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

S.no.	Study ID (Trial registry no.)	Objective	Country	Duration of the treatment	Population	Sample size	Erythropoiesis-Stimulating Agent status	Type of Dialysis	Frequency of dialysis	Intervention	Comparator
1.	Akizawa 2020a (NCT02952092)	To evaluate the non-inferiority of roxadustat to DA when both drugs are titrated to maintain Hb levels of 10–12 g/dl in Japanese CKD patients with renal anemia on Haemodialysis (HD)	Japan	24 weeks	Patients aged ⩾20 years with CKD anemia. Hb levels within 10–12 g/dl, and transferrin saturation (TSAT) ⩾ 20% or serum ferritin ⩾ 100 ng/ml	n=303	ESA conditioned	Haemodialysis	Not reported	Roxadustat, 70 mg or 100 mg orally three time weekly	Darbepoetin Alfa, injections once weekly
2.	Akizawa 2020b (NCT02969655)	To evaluate the efficacy (noninferiority) and safety of	Japan	1 year 2 weeks	Patients aged ⩾ 20 years.	n=271	ESA conditioned	Haemodialysis	Not reported	Daprodustat, orally once daily	Darbepoetin alfa, intravenous once weekly

		daprodustat compared with darbepoetin alfa for 52 weeks in Japanese patients on Haemodialysis with anemia of CKD currently treated with ESAs			Hemoglobin levels 9.5 to 12.5 g/dl, and ferritin >100 ng/ml or transferrin saturation (TSAT) >20% at screening						
3.	Akizawa 2021a (JapicCTI-183938)	To compare the efficacy and safety of enarodustat with darbepoetin alfa (DA) in Japanese anemic patients with CKD receiving maintenance	Japan	26 weeks	Patients aged ⩾20 years, had transferrin saturation (TSAT) >20% or ferritin >75 ng/mL at Screening visit 1, and had Hb levels 9.5–12.0 g/dL	n= 173	ESA conditioned	Haemodialysis	Not reported	Enarodustat, orally once daily	Darbepoetin Alfa, injection(s) weekly and once-daily oral placebo tablet(s)

		Haemodialysis.									
4.	Akizawa 2021b (NCT03543657)	To compare the efficacy and safety of molidustat and an ESA (darbepoetin alfa [darbepoetin]) for the maintenance treatment of renal anemia in Japanese patients receiving dialysis and who were previously treated with ESAs	Japan	1 year 4 weeks	Adults (aged ⩾20 years) with end-stage kidney disease who received dialysis at least weekly for ⩾12 weeks. Mean Hb levels of ⩾ 9.5 and <12.0 g/dl (with a difference between the lowest and highest measured level of <1.2 g/dl), and either ferritin levels ⩾100 ng/ml or transferrin saturation ⩾20% at screening	n= 229	ESA conditioned	Haemodialysis	Not reported	Molidustat, orally once daily	Darbepoetin Alfa, intravenous injection weekly or once every 2 weeks

5.	Charytan 2021 (NCT02273726)	To evaluate the efficacy and safety of roxadustat for the treatment of anemia in patients with DD-CKD	United States	1 year	Patients (⩾ 18 years) had ESKD and were on dialysis for ⩾183 months before screening	n=741	ESA conditioned	Haemodialysis and peritoneal dialysis	Prevalent and incident dialysis	Roxadustat oral thrice weekly (TIW)	Epoetin alfa parenteral thrice weekly (TIW)
6.	Chen 2017 (NCT01596855)	To explore the safety and efficacy of FG-4592 (USAN name: roxadustat, CDAN name), a HIF-PHI, in patients with anemia of chronic kidney disease (CKD), both patients who were dialysis-dependent	China	6 weeks	Subjects on Haemodialysis whose mean Hb in three screening tests was between 9.0 and 12.0 g/dL, who received stable doses of epoetin alfa (administered IV or subcutaneously) during the 7 weeks prior to randomization	n=87	ESA conditioned	Haemodialysis	Not reported	Roxadustat, 1.1–1.8mg/kg (low), 1.5–2.3mg/kg (medium) and 1.7–2.3mg/kg (high) per dose thrice weekly TIW on dialysis days	Epoetin alfa, Intravenously (IV) or subcutaneously > or ⩽ 6000 IU/week TIW on dialysis days

