# 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.
	+ 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.
	+ 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 ≥80 and <100 g/L (at least two measurements must be taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <12 g/L), 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 ≥5 g/L 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 ≥80 and <110 g/L (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <12 g/L), 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 ≥100 and <130 g/L (based on the last two measurements taken ≥2 days apart, assessed by the central laboratory; the difference between the two measurements must be <12 g/L), 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 ≥5 g/L 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 ≥95 and <120 g/L 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 <12 g/L), 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 >20 mg/L, 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/L)** | **Hb level (g/L)** **in MIYABI HD-C** | **Hb level (g/L)** **in MIYABI PD** | **Titration step** |
| <5 | <95 | <105 | Increase to the next higher dose |
|  | ≥95 | ≥105 |  |
| ≥5 and <10 | Any value | Any value | Maintain the same dose |
| ≥10 and ≤20 | ≤100 | ≤110 |  |
|  | >100 | >110 | Decrease to the next lower dose |
| >20 | 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.

**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/L)** **in MIYABI HD-C and MIYABI HD-M** | **Hb level (g/L)** **in MIYABI PD** | **Titration step** |
| <100 | <110 | Increase to the next higher dose |
| ≥100 and <120 | ≥110 and <125 | Maintain the same dose |
| ≥120 and <130 | ≥125 and <130 | Decrease to the next dose |
| ≥130 | ≥130 | 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.