusion criteria

- Any current condition leading to significant blood loss

- Active haemolysis or diagnosis of haemolytic syndrome
- Previous or concurrent myelodysplastic syndrome, multiple myeloma, marrow fibrosis or PRCA
- Previous or concurrent haemosiderosis or haemochromatosis
- Previous or concurrent hereditary haemoglobinopathies (eg, sickle-cell disease, beta thalassaemia, thalassaemia major)
- Previous or concurrent aplastic anaemia
- Previous or concurrent chronic lymphoproliferative diseases
- Proliferative choroidal or retinal disease, such as neovascular age-related macular degeneration or proliferative diabetic retinopathy requiring invasive treatment (eg, intraocular injections or laser photocoagulation) at screening
- Chronic inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease, which is determined to be the principal cause of the anaemia
- Known hypersensitivity to the study drugs (active substances or excipients of the preparations)
- Uncontrolled and symptomatic hyperparathyroidism
- Uncontrolled active infection at study drug assignment
- Previous or concurrent cancer except cervical carcinoma *in situ*, treated basal cell carcinoma, superficial bladder tumours (Ta, Tis and T1) or any cancer curatively treated >3 years before study drug assignment
- Previous or scheduled organ transplantation (being on a transplant waiting list does not exclude a patient)
- History of alcohol or drug abuse during the 2 years before study drug assignment
- RBC-containing transfusion for treatment of anaemia during the 8 weeks before study drug assignment
- Treatment with uridine-diphosphate-glucuronosyltransferase 1 family, polypeptide A1 inhibitors during the 7 days before study drug assignment:
    - antiretroviral drugs (eg, ritonavir, saquinavir, atazanavir, indinavir, lopinavir, nelfinavir)
    - tyrosine kinase inhibitors (eg, erlotinib, pazopanib, nilotinib, sorafenib, regorafenib)
    - tranilast
- Patients treated with immune- or myelosuppressive therapy during the 8 weeks before study drug assignment (eg, everolimus, sirolimus, rituximab, azathioprine, mycophenolate mofetil, mycophenolic acid, cyclosporine, methotrexate, tacrolimus, chemotherapeutic agents and other anticancer agents, and systemic steroids treatment [except inhaled steroids] for 7 days or more)
- Treated with the following therapies during the 8 weeks before study drug assignment: anabolic hormone, testosterone enanthate or

mepitiostane

- History of cardiovascular or cerebrovascular events (eg, unstable angina, myocardial infarction, stroke, pulmonary thromboembolism and ALI) during the 6 months before study drug assignment
- Sustained, poorly controlled arterial hypertension (defined as systolic BP ≥180mmHg or diastolic BP ≥110mmHg) or hypotension (defined as systolic BP <90mmHg) at study drug assignment
- NYHAclass III or IV congestive heart failure
- Severe hepatic disorder (defined as ALT or AST >3 x the upper limit of normal, total bilirubin >2 mg/dL, or Child-Pugh B or C) at screening
- Previous use of molidustat
- A patient in need of surgery that may be expected to lead to significant blood loss
- Expected need for rescue treatment during the next 7 days after study drug assignment
- Active hepatitis, as assessed by the investigator
- Any medical condition that in the opinion of the investigator may pose a safety risk to a patient in this study, may confound safety or efficacy assessment or may interfere with study participation
- Previous assignment to study treatment during this study
- Previous (during the 30 days before study drug assignment) or concomitant participation in another clinical study with investigational medicinal product(s)
- Close affiliation with the investigational site, for example, a close relative of the investigator, dependent person (eg, employee or student at the investigational site)
- Pregnant or breastfeeding women

MIYABI PD had two additional exclusion criteria

- Previous or concurrent indications for removal of peritoneal dialysis catheter (eg, recurrent peritoneum inflammation, refractory tunnel infection)
- Concomitant use of maintenance dialysis (eg, haemodialysis, haemodiafiltration) other than peritoneal dialysis

ALI, acute limb ischaemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; FSH, follicle-stimulating hormone; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor prolyl hydoxylase; IV, intravenous; LLN, lower limit of normal; NYHA, New York Heart Association; PRCA, pure red cell aplasia; RBC, red blood cell; SC, subcutaneous.

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Supplementary table 2 Dose titration for molidustat at week 4 for all patients in the MIYABI HD-C trial* and for patients not treated with ESA at study drug assignment in the MIYABI PD trial

Rise in Hb in the first 4 weeks (g/dL)	Hb level (g/dL) in MIYABI HD-C	Hb level (g/dL) in MIYABI PD	Titration step
<0.5	<9.5	<10.5	Increase to the next higher dose
	≥9.5	≥10.5	Maintain the same dose
≥0.5 and <1.0	Any value	Any value	
≥1.0 and ≤2.0	≤10.0	≤11.0	
	>10.0	>11.0	Decrease to the next lower dose
>2.0	Any value	Any value	

*All patients in MIYABI HD-C will not be treated with ESAs at study drug assignment or during the trial.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

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Supplementary table 3 Dose titration from week 8 in MIYABI HD-C, from week 4 or 8 in MIYABI PD*, and from week 2 or 4 in MIYABI HD-M†

Hb level (g/dL) in MIYABI HD-C and MIYABI HD-M	**Hb level (g/dL) in MIYABI PD**	**Titration step**
<10.0	<11.0	Increase to the next higher dose
≥10.0 and <12.0	≥11.0 and <12.5	Maintain the same dose
≥12.0 and <13.0	≥12.5 and <13.0	Decrease to the next dose
≥13.0	≥13.0	Suspend a dose until the next scheduled visit

*In MIYABI PD, patients treated with ESAs at study drug assignment will start this dose-titration schedule for molidustat at week 4, whereas patients not treated with ESAs at study drug assignment will start this dose titration schedule for molidustat at week 8.

†In MIYABI HD-M, doses of darbepoetin alfa or darbepoetin alfa placebo will be titrated from week 2, whereas doses of molidustat will be titrated from week 4.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies

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Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies

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ABSTRACT

Introduction: New medications for anaemia associated with chronic kidney disease (CKD) are desirable, owing to the limitations of erythropoiesis-stimulating agents (ESAs), the current standard of care. Molidustat is a novel hypoxia-inducible factor prolyl-hydroxylase inhibitor that stimulates erythropoietin production, predominately in the kidney. We report methodological details of three phase 3 trials, named **M**ol**I**dustat once dail**Y** improves renal **A**nemia **B**y **I**nducing erythropoietin (MIYABI), designed primarily to investigate the efficacy of molidustat therapy in adults with renal anaemia and dialysis-dependent CKD.

