Appendix 4: Characteristics of Included studies for Management of Anaemia in Non-Dialysis dependent chronic kidney disease with Hypoxia-inducible Factor Prolyl Hydroxylase Inhibitors

Sr.No	Study ID Study ID (Trial registry no.)	Objective	Country	Duration of the treatment	Population	Sample size	Erythropoiesis-Stimulating Agent status	Intervention	Comparator
1.	Agrawal 2022 (NR)	To evaluate the efficacy and safety of desidustat against darbepoetin in the treatment of anemia due to CKD without dialysis need.	India and Sri Lanka	26 weeks	Male or female subjects aged 18–80 years with a clinical diagnosis of anemia due to CKD (Stages 3–5) without dialysis need and with a baseline hemoglobin level of 7.0–10.0 g/dL	n= 588	ESA naïve	Desidustat 100 mg oral tablets thrice a week	Darbepoetin alfa 0.75 µg/kg subcutaneous injection once in 2 weeks
2.	Akizawa 2021a (NCT02988973)	To evaluate the efficacy and safety of roxadustat after conversion from recombinant human erythropoietin (rHuEPO) or	Japan	1 Year	Patients aged ⩾20 years old, had been diagnosed with CKD and not	n=263	ESA conditioned	Roxadustat 70 mg TIW to participants on <4500 IU/week of rHuEPO or <20 microgram (µg)/week of darbepoetin	Darbepoetin alfa (DA)

		darbepoetin alfa (DA) to roxadustat, as well as to evaluate the long-term efficacy and safety of roxadustat after conversion from epoetin beta pegol (EBP) to roxadustat, in Japanese NDD CKD patients with anemia of CKD; DA was used as an active comparator.			receiving dialysis			alfa (DA) and 100mg TIW to participants on ⩾4500 IU/week rHuEPO or ⩾ 20 μg/week DA initially plus maintenance dose after 4 weeks	
3.	Akizawa 2021b (JapicCTI-183870)	To evaluate and compare the relative efficacy and safety of enarodustat in Japanese anemic patients with CKD not requiring dialysis with darbepoetin alfa [DA].	Japan	26 weeks	Patients aged ⩾20 years old, diagnosed with CKD and not receiving dialysis	n=216	Both	Enarodustat once daily orally. Initial dose was 2mg/day. From week 4 onward, the dose was adjusted every 4 weeks within the range of 1 to 8 mg/d. During the overall treatment period, the mean prescribed dose	Darbepoetin alfa Subcutaneous administration every 2 or 4 weeks. ESA-naïve patients received 30 mg/2 wks as the initial dose whereas dose and frequency administered to ESA-treated patients were determined based on their prior ESA

								of enarodustat was 2.68 mg/d.	regimen. From week 4 onward, the dose was adjusted in the range of 15 to 180 mg/2 or 4 weeKs
4.	Barrat 2021 (NCT02021318, EudraCT number: 2013-000951-42)	To compare the efficacy, safety and tolerability of roxadustat with darbepoetin alfa (DA) for treatment of anaemia in NDD CKD patients.	Europe	2 Years 4 weeks	Patients aged >18 years with Stages 3–5 CKD who were not receiving dialysis	n=616	ESA naïve	Roxadustat TIW orally,an initial weight-based dose (weight 45.0 to 70.0 kg, roxadustat 70 mg; weight >70.0 to 160.0 kg, roxadustat 100 mg) plus maintenance dose after 4 weeks	Darbepoetin alfa
5.	Chertow 2021 (NCT02648347)	To compare vadadustat with the erythropoiesis-stimulating agent (ESA) darbepoetin alfa in patients with non–dialysis-dependent chronic kidney disease (NDD-CKD)	Argentina, Australia, Brazil, Bulgaria, France, Hungary, Israel, Italy, Korea, Republic of, Malaysia, Mexico, New Zealand,	1 Year 5 weeks	Adults (⩾ 18 years old) with diagnosis of CKD not expected to start dialysis <6 months before screening	n=1751	Both	Vadadustat 300 mg orally once daily, with doses of 150 mg, 450 mg, and 600 mg available for adjustment to a maximum dose of 600 mg daily	Darbepoetin alfa administered subcutaneously or intravenously. initial dose of darbepoetin alfa was based on the patient's previous dose of darbepoetin

		not previously treated with an ESA who had a hemoglobin concentration of less than 10 g per deciliter	Poland, Puerto Rico, Russian Federation, South Africa, Spain, Ukraine, United Kingdom, United States						alfa or on the local product label for patients who had not been receiving darbepoetin alfa before randomization.
6.	Holdstock 2019 (NCT01977573)	To assess the short-term safety and efficacy of daprodustat (an oral hypoxia-inducible factor-prolyl hydroxylase inhibitor) to achieve a target hemoglobin in patients with anemia of chronic kidney disease (CKD)	Australia, Canada, Czechia, Denmark, France, Germany, Hungary, Japan, Korea, Republic of, Poland, Russian Federation, Spain, Sweden, United Kingdom, United States	28 weeks	Patients with anemia associated with chronic kidney disease (CKD) who were not on dialysis and >18 years of age.	n=252	Both	Daprodustat rhEPO naïve- Orally once-daily; 1, 2 or 4mg; rhEPO users- Orally once-daily; 2mg; Pooled daprodustat	rhEPO (epoetins or their biosimilars or darbepoetin)
7.	Macdougall 2019a (NCT02021409)	To assess the safety and efficacy of molidustat in the treatment of anemia associated	European Union, Israel, South Korea,	28 weeks	Men and women (aged ⩾18 yr) with a	n=124	ESA conditioned	Molidustat Total; Fixed starting dose of 25 mg; 50 mg; 75 mg of	Darbepoetin intravenous or subcutaneous administered according to