		(DD) and patients who were not dialysis-dependent (NDD)									
7.	Chen 2019 (NCT02652806)	To evaluate the efficacy and safety of roxadustat for the treatment of anemia in patients undergoing dialysis in China	China	27 weeks	Patients, 18 to 75 years of age, had end-stage kidney disease, and had a mean hemoglobin value (from the last two screening assessments) of 9.0 to 12.0 g per deciliter.	n=305	ESA conditioned	Haemodialysis and peritoneal dialysis	Not reported	Roxadustat, orally three times per week	Epoetin alfa, parenteral three times per week
8.	Coyne 2022 (2017-004372-56 (EudraCT Number); NCT03400033)	To compare the effect of daprodustat to epoetin alfa on Hgb efficacy when administered three-	Argentina, Australia, Brazil, Canada, France, Italy, Republic of Korea, Poland, Romania,	1 year 6 weeks	Male and female subjects patients on Haemodialysis with a baseline hemoglobin of 8–11.5 g/dl	n=407	ESA conditioned	Haemodialysis	Not reported	Daprodust, orally three times weekly and intravenous saline	Epoetin alfa , intravenous once weekly or three times weekly

		times weekly to Haemodialysis-dependent participants (noninferiority)	Russian Federation, Spain, United Kingdom, United States		receiving an ESA						
9.	Csiky 2021 (EudraCT number 2013-001497-16; NCT02278341)	To evaluate the efficacy and safety of roxadustat compared with ESA (epoetin alfa or DA) in the maintenance treatment of anemia in patients with end-stage kidney disease (ESKD) on stable (prevalent) dialysis for at least 4	Europe - Bulgaria Hungary Russian Federation Serbia Croatia Romania Italy Poland Spain Germany Slovakia Portugal Belgium	2 years 4 weeks	Patients aged 18 years; had mean Hb values within 9.5–12.0 g/dL, with an absolute difference no greater than 1.3 g/dL between the highest and the lowest value during the screening period; and were iron replete (ferritin ⩾ 100 ng/mL	n=838	ESA conditioned	Haemodialysis and peritoneal dialysis	Prevalent dialysis	Roxadustat 20,50,100 mg orally three times per week	Epoetin alfa or darbepoetin alfa, SC or IV once weekly, twice weekly, or TIW for epoetin alfa, and once weekly or once every other week for darbepoetin alfa

		months who were receiving stable doses of either epoetin alfa or DA for the treatment of anemia.			and transferrin saturation [TSAT] ⩾ 20% at screening).						
10.	Eckardt 2021 (NCT02865850)	To evaluate the safety and efficacy of vadadustat, as compared with darbepoetin alfa, in patients with anemia and incident or prevalent dialysis-dependent chronic kidney disease (DD-CKD)	Argentina, Brazil, Germany, Italy, Republic of Korea, Mexico, Poland, Portugal, Russian Federation, Ukraine, United States	1 year 5 weeks	Patients at least 18 years of age, had CKD, had a serum ferritin concentration of at least 100 ng per milliliter and a transferrin saturation of at least 20%, and had not received a red-cell transfusion within the	n=369	Both ESA naïve and conditioned	Haemodialysis and peritoneal dialysis	Prevalent and incident dialysis	Vadadustat, 300 mg orally once daily, with doses of 150, 450, and 600 mg available for adjustment of the dose to a maximum of 600 mg daily.	Darbepoetin alfa, subcutaneously or intravenously