Methods and analysis: MIYABI Haemodialysis-Correction (HD-C) is a single-arm trial (24-week treatment duration) in approximately 25 patients on haemodialysis, currently untreated with ESAs. MIYABI Peritoneal Dialysis (PD) is a single-arm trial (36-week treatment duration) in approximately 50 patients on peritoneal dialysis, treated or untreated with ESAs. MIYABI Haemodialysis-Maintenance (HD-M) is a randomised, active-controlled, double-blinded, double-dummy trial (52-week treatment duration) comparing molidustat with darbepoetin alfa in approximately 225 patients on haemodialysis, treated with ESAs. Molidustat (starting dose 75 mg/day) will be titrated 4-weekly to maintain haemoglobin in pre-determined target ranges. The primary objective is to evaluate the efficacy of molidustat, using the following measures: the rate of rise in haemoglobin (g/dL/week) at the first dose change up to week 8 (MIYABI HD-C); responder rate (MIYABI HD-C and MIYABI PD); mean haemoglobin level during weeks 33–36 and non-inferiority to darbepoetin alfa shown by change in mean haemoglobin level from baseline (MIYABI HD-M). The secondary objectives are to assess safety, pharmacokinetics and pharmacodynamics. These trials will provide the first evaluations of molidustat therapy in patients receiving either peritoneal dialysis or currently untreated with ESAs on haemodialysis, and provide further evidence in patients treated with ESAs on haemodialysis.

Ethics and dissemination: The protocols were approved by ethics committees at all participating sites. The trials will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Results arising from these studies will be published in peer-reviewed journal(s).

Trial registration numbers: NCT03351166, NCT03418168, NCT03543657

Keywords: Chronic kidney disease; dialysis; molidustat; renal anaemia

STRENGTHS AND LIMITATIONS OF THESE STUDIES

- Due to recruitment feasibility limitations, MIYABI HD-C and MIYABI-PD are single arm, open-label studies.
- In MIYABI HD-M, a randomised, double-blind study, molidustat treatment will be directly compared with an ESA (darbepoetin alfa), the current standard of care for renal anaemia, and will build on the results of a previous open-label phase 2b trial in patients on haemodialysis.
- The MIYABI HD-M trial will involve a larger patient population (n=150) receiving a 75 mg starting dose than in the phase 2b trial.
- Treatment durations will be longer (eg, 52 weeks in MIYABI HD-M) than in the phase 2b trial (16 weeks), although some molidustat-treated patients in the phase 2b trial (n=57) continued treatment in an extension study for up to 36 months.
- These are the first studies to directly investigate the efficacy of molidustat therapy in patients on peritoneal dialysis and in patients currently untreated with ESAs on haemodialysis.

INTRODUCTION

Anaemia is a common and serious complication of chronic kidney disease (CKD),[1] which worsens as CKD progresses.[2-4] The main cause of anaemia associated with CKD (also known as renal anaemia) is erythropoietin (EPO) deficiency.[5]

Treatment with erythropoiesis-stimulating agents (ESAs) is the current standard of care for renal anaemia.[6] However, this approach has limitations. In 10–20% of patients, irrespective of dialysis status, ESAs are ineffective at raising haemoglobin (Hb) to prespecified levels.[7-9] ESAs may also cause several adverse events (AEs), including development or worsening of hypertension,[10-12] rare cases of antibody-mediated pure red cell aplasia,[13] poor cardiovascular outcomes and death.[14-16] In patients with cancer and anaemia, ESA use is associated with increased risk of thrombosis.[17] These AEs may be related to injecting high doses of ESAs to achieve Hb targets[15 17-19] and excessive increases in Hb levels.[20]

A new approach under investigation involves using small molecules to inhibit hypoxia-inducible factor prolyl-hydroxylases (HIF-PH), thereby inducing EPO production. In addition to addressing EPO deficiency, the main cause of renal anaemia, the therapeutic effect of HIF-PH inhibition may also be mediated by increasing the availability of iron for erythropoiesis, as indicated by reductions in hepcidin levels.[21-26] These findings are particularly notable, given that functional iron deficiency may contribute to the inadequate responses that 10–20% of patients experience during treatment with ESAs, even though these patients often receive intravenous iron supplementation.[5-9] HIF-PH inhibition may theoretically also have a downside, because HIF transcriptionally upregulates a large number of genes; although EPO gene upregulation is helpful in treating anaemia associated with CKD, vascular endothelial growth factor (VEGF) upregulation could result in neoplasia and diabetic retinopathy.[22] However, in clinical trials of HIF-PH inhibitors, no safety signals or changes in VEGF levels were reported.[24-26]

Molidustat, a novel, orally administered inhibitor of HIF-PH, induces circulating levels of EPO close to the normal physiological range, with high relative selectivity for the induction of EPO gene expression, predominately in the kidney.[21] Results from preclinical[21] and clinical studies[27] suggest that molidustat is a promising option for the treatment of EPO-sensitive anaemia in patients with CKD. In preclinical studies, molidustat restored renal EPO

production with minor induction of hepatic EPO. Molidustat increased plasma EPO and EPO mRNA in the kidney and prevented decline in haematocrit and corrected decreases in Hb level.[21] In a randomised, placebo-controlled, phase 1 study involving 59 healthy participants, single doses of molidustat (5–50 mg) elicited a dose-dependent increase in EPO and were well tolerated.[27] In three 16-week, randomised, phase 2b, dose-ranging studies, comprising one study with patients on haemodialysis and two studies with patients not on dialysis, more than 400 patients with CKD were enrolled. These studies demonstrated that, during treatment with flexible-dose molidustat, Hb levels could be corrected relative to placebo or maintained at levels comparable to those in patients who continued treatment with ESAs, with manageable side effects.[28] Comparable results and no significant safety concerns were observed in extension studies up to 36 months (unpublished data).

Based on the positive findings of the preclinical and phase 2b clinical studies, the **M**ol**I**dustat once dail**Y** improves renal **A**nemia **B**y **I**nducing EPO (MIYABI) programme of five phase 3 trials has been designed to investigate molidustat therapy further in patients with renal anaemia in Japan. Here, we report the methodological details of the three MIYABI trials in which the efficacy (up to 36 weeks), safety, pharmacokinetics and pharmacodynamics (up to 52 weeks) of molidustat therapy will be investigated in patients receiving dialysis. These three trials will provide the first evaluations of molidustat therapy in patients on peritoneal dialysis and in patients currently untreated with ESAs on haemodialysis, as well as extending the evidence in patients treated with ESAs on haemodialysis.