		with CKD in different populations: treatment naïve and previously ESA-treated patients not on dialysis, and previously ESA-treated patients on hemodialysis.	Australia, and Japan		diagnosis of anemia of CKD but not on dialysis			Molidustat oral tablet (once daily dose) titrated at the scheduled dose control visits. Titration occuring every 4-weeks will be based on the subject's hemoglobin (Hb) response and tolerability of the prior dose. Total treatment time is 16 weeks. Planned doses include 15, 25, 50, 75, 100, and 150 mg once daily.	the local label and titrated at the scheduled dose control visits. Titration will be based on the subject's Hb response and tolerability of the prior dose
8.	Nangaku 2021a (NCT03329196)	To evaluate the efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese patients with anemia in NDD-CKD, with and without a recent history of ESA	Japan	1 Year 2 weeks	Patients aged >20 years with CKD who were not on dialysis	n=304	Both	Vadadustat Oral; 300 mg once daily and doses were adjusted (dose range: 150–600 mg once daily)	Darbepoetin Alfa subcutaneous; ESA user: according to prior ESA. ESA non-user: 30 mg once every 2 weeks in ESA non–users. Doses of darbepoetin

		treatment, for up to 52 weeks.							alfa were adjusted between 15 and 180 mg once every 4 weeks, every 2 weeks, or weekly. The dose-increase interval of darbepoetin alfa was to be ⩾2 weeks.
9.	Nangaku 2021b (NCT02791763)	To test the hypothesis that daprodustat is noninferior to epoetin beta pegol (continuous erythropoietin receptor activator [CERA], also known as methoxy polyethylene glycol-epoetin beta) in maintaining hemoglobin levels in Japanese ND patients with anemia of CKD.	Japan	1 Year	Patients aged ⩾20 years and CKD Stages G3, G4, and G5	n=299	Both	Daprodustat; Total; 2 or 4 mg once daily depending on baseline hemoglobin. From week 4 onward, daprodustat dose was titrated every 4 weeks within the range of 1–24 mg according to a prespecified dose adjustment algorithm	Epoetin Beta Pegol; CERA was started at 25 µg every 2 weeks for ESA-naïve patients and 25–250 µg every 4 weeks for ESA users based on previous ESA dose. From week 4 onward, dose adjustments were made every 4 weeks according to a prespecified algorithm

10.	Singh 2021 (NCT02876835)	To compare the efficacy and safety of daprodustat with the conventional ESA darbepoetin alfa in patients with CKD who were not undergoing dialysis	39 countries - Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Rupblic of Korea, Malysia, Mexico, Netherlands, New Zealand, Philippines, Poland, Portugal, Romania, Russian Federation, Singapore, South Africa, Spain, Sweden,	1 Year 6 weeks	Age: 18 to ⩽99 years of age CKD stages 3, 4, or 5 (at screening)	n=3872	Both	Daprodustat starting dose was between 1 and 4 mg daily; stepped changes ranging from 1 to 24 mg were available for dose adjustments.	Darbepoetin alpha; starting dose was determined based on weight and baseline Hgb

			Taiwan (Province of China), Thailand, Turkey, Ukraine, United Kingdom, United States, Vietnam						
11.	Yamamoto 2021a (NCT03350347)	To investigate the safety and efficacy of molidustat in Japanese patients with renal anemia not undergoing dialysis and previously treated with ESAs	Japan	1 Year 4 weeks	Men and women aged 20 years or older with a diagnosis of renal anemia who were not undergoing dialysis and who were treated with ESAs	n=164	ESA conditioned	Molidustat was administered orally once daily at a starting dose of 25 mg or 50 mg in accordance with the previous ESA dose. titrated based on the subject's Hb response	Darbepoetin alpha; patients who were previously treated with epoetin alfa or beta, a cut-off value of 1,500 IU/ week was used according to the darbepoetin label. Darbepoetin was injected subcutaneously at a starting dose in accordance with the previous ESA dose and given once every 2 weeks (Q2W)

									or once every 4 weeks (Q4W).
12.	Yamamoto 2021b (NCT03350321)	To investigate the efficacy and safety of molidustat in Japanese patients with renal anaemia who were not undergoing dialysis and were not receiving erythropoiesis-stimulating agent (ESA) treatment	Japan	1 Year 4 weeks	Patients aged ⩾20 years at screening, CKD stage 3–5, not undergoing dialysis and not expected to start undergoing dialysis during the study period.	n=162	ESA naïve	Molidustat orally once daily after breakfast at a starting dose of 25 mg for the first 4 weeks of the study	Darbepoetin was injected subcutaneously every 2 weeks at a starting dose of 30 μg; titrations were initially scheduled every 2 weeks during the treatment period, but the frequency changed to every 4 weeks once Hb levels were stabilised within the target range