					previous 8 weeks						
11.	Fishbane 2022 (NCT02174731)	To assess the efficacy of roxadustat compared with epoetin alfa in 2133 patients with anemia of CKD on dialysis.	Australia, Bulgaria, Canada, Czechia, Hungary, India, Mexico, Peru, Philippines, Poland, Russian Federation, Slovakia, Spain, Sweden, Thailand, Ukraine, United States, Vietnam	4 years	Patients aged ⩾18 years, hemoglobin (Hb) <10 g/dl if ESA-untreated or Hb <12 g/dl	n=2133	Both ESA naïve and conditioned	Haemodialysis and peritoneal dialysis	Prevalent and incident dialysis	Roxadustat, orally three times weekly (TIW)	Epoetin alfa, parenteral
12.	Gang 2022 (CTRI/2019/12/022312)	To evaluate the efficacy and safety of desidustat against epoetin alfa in the	38 centres in India	26 weeks	Males or females aged ⩾18 years; clinical diagnosis of anemia due to CKD	n=392	Both ESA naïve and conditioned	Haemodialysis	Not reported	Desidustat, oral tablet ESA naïve patients, the initial dose of desidustat	Epoetin alfa subcutaneous injection. For ESA naïve patients the initial dose of epoetin alfa

		treatment of anemia due to CKD with a need of dialysis			(stage 5) on dialysis (⩾2 times in a week) for at least 12 weeks prior to screening; baseline hemoglobin level of 8.0–11.0 g/dL (inclusive); serum ferritin >200 ng/mL and/or transferrin saturation (TSAT) >20% ; no iron, folate, or vitamin B12 deficiency.					was 100 mg thrice a week; For ESA users, the initial dose of desidustat (100 mg/125 mg/150 mg)	was 50 IU/kg, thrice a week
13.	Holdstock 2016 (NCT01587924)	To assess the hemoglobin dose response, safety, and tolerability of a 4-week administrat	United States, Canada, Germany, Denmark, Norway, and Sweden	6 weeks	Patients aged >/=18 years of age, had stable hemoglobin concentrations between 9.5	n=83	ESA conditioned	Haemodialysis	Not reported	Daprodustat, 0.5 mg, 2mg, or 5mg orally once daily	Recombinant human erythropoietin (rhEPO)

		ion of GSK1278863, including a study in anemic patients with CKD who were not dialysis dependent and were not currently receiving rhEPO (nondialysis study) and a study in patients who were on Haemodialysis and were treated with stable doses of rhEPO (HDD study).			and 12.0 g/dl during the 2-week run-in period						
14.	Hou 2022 (ChiCTR2000035054)	To investigate the efficacy	China	26 weeks	Patients diagnosed with CKD	n=129	Both ESA naïve and	Peritoneal dialysis	Not reported	Roxadustat, orally 100 mg for	erythropoiesis-stimulating agents

		and safety of roxadustat in Chinese patients with anemia on peritoneal dialysis (PD).			and renal anemia who received PD were included. Moreover, their Hb values during the screening period had to be < 12 g/dL. Patients who were undergoing Haemodialysis or were intended to change dialysis modality at the time of the study were excluded		conditioned			patients weighing 45 to <60 kg and 120 mg for patients weighing ⩾60 kg	(ESAs), subcutaneous, Pre randomization doses
15.	Macdougall 2019 (NCT01975818)	To evaluate the efficacy, safety, and tolerability of molidustat	Japan, United States	20 weeks	Men and women (aged ⩾18 yr) with a diagnosis of anemia of CKD	n=199	ESA conditioned	Haemodialysis	Not reported	Molidustat, doses 25, 50, 75, or 150 mg and plus optional 15, 100,	Epoetin alfa/beta, subcutaneously or intravenously three times per week

		compared with placebo or alternative ESA therapy in patients with anemia of CKD.								200 mg once daily	
16.	Nangaku 2021 (NCT03439137)	To evaluate the efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese Haemodialysis patients receiving ESA therapy.	Japan	1 year 2 weeks	Subjects at least 20 years of age diagnosed with CKD and had a mean Hb level of ⩾ 9.5 to ⩽ 12.0 g/dL, a serum ferritin level of ⩾ 100 ng/mL or a transferrin saturation (TSAT) of ⩾ 20%	n=323	ESA conditioned	Haemodialysis	Not reported	Vadadustat, 300 mg once daily, and the dose was adjusted to 150–600 mg	Darbepoetin alfa, 15–60 µg once weekly or biweekly