METHODS AND PLANNED ANALYSES

Study designs, objectives and populations

Each of the three phase 3 trials is a multicentre study conducted in adults aged 20 years or older with renal anaemia and dialysis-dependent CKD in Japan. In each trial, the primary objective is to evaluate the efficacy of molidustat in the respective patient populations and, in the MIYABI Haemodialysis Maintenance (HD-M) trial, to show non-inferiority to darbepoetin alfa. The secondary objectives of each trial are to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of molidustat during the treatment periods. The three trials commenced in the first half of 2018 and have finished recruiting. The planned end dates for MIYABI HD-C, MIYABI PD, and MIYABI HD-M are November 2018,

August 2019 and December 2019, respectively. Patient eligibility was assessed during screening periods lasting up to 12 weeks in the MIYABI Haemodialysis Correction (HD-C) and MIYABI Peritoneal Dialysis (PD) studies and up to 8 weeks in MIYABI HD-M. To be eligible, the mean of at least two Hb measurements (both taken before dialysis, at least 2 days apart, with the last measurement taken within 14 days before study drug assignment, and with a difference of less than 1.2 g/dL between the lowest and highest values) was required to lie within pre-specified levels (table 1). The main inclusion criteria are summarised in table 1. All inclusion and exclusion criteria are shown in supplementary table 1.

MIYABI HD-C is a single-arm study in patients on haemodialysis who are not currently treated with ESAs, with a 24-week treatment duration (figure 1 and table 1). Japanese guidelines for the clinical evaluation of medications for renal anaemia recommend demonstrating efficacy in the correction and maintenance of renal anaemia in patients on dialysis, as well as in patients not on dialysis.[29] However, the number of patients with renal anaemia on dialysis who do not receive ESAs is limited in Japan. A single-arm study design was chosen for MIYABI HD-C owing to the feasibility of patient recruitment.[30]

MIYABI PD is a single-arm study in patients on peritoneal dialysis who are treated or not treated with ESAs, with a 36-week treatment duration (figure 1 and table 1). A single-arm study design was chosen for MIYABI PD owing to the limited number of peritoneal dialysis patients with renal anaemia in Japan.

MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group study comparing molidustat with darbepoetin alfa in patients on haemodialysis who are treated with ESAs (figure 1 and table 1). The study has a treatment duration of 52 weeks. As most patients with renal anaemia on dialysis in Japan are treated with ESAs, it is feasible to recruit sufficient patients to perform a confirmatory, randomised, double-blinded trial of molidustat in this patient population. Therefore, in MIYABI HD-M, eligible patients will be randomised in a ratio of 2:1 to the molidustat group or darbepoetin alfa group. Allocation to treatment arms will be achieved using an interactive voice/web response system (IxRS) at the first (baseline) visit. Randomisation will be stratified by previous ESA dose group (low or high) and by medical history of thromboembolic events (yes or no for myocardial infarction, pulmonary thromboembolism, stroke [excluding haemorrhagic

stroke] or acute limb ischaemia). All investigators and patients in MIYABI HD-M will be blinded to treatment allocation. In cases of emergency, such as occurrence of a suspected, unexpected, serious AE, when the investigator needs to know which drug has been allocated, unblinding will occur by entering the emergency key code for the relevant patient into the IxRS.

Each study is being overseen by a data monitoring committee consisting of independent clinical experts and an independent biostatistician supported by an independent statistical analysis centre, whose main responsibility is to recommend a change, interruption or termination of the study (or all phase 3 studies) based on safety findings. The data monitoring committee will be unblinded to treatment allocation in MIYABI HD-M.

Treatments

Study treatments are summarised in table 1. In each study, a starting dose of 75 mg molidustat once daily (OD) will be titrated every 4 weeks using the IxRS, based on the patient's Hb response to the previous dose. In each study, planned doses for the titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD. The dose of molidustat will be adjusted to correct and maintain Hb levels in the target ranges of ≥10.0 to <12.0 g/dL in MIYABI HD-C and MIYABI HD-M and ≥11.0 to <13.0 g/dL in MIYABI PD, as per Japanese guideline recommendations.[31]

For patients untreated with ESAs (all patients in MIYABI HD-C and some patients in MIYABI PD, but no patients in MIYABI HD-M), a dose adaptation visit will occur at week 4 to avoid excessive elevation of Hb levels after the initiation of molidustat treatment. In MIYABI HD-C and MIYABI PD, dose titration at week 4 will be based on both the magnitude of the rise in Hb and the Hb level (supplementary table 2) and from week 8 according to the Hb level alone (supplementary table 3). For patients treated with ESAs (all patients in MIYABI HD-M and some patients in MIYABI PD, but no patients in MIYABI HD-C), the dose will be titrated from week 4 according to Hb level (supplementary table 3).

In MIYABI HD-M, patients will receive molidustat or molidustat placebo orally and darbepoetin alfa or darbepoetin alfa placebo intravenously. Patients in the molidustat group will receive molidustat plus darbepoetin alfa placebo, while patients in the darbepoetin alfa

group will receive darbepoetin alfa plus molidustat placebo. The starting dose of darbepoetin alfa or darbepoetin alfa placebo will be selected for each patient based on their previous ESA dosage. Patients treated with darbepoetin alfa at screening will continue this treatment or start treatment with darbepoetin alfa placebo at the previous dose and interval (ie, weekly or biweekly). Patients treated with an epoetin therapy at screening will be treated with darbepoetin alfa or darbepoetin alfa placebo at a starting dose and interval determined by their epoetin dosage at screening. Then, depending on the Hb level (supplementary table 3), doses of darbepoetin alfa and darbepoetin alfa placebo will be titrated at biweekly intervals from week 2, and doses of molidustat and molidustat placebo will be titrated from week 4 at 4-weekly intervals.

In all studies, in cases of excessive elevation of a patient's Hb level (rate of Hb rise >1.0 g/dL per 2 weeks or >2.0 g/dL per 4 weeks) during the treatment period, investigators may decrease the dose of molidustat (or darbepoetin alfa for MIYABI HD-M) at any time. If the administered dose is the minimum dose step, the dose may be suspended.

In each study, iron, vitamin B12 and folate supplementation is permitted if required and will be administered according to Japanese guideline recommendations.[31] Iron supplementation will be administered to reach a target serum ferritin level of at least 100 ng/mL or transferrin saturation of at least 20%.

For all studies, after the final administration of the study drug, further ESA treatment may be initiated at the discretion of the investigator. Details of the ESA treatment regimen will be recorded if treatment is initiated during the four week follow-up period.

