Supplementary Information

# Supplementary table 1 Exclusion criteria for MIYABI ND-C and MIYABI ND-M

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| ****Medical conditions and history****   1. Any current condition leading to significant blood loss 2. Active haemolysis or diagnosis of haemolytic syndrome 3. Previous or concurrent myelodysplastic syndrome, multiple myeloma, marrow fibrosis or PRCA 4. Previous or concurrent haemosiderosis or haemochromatosis 5. Previous or concurrent hereditary haemoglobinopathies\* 6. **Previous or concurrent aplastic anaemia** 7. **Previous or concurrent chronic lymphoproliferative disorders** 8. **Proliferative choroidal or retinal disease at screening** 9. **Chronic inflammatory disease that is determined to be the principal cause of the anaemia** 10. **Known hypersensitivity to the study drugs (active substances or excipients of the preparations)** 11. **Uncontrolled and symptomatic hyperparathyroidism** 12. **Uncontrolled active infection at randomisation** 13. **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 more than 3 years before randomisation** 14. **Prior or scheduled organ transplantation**† 15. **History of alcohol or drug abuse during the 2 years before randomisation**   ****Excluded and restricted concomitant medication****   1. **RBC-containing transfusion for treatment of anaemia during the 8 weeks before randomisation** 2. **Treatment with UGT1A1 inhibitors**ǂ **during the 7 days before randomisation** 3. **Immunotherapy or myelosuppressive therapy during the 8 weeks before randomisation for 7 days or more** 4. **Treatment with anabolic hormone, testosterone enanthate or mepitiostane during the 8 weeks before randomisation**   ****Cardiovascular****   1. **History of cardiovascular or cerebrovascular events**§ **during the 6 months before randomisation** 2. **Sustained, poorly controlled arterial hypertension (defined as systolic BP ≥180 mmHg or diastolic BP ≥110 mmHg) or hypotension (defined as systolic BP <90 mmHg) at randomisation** 3. **NYHA class III or IV congestive heart failure**   ****Laboratory examinations****   1. **Severe hepatic disorder**¶ **at screening**   ****Other****   1. **Previous use of molidustat** 2. **Necessity for surgery that would be expected to lead to significant blood loss** 3. **Expected need for rescue treatmentǁ during the 7 days after randomisation** 4. **Active hepatitis, as assessed by the investigator** 5. **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 participation in the study** 6. **Previous randomisation to molidustat during this study** 7. **Previous (during the 30 days before randomisation) or concomitant participation in another clinical study with investigational medicinal product(s)** 8. **Close affiliation with the investigational site; for example, a close relative of the investigator, a dependent person (e.g. employee or student of the investigational site)** 9. **Pregnant or breastfeeding women** |

**BP, blood pressure; NYHA**, New York Heart Association; RBC, red blood cell; UGT1A1, uridine-diphosphate-glucuronosyltransferase 1 family, polypeptide A1; **PRCA, pure red cell aplasia.**

\*Including, but not limited to, sickle cell disease, beta thalassemia, and thalassemia major.

†Being on a transplant waiting list is not a reason for exclusion.

ǂIncluding antiretroviral drugs, tyrosine kinase inhibitors and tranilast.

§For example, unstable angina, myocardial infarction, stroke, pulmonary embolism and acute limb ischaemia.

¶Defined as alanine aminotransferase or aspartate aminotransferase more than three times the upper limit of normal, total bilirubin above 20 mg/L or Child–Pugh B or C at screening.

**ǁ**Defined as RBC transfusion due to anaemia associated with a renal disease or any erythropoiesis-stimulating agent treatment started owing to lack of efficacy as judged by the investigator.

# Supplementary table 2 Dose titration of molidustat or darbepoetin alfa at dose adaptation visits in MIYABI ND-C

|  |  |  |
| --- | --- | --- |
| **Rise in haemoglobin level (g/L) from baseline visit** | **Haemoglobin level (g/L)** | **Titration step** |
| <5 | <105 | Increase to the next higher dose |
| ≥105 | Maintain the same dose |
| ≥5 and <10 | Any value |
| ≥10 and ≤20 | ≤110 |
| >110 | Decrease to the next lower dose |
| >20 | Any value |

# Supplementary table 3 Starting dose of molidustat in accordance with the previous erythropoiesis-stimulating agent dose in MIYABI ND-M

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Molidustat starting dose (mg)** | **Previous darbepoetin alfa dose (μg)** | | **Previous epoetin beta pegol dose (μg)** | **Previous epoetin alfa or beta dose (IU)** | |
| **Every 2 weeks** | **Every 4 weeks** | **Every 4 weeks** | **Once a week** | **Every 2 weeks** |
| 25 | ≤15 | ≤30 | 25 | ≤1500 | ≤3000 |
| 50 | >15 | >30 | >25 | >1500 | >3000 |

# Supplementary table 4 Regular dose titration of molidustat or darbepoetin alfa at dose control visits in MIYABI ND-C and MIYABI ND-M

|  |  |
| --- | --- |
| **Haemoglobin level (g/L)** | **Titration step** |
| <110 | Increase to the next higher dose |
| ≥110 and <125 | Maintain the same dose\* |
| ≥125 and <130 | Decrease to the next lower dose |
| ≥130 | Suspend a dose until the next dose control visit |

\*Investigators may decrease to the next lower dose if the haemoglobin level is >120 g/L and the patient has a medical history of previous thromboembolic events (ie, myocardial infarction, pulmonary thromboembolism, stroke excluding haemorrhagic stroke or acute limb ischaemia).