Variables

All efficacy and safety variables, and associated definitions, are shown in table 2. The primary efficacy variables in MIYABI HD-C are the rate of rise in Hb level (g/dL/week) at the first dose change up to week 8 and responder rate. In MIYABI PD, the primary efficacy variable will be the responder rate. In MIYABI HD-M, the primary efficacy variables will be mean Hb level during the evaluation period and its change from baseline. In all three studies, a responder is defined as a patient who meets all of the following criteria: (i) mean of the Hb levels during the evaluation period is in the target range; (ii) ≥50% of the Hb levels during the evaluation period are in the target range; (iii) no rescue treatment received up to

the end of the evaluation period. Secondary variables for the three trials are shown in table 2. In each study, exploratory variables will include measures of iron metabolism, VEGF levels and assessment of health-related quality of life using the EuroQol 5-dimension 5-level questionnaire.

In each study, to investigate systemic exposure to molidustat and the relationship between molidustat exposure and response, sparse sampling from all patients will be conducted for pharmacokinetics and pharmacodynamics. If possible, molidustat exposure parameters (eg, C_{max}, AUC) and the relationship between molidustat exposure and treatment effects will be evaluated using population approaches (eg, non-linear mixed effect modelling), including potential influence of relevant patient covariables.

Quality assurance and data management

For all studies, audits may be conducted by a member of the sponsor's quality assurance unit to assess the performance of the study at any of the study sites. In addition, sites may be inspected by regulatory health authority representatives, independent ethics committees and institutional review boards.

For all studies, data will be recorded by investigational site personnel onto the validated and password-protected electronic data capture system Rave (Medidata Solutions). All records identifying the patient will be kept confidential and will not be made available either to the public or the sponsor. All personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. Data will be pseudonymised for analysis. The sponsor will have access to the full trial dataset.

The sponsor maintains clinical trial insurance coverage for each of the studies to provide compensation in the unlikely event that a patient is harmed from participation in any of these clinical trials.

Statistical analysis

All variables (including demographic and other baseline characteristics) will be analysed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by summary statistics (mean, standard deviation, minimum,

median and maximum). Summary statistics will be presented for the original data as well as for the difference from baseline.

In each study, the primary analysis set for efficacy will be the full analysis set, which includes all patients assigned to treatment who have at least one baseline Hb level (ie, at least one Hb level before the first dose of the study drug).

In MIYABI HD-C, the primary efficacy variables (rate of rise in Hb and responder rate) and their two-sided 95% confidence intervals (CI) will be estimated using one-sample *t*-statistics and the Clopper–Pearson method, respectively. In MIYABI PD, the primary efficacy variable (responder rate) and its two-sided 95% CI will be estimated using the Clopper–Pearson method. In MIYABI HD-M, the primary efficacy variables (mean Hb level and change in mean Hb level) will be analysed by sequentially testing two hypotheses. In MIYABI HD-M, the primary objective will be achieved if the following two hypotheses are confirmed. (i) In the molidustat treatment group, the mean Hb level during the evaluation period (weeks 33–36) remains within the target range (≥10.0 to <12.0 g/dL). The mean Hb level in the molidustat treatment group will be calculated using the mean Hb level per patient. If the lower limit of the two-sided 95% CI of the mean of the mean Hb level is greater than or equal to the lower limit of the target Hb level (ie, ≥10.0 g/dL) and if the upper limit of the two-sided 95% CI is less than the upper limit of the target Hb level (ie, <12.0 g/dL), it will be established that the mean Hb level is within the target range. Two-sided 95% CI will be estimated using one sample *t*-statistics. (ii) Molidustat is not inferior to darbepoetin alfa. The non-inferiority of molidustat to darbepoetin alfa will be established if the lower limit of the two-sided 95% CI for the difference (molidustat minus darbepoetin alfa) is above –1.0 g/dL with non-inferiority margin of 1.0 g/dL. This margin was chosen because a variation of approximately 1.0 g/dL is considered acceptable in Japanese clinical practice.[31] In MIYABI HD-M, the difference in change between the treatment groups and its two-sided 95% CI will be estimated using an analysis of covariance (ANCOVA) model, including treatment group, previous ESA dose group (low/high) and previous thromboembolic events (yes/no) as fixed effects and baseline Hb level as a covariate.

Several descriptive and exploratory subgroup analyses are planned for all studies, including age, sex, baseline weight, prior thromboembolic event and main cause of CKD. Subgroup

analysis will also be conducted for previous ESA dose group for MIYABI HD-M, for baseline Hb level and duration of dialysis for MIYABI HD-C and for pre-treatment with ESAs at assignment and duration of dialysis for MIYABI PD.

Determination of sample size

In MIYABI HD-C and MIYABI PD, the respective sample sizes of approximately 25 and 50 patients are determined based on feasibility.

In MIYABI HD-M, the sample size of 150 patients in the molidustat group and 75 patients in the darbepoetin alfa group should result in sufficient data to assess the long-term safety of molidustat therapy, assuming a dropout rate of approximately 30%. If 150 patients are randomised to the molidustat group, the power to establish that mean Hb levels are within target levels during the evaluation period is ≥98%, assuming a standard deviation of 1.3–1.5g/dL from the previous phase 2b studies. This sample size has >90% power to reject the null hypothesis that molidustat is inferior to darbepoetin alfa with a non-inferiority margin of 1.0 g/dL at a one-sided 2.5% significance level, assuming the expected difference between molidustat and darbepoetin alfa to be 0 g/dL and with a common standard deviation of 1.3–1.5 g/dL.

Patient and public involvement

Patients are not involved in the design and conduct of the studies.

DISCUSSION

Renal anaemia due to EPO deficiency is a common and serious complication of CKD.[1] However, new approaches to the treatment of renal anaemia are needed, owing to safety issues and limitations with current treatments. Results from previous studies, including three phase 2b dose-ranging trials, suggest that molidustat is a promising option for the treatment of EPO-sensitive anaemia in patients with CKD.

At present, only one phase 2b trial assessing molidustat has been conducted in patients with renal anaemia who are on dialysis. It is anticipated that the three phase 3 trials described here will demonstrate the efficacy and safety of molidustat in patients with renal anaemia on dialysis, and that the trials will have the following strengths, relative to the one phase 2b trial conducted in patients on dialysis: (i) in MIYABI HD-M, molidustat treatment will be

compared with an ESA (darbepoetin alfa), the current standard of care for renal anaemia, in a double-blinded manner, whereas an open-label design was used in the phase 2b trial, in which molidustat treatment was compared with another ESA (epoetin); (ii) a larger patient population in the MIYABI HD-M trial (n=150) receiving a starting dose of 75 mg molidustat OD than in the phase 2b trial (n=44 of the 157 patients treated with molidustat received a 75 mg starting dose); (iii) the treatment periods will be longer (eg, 52 weeks in MIYABI HD-M) than in the phase 2b trial (16 weeks), although about one-third of the molidustat-treated patients in the phase 2b trial (n=57) continued treatment in an extension study, with a duration of up to 36 months; (iv) molidustat therapy will be investigated for the first time in patients who are not treated with ESAs on haemodialysis in the MIYABI HD-C trial, and MIYABI HD-M will provide further evaluations of molidustat in patients treated with ESAs, whereas the phase 2b trial only included patients who switched from epoetin; (v) the efficacy of molidustat therapy will be investigated for the first time in patients on peritoneal dialysis in MIYABI PD, whereas only patients undergoing haemodialysis were included in the phase 2b trial.

Approximately 600 patients are planned to be involved in the five studies in the phase 3 MIYABI programme; three studies in patients on dialysis and two studies in patients not on dialysis. While safety assessments will be conducted for all patients in the MIYABI programme, including assessments of vital signs and 12-lead electrocardiogram parameters, the sample size is insufficient to determine the risk of cardiovascular events. The MIYABI HD-C and MIYABI PD studies will also be limited to investigating molidustat therapy in the absence of a comparator and with small sample sizes (approximately 25 and 50, respectively), owing to the feasibility of patient recruitment (in Japan, limited numbers of patients with renal anaemia are on dialysis while not receiving ESAs or are on peritoneal dialysis), although molidustat will be compared with the current standard of care (darbepoetin alfa) as a maintenance treatment in a study powered to assess efficacy and safety in 150 patients on dialysis.

In the three MIYABI trials in patients on dialysis, the efficacy of molidustat will primarily be assessed by investigating Hb levels, including changes from baseline and maintenance of prespecified Hb targets. However, several exploratory variables will be also investigated.

These include assessments of VEGF levels and ophthalmological examinations, conducted to evaluate the theoretical risk of VEGF-mediated diabetic retinopathy,[22] and biomarkers of iron metabolism as, in addition to increasing EPO production predominately in the kidney, molidustat may increase the availability of iron for erythropoiesis.[21-23]

In summary, the three trials in patients on dialysis described here, together with two other trials in patients who are not receiving dialysis (the MIYABI ND-C and MIYABI ND-M randomised, open-label, active-controlled, parallel-group, multicentre trials), comprise the MIYABI phase 3 programme. The design and rationale of MIYABI ND-C and MIYABI ND-M are published in a companion article.[32] This programme will investigate the efficacy and safety of molidustat in a broad clinical spectrum spanning approximately 600 patients with renal anaemia and CKD in Japan.

ETHICS AND DISSEMINATION

The studies are being conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP). Documented approval from appropriate independent ethics committees and institutional review boards has been obtained, according to GCP and local laws, regulations and organisations. The MIYABI HD-C study has been approved by the institutional review board of All Tohoku Clinical Trial Review and Audit Organization (application number: 20171204) and another 20 sites. The MIYABI PD study has been approved by the institutional review board of Kyushu University Hospital (application number: 20180221) and another 26 sites. The MIYABI HD-M study has been approved by the institutional review board of Ibaraki Prefectural Central Hospital (application number: 20180524), Asahikawa-Kosei General Hospital (20180806) and another 51 sites.

Informed consent was obtained from patients by the site investigator or a designated person before entering the studies and may be withdrawn at any time. Proposed protocol amendments must be agreed by the sponsor and investigators and approved by independent ethics committees and institutional review boards. Protocol amendments must be signed by the principal investigator and have received all external approvals before coming into effect at the respective centre. If there is a change in the protocol that

necessitates a change in consent, the investigator will inform patients of the changes in a timely manner and ask each patient to reconfirm their participation in the study by signing a revised consent form.

The studies have been registered on ClinicalTrials.gov (NCT03351166 [MIYABI HD-C], NCT03418168 [MIYABI PD], NCT03543657 [MIYABI HD-M]). Results will be disseminated through peer-reviewed publication(s) but there are no plans to publicly release the full protocol, participant-level dataset or statistical code from any of the studies.

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AUTHOR CONTRIBUTORS

TA, HY and TY contributed to designing these studies. TY contributed to developing the original study protocols. MT contributed to drafting the article and revising it. TA, HY, MT and KI critical revised the article for important intellectual content. YM contributed to developing the statistical analysis plan and assisted in the preparation of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately resolved.

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COMPETING INTERESTS MT, YM, KI and TY are employees of Bayer Yakuhin Ltd. TA received consulting and lecture fees from Bayer Yakuhin Ltd during the conduct of the study. TA also received consulting, lecture or manuscript fees outside the submitted work from Astellas, GlaxoSmithKline, JT Pharmaceuticals, Kissei Pharmaceutical Co. Ltd, Kyowa Hakko Kirin, Nipro Corporation, Fuso Pharmaceutical Industries Ltd, and Ono Pharmaceutical Co. Ltd, and lecture fees from Bayer Yakuhin, Chugai Pharmaceutical Co. Ltd, Kyowa Hakko Kirin, and Torii Pharmaceutical Co. Ltd. HY received consulting fees from Bayer Yakuhin Ltd during the conduct of the study.

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FIGURE LEGEND

Figure 1 Trial designs for (**A**) MIYABI HD-C, (**B**) MIYABI PD and (**C**) MIYABI HD-M. MIYABI HD-C and MIYABI PD are single-arm, multicentre trials. MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre trial. Haemoglobin levels and safety will be assessed at each study visit, conducted at the time points shown.

BL, baseline; EOF, end of follow-up; EOT, end of treatment; ESA, erythropoiesis-stimulating agent.

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TABLES

Table 1 Trial designs, patient populations and treatments

	MIYABI HD-C [NCT03351166]	MIYABI PD [NCT03418168]	MIYABI HD-M [NCT03543657]
Trial design	Single-arm, multicentre	Single-arm, multicentre	Randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre
Patient population	Men and women (aged ≥20 years, body weight >40 and ≤160 kg) with a diagnosis of renal anaemia		
Key inclusion criteria	Patients with ESKD on haemodialysis at least weekly for ≥2 weeks	Patients with ESKD on peritoneal dialysis	Patients with ESKD on haemodialysis at least weekly for ≥12 weeks
	Mean of the last two Hb levels between ≥8.0 and <10.0 g/dL	Mean of the last two Hb levels between ≥8.0 and <11.0 g/dL for ESA untreated and ≥10.0 and <13.0 g/dL for ESA treated	Mean of all Hb levels (at least two measurements) between ≥9.5 and <12.0 g/dL
	Not treated with ESAs during the 8 weeks before study drug assignment	Not treated or treated with ESAs during the 8 weeks before study drug assignment*	Treated with the same ESA for ≥8 weeks before randomisation (weekly or biweekly dose of darbepoetin alfa, monthly or biweekly dose of epoetin beta pegol, OR weekly, biweekly, twice or three times per week dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before randomisation)*

	Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment	Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment	
Study treatments	A starting dose of 75 mg molidustat OD, titrated based on Hb response of the previous dose. Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD Hb target range ≥10.0 to <12.0 g/dL	A starting dose of 75 mg molidustat OD, titrated based on Hb response of the previous dose. Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD Hb target range ≥11.0 to <13.0 g/dL	Two groups: molidustat + darbepoetin alfa placebo, or molidustat placebo + darbepoetin alfa A starting dose of 75 mg molidustat or molidustat placebo OD, titrated based on Hb response of the previous dose Planned doses for titration are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg OD. Hb target range ≥10.0 to <12.0 g/dL A starting dose of darbepoetin alfa or darbepoetin alfa placebo will be decided in accordance with the previous ESA dosages and schedule of once a week or every 2 weeks per Japanese label
Treatment duration, weeks	24	36	52

ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor prolyl-hydroxylase; OD, once daily.

*For patients 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 be >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol.

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Table 2 Efficacy and safety variables

	MIYABI HD-C	MIYABI PD	MIYABI HD-M
Primary efficacy variables specific to each trial	• Rate of rise in Hb level (g/dL/week) at the first dose change up to week 8* • Responder rate during the evaluation period (weeks 21–24)†	• Responder rate during the evaluation period (weeks 30–36)†	• Mean Hb level during the evaluation period (weeks 33–36) • Change in mean Hb level from baseline during the evaluation period
Secondary efficacy variables in all three trials	• Proportions of patients who meet the three response criteria during the evaluation period† • Hb level and change from baseline (measurement at each visit and mean during the evaluation period) • Proportion of patients whose mean Hb level is in, above or below the target range during the evaluation period • Proportion of patients whose Hb level is in, above or below the target range, respectively, at each visit • Proportion of patients whose maximum rise in Hb between each consecutive visit is >0.5 g/dL/week (defined as change in Hb level/duration between two visits [weeks])		
Secondary efficacy variables specific to each trial	• Rate of rise in Hb (g/dL/week) at the dose change up to week 4 • Cumulative proportion of patients who achieve the lower limit of the target Hb range at least once at each visit	• Rate of rise in Hb level (g/dL/week) at the dose changes up to weeks 4 and 8* • Change in mean Hb level from baseline during the evaluation period • Mean Hb level during the evaluation period	• Responder rate during the evaluation period†
Other efficacy variables in MIYABI HD-C and MIYABI HD-M (secondary variables	• Rate of rise in Hb level (g/dL/week) during each visit interval • Percentage of days in the target Hb range during the evaluation period and treatment period, respectively (defined as the number of days in the target range/number of days during the period × 100 [%])		

in MIYABI PD)	• Percentage of Hb levels in target range during the evaluation period and treatment period, respectively (defined as the number of measurements in the target range/number of measurements × 100 [%]) • Proportion of patients who received at least one rescue treatment (RBC transfusion, ESA treatment)
Safety variables in all three trials	• Adjudicated AEs‡ • AEs including serious AEs • Change in vital signs (pulse rate and blood pressure) • 12-lead electrocardiogram parameters • Observations of ophthalmological examination (fundus and anterior ocular segment examination and intraocular pressure measurement) • Laboratory examinations (including haematology, coagulation, clinical chemistry, electrolyte, HbA_{1c}, PTH and TSH levels)
Exploratory variables in all three trials	• Parameters of iron metabolism • EQ-5D-5L • Vascular endothelial growth factor

AEs, adverse events; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; ESA, erythropoiesis-stimulating agents; Hb, haemoglobin; HbA_{1c}, glycated haemoglobin; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; RBC, red blood cell.

*Rate of rise in Hb (g/dL/week) at the first dose change up to week 8 is defined as the change in Hb level from baseline to the first dose change of study drug up to week 8 divided by the duration of the starting dose (in weeks). If no dose change is performed up to week 8, then an Hb level at week 8 and the date of the week 8 visit will be used to calculate the change in Hb level and duration.

†A responder is defined as a patient who meets all of the following criteria:

(i) mean of the Hb levels during the evaluation period is in the target range

(ii) ≥50% of the Hb levels during the evaluation period are in the target range

(iii) no rescue treatment up to the end of the evaluation period.

‡Adjudicated AEs include death, myocardial infarction, unstable angina pectoris, stroke or transient ischaemic attack, pulmonary thromboembolism or acute limb ischaemia.

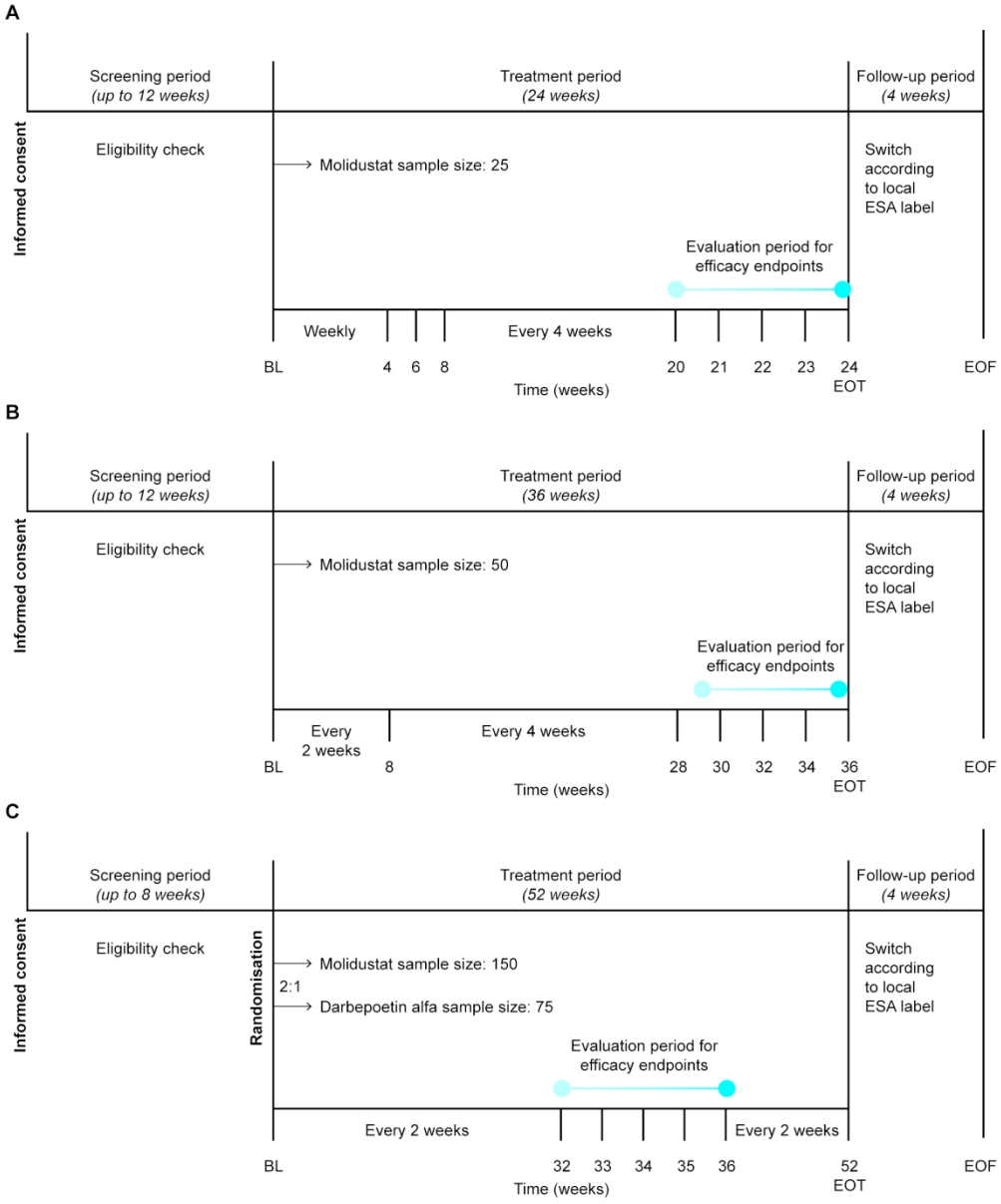

Figure 1 Trial designs for (A) MIYABI HD-C, (B) MIYABI PD and (C) MIYABI HD-M. MIYABI HD-C and MIYABI PD are single-arm, multicentre trials. MIYABI HD-M is a randomised, active-controlled, double-blinded, double-dummy, parallel-group, multicentre trial. Haemoglobin levels and safety will be assessed at each study visit, conducted at the time points shown.
BL, baseline; EOF, end of follow-up; EOT, end of treatment; ESA, erythropoiesis-stimulating agent.

SUPPLEMENTARY TABLES

Supplementary table 1 An overview of all inclusion and exclusion criteria

Inclusion criteria
All three trials had the following inclusion criteria • Written informed consent before performing any study-specific tests or procedures • Body weight (after dialysis) >40 and ≤160 kg at screening • Male or female ≥20 years of age at screening • At least one kidney • Serum folate level and serum vitamin B12 level above LLN at screening • Women of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form until 12 weeks after the last administration of the study drug. o Acceptable methods of contraception may include, but are not limited to, condoms (male or female) with or without a spermicidal agent; diaphragm or cervical cap with spermicide; intra-uterine device; hormone-based contraception. o Patients must agree to utilise two reliable and acceptable methods of contraception simultaneously. Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhoea with an appropriate clinical profile (eg, age-appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhoea with serum FSH levels >40 mIU/mL or have had surgical treatment such as bilateral tubal ligation, bilateral ovariectomy or hysterectomy. • Ability to understand and follow study-related instructions.
MIYABI HD-C had four additional inclusion criteria • Patients with ESKD on dialysis (including haemodiafiltration, haemodialysis and other modalities except for peritoneal dialysis) weekly or more than weekly for ≥2 weeks before study drug assignment • Mean screening Hb level ≥8.0 and <10.0 g/dL (at least two measurements must be taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug

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assignment

- Not treated with any ESAs or HIF-PH inhibitors during the 8 weeks before study drug assignment. For patients 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 be >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol
- Ferritin ≥50 ng/mL at screening

MIYABI PD had five additional inclusion criteria

- Patients with ESKD on peritoneal dialysis before study drug assignment and not expected to start maintenance dialysis (eg, haemodialysis, haemodiafiltration) other than peritoneal dialysis during the study period
- Not treated with HIF-PH inhibitors during the 8 weeks before study drug assignment
- Patients who meet one of the following criteria

  A: Untreated with ESA at study drug assignment

  Mean screening Hb level ≥8.0 and <11.0 g/dL (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment

  B: Pre-treated with ESA at study drug assignment

  Mean screening Hb level ≥10.0 and <13.0 g/dL (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <1.2 g/dL), with the last screening Hb measurement during the 14 days before study drug assignment
- Patients who meet one of the following criteria

  A: Untreated with ESA at study drug assignment

  - Patient with ESKD on peritoneal dialysis for ≥2 weeks before study drug assignment

  and

  - Not treated with ESA for the 8 weeks before study drug assignment

  or

  - Washed out from ESAs, when the mean Hb level (based on at least two measurements taken ≥2 days apart, assessed by the central laboratory) has decreased by ≥0.5 g/dL after the last ESA administration, AND the interval from the last ESA administration to study drug assignment should be >2 weeks for epoetin alfa/beta and >4 weeks for darbepoetin alfa or epoetin beta pegol

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B: Pre-treated with ESA at study drug assignment

- Patient with ESKD on peritoneal dialysis for ≥12 weeks before study drug assignment
- Treated with IV or SC ESA during the 8 weeks before study drug assignment
- Treated with 2- or 4-weekly dose of darbepoetin alfa, 4-weekly dose of epoetin beta pegol, OR 3 times per week, twice per week, weekly or biweekly dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before study drug assignment

- Patients who meet one of the following criteria

A: Untreated with ESA at study drug assignment

Ferritin ≥50 ng/mL at screening

B: Pre-treated with ESA at study drug assignment

- Ferritin ≥100 ng/mL or transferrin saturation ≥20%

MIYABI HD-M had five additional inclusion criteria

- Patients with ESKD on dialysis (including haemodiafiltration, haemofiltration, haemodialysis and other modalities except for peritoneal dialysis) weekly or more than weekly for ≥12 weeks before randomisation
- Treated with the same ESA for ≥8 weeks before screening
- Treated with weekly or biweekly dose of darbepoetin alfa, monthly or biweekly dose of epoetin beta pegol, OR weekly, biweekly, twice or three times per week dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before randomisation
- Mean screening Hb level ≥9.5 and <12.0 g/dL before dialysis (based on at least two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the lowest level and highest level <1.2 g/dL), with the last screening Hb level measurement during the 14 days before randomisation
- Ferritin ≥100 ng/mL or transferrin saturation ≥20% at screening

Exclusion criteria

All three trials had the following exclusion criteria

- Any current condition leading to significant blood loss
- Active haemolysis or diagnosis of haemolytic syndrome
- Previous or concurrent myelodysplastic syndrome, multiple myeloma, marrow fibrosis or PRCA
- Previous or concurrent haemosiderosis or haemochromatosis

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- Previous or concurrent hereditary haemoglobinopathies (eg, sickle-cell disease, beta thalassaemia, thalassaemia major)
- Previous or concurrent aplastic anaemia
- Previous or concurrent chronic lymphoproliferative diseases
- Proliferative choroidal or retinal disease, such as neovascular age-related macular degeneration or proliferative diabetic retinopathy requiring invasive treatment (eg, intraocular injections or laser photocoagulation) at screening
- Chronic inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease, which is determined to be the principal cause of the anaemia
- Known hypersensitivity to the study drugs (active substances or excipients of the preparations)
- Uncontrolled and symptomatic hyperparathyroidism
- Uncontrolled active infection at study drug assignment
- Previous or concurrent cancer except cervical carcinoma *in situ*, treated basal cell carcinoma, superficial bladder tumours (Ta, Tis and T1) or any cancer curatively treated >3 years before study drug assignment
- Previous or scheduled organ transplantation (being on a transplant waiting list does not exclude a patient)
- History of alcohol or drug abuse during the 2 years before study drug assignment
- RBC-containing transfusion for treatment of anaemia during the 8 weeks before study drug assignment
- Treatment with uridine-diphosphate-glucuronosyltransferase 1 family, polypeptide A1 inhibitors during the 7 days before study drug assignment:
    - antiretroviral drugs (eg, ritonavir, saquinavir, atazanavir, indinavir, lopinavir, nelfinavir)
    - tyrosine kinase inhibitors (eg, erlotinib, pazopanib, nilotinib, sorafenib, regorafenib)
    - tranilast
- Patients treated with immune- or myelosuppressive therapy during the 8 weeks before study drug assignment (eg, everolimus, sirolimus, rituximab, azathioprine, mycophenolate mofetil, mycophenolic acid, cyclosporine, methotrexate, tacrolimus, chemotherapeutic agents and other anticancer agents, and systemic steroids treatment [except inhaled steroids] for 7 days or more)
- Treated with the following therapies during the 8 weeks before study drug assignment: anabolic hormone, testosterone enanthate or mepitiostane
- History of cardiovascular or cerebrovascular events (eg, unstable angina, myocardial infarction, stroke, pulmonary thromboembolism and ALI) during the 6 months before study drug assignment
- Sustained, poorly controlled arterial hypertension (defined as systolic BP ≥180mmHg or diastolic BP ≥110mmHg) or hypotension (defined as

systolic BP <90mmHg) at study drug assignment

- NYHAclass III or IV congestive heart failure
- Severe hepatic disorder (defined as ALT or AST >3 x the upper limit of normal, total bilirubin >2 mg/dL, or Child-Pugh B or C) at screening
- Previous use of molidustat
- A patient in need of surgery that may be expected to lead to significant blood loss
- Expected need for rescue treatment during the next 7 days after study drug assignment
- Active hepatitis, as assessed by the investigator
- Any medical condition that in the opinion of the investigator may pose a safety risk to a patient in this study, may confound safety or efficacy assessment or may interfere with study participation
- Previous assignment to study treatment during this study
- Previous (during the 30 days before study drug assignment) or concomitant participation in another clinical study with investigational medicinal product(s)
- Close affiliation with the investigational site, for example, a close relative of the investigator, dependent person (eg, employee or student at the investigational site)
- Pregnant or breastfeeding women

MIYABI PD had two additional exclusion criteria

- Previous or concurrent indications for removal of peritoneal dialysis catheter (eg, recurrent peritoneum inflammation, refractory tunnel infection)
- Concomitant use of maintenance dialysis (eg, haemodialysis, haemodiafiltration) other than peritoneal dialysis

ALI, acute limb ischaemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; FSH, follicle-stimulating hormone; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor propyl hydoxylase; IV, intravenous; LLN, lower limit of normal; NYHA, New York Heart Association; PRCA, pure red cell aplasia; RBC, red blood cell; SC, subcutaneous.

Supplementary table 2 Dose titration for molidustat at week 4 for all patients in the MIYABI HD-C trial* and for patients not treated with ESA at study drug assignment in the MIYABI PD trial

Rise in Hb in the first 4 weeks (g/dL)	Hb level (g/dL) in MIYABI HD-C	Hb level (g/dL) in MIYABI PD	Titration step
<0.5	<9.5	<10.5	Increase to the next higher dose
	≥9.5	≥10.5	Maintain the same dose
≥0.5 and <1.0	Any value	Any value	
≥1.0 and ≤2.0	≤10.0	≤11.0	
	>10.0	>11.0	Decrease to the next lower dose
>2.0	Any value	Any value	

*All patients in MIYABI HD-C will not be treated with ESAs at study drug assignment or during the trial.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

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Supplementary table 3 Dose titration from week 8 in MIYABI HD-C, from week 4 or 8 in MIYABI PD*, and from week 2 or 4 in MIYABI HD-M†

Hb level (g/dL) in MIYABI HD-C and MIYABI HD-M	Hb level (g/dL) in MIYABI PD	Titration step
<10.0	<11.0	Increase to the next higher dose
≥10.0 and <12.0	≥11.0 and <12.5	Maintain the same dose
≥12.0 and <13.0	≥12.5 and <13.0	Decrease to the next dose
≥13.0	≥13.0	Suspend a dose until the next scheduled visit

*In MIYABI PD, patients treated with ESAs at study drug assignment will start this dose-titration schedule for molidustat at week 4, whereas patients not treated with ESAs at study drug assignment will start this dose titration schedule for molidustat at week 8.

†In MIYABI HD-M, doses of darbepoetin alfa or darbepoetin alfa placebo will be titrated from week 2, whereas doses of molidustat will be titrated from week 4.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.