17.	Provenzano 2016 (NCT01147666)	To demonstrate roxadustat's efficacy in maintaining Hb levels when converting from an ESA and to establish the optimum starting dose and dose adjustment regimen to maintain target Hb values	United States	23 weeks	Patients aged 18 to 75 years and receiving maintenance Haemodialysis thrice weekly for 4 or more months. Hb levels were 9.0 to 13.5 g/dL for 8 weeks, and patients had stable epoetin alfa dosages ⩽ 450 U/kg/wk for 4 weeks prior to randomization	n=144	ESA conditioned	Haemodialysis	Not reported	Roxadustat, 1.0, 1.5, 1.8, or 2.0 mg/kg orally thrice weekly	Epoetin alfa
18.	Provenzano 2021 (NCT02052310)	To evaluate the efficacy and safety of roxadustat versus epoetin	Argentina, Bulgaria, Chile, Colombia, Korea, Republic of Latvia,	1 year 6 weeks	Patients were aged ⩾18 years and were on Haemodialysis or peritoneal	n=1043	ESA naïve	Haemodialysis and peritoneal dialysis	Incident dialysis	Roxadustat, 70 mg (patients weighing ⩽70 kg) or 100 mg (patients	Epoetin alfa parenteral thrice weekly

		alfa for the treatment of chronic kidney disease-related anemia in patients new to dialysis.	Malaysia, Mexico, Poland, Romania, Russian Federation, Taiwan, Thailand, Ukraine, United States		dialysis for ESRD for 2 weeks to ⩽4 months prior to randomization. Mean Hb level (from the last two pre-dialysis screening assessments) was ⩽ 10.0 g/dL					weighing > 70–160 kg)	
19.	Singh 2021 (NCT02879305; 2016-000541-31 (EudraCT Number)	To examine the hematologic efficacy, cardiovascular safety, and iron kinetics of the oral HIF-PHI daprodustat as compared with conventional therapy with ESAs.	Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czechia, Denmark, Estonia, France, Germany, Greece, Hungary, India, Italy, Republic	1 year	Adults with CKD who had been undergoing dialysis for at least 90 days, had received an ESA for at least 6 weeks, and who had a hemoglobin level between 8.0 and 12.0 g per deciliter were	n=2964	ESA conditioned	Haemodialysis and peritoneal dialysis	prevalent dialysis	Daprodustat, 4 and 12 mg daily	Erythropoiesis-stimulating agents (ESAs)

			of Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Russian Federation, Singapore, South Africa, Spain, Sweden, Taiwan, Turkey, Ukraine, United Kingdom, United States		eligible for screening						
20.	Singh 2022 (NCT03029208; EudraCT Number: 2016-000507-86)	To evaluate the efficacy and safety of daprodustat vs	Argentina, Australia, Canada, Germany, India,	1 year 6 weeks	Patients with advanced CKD planned to start dialysis	n=312	ESA naïve	Haemodialysis and peritoneal dialysis	Incident dialysis	Daprodustat, oral 1 mg, 2 mg, or 4 mg a day depending	Darbepoetin alfa, subcutaneously (Peritoneal Dialysis) or

		darbepoetin alfa for 52 weeks in incident dialysis patients.	Italy, Republic of Korea, Malaysia, Mexico, Poland, Russian Federation, South Africa, Spain, United Kingdom, United States		within 6 weeks from the screening visit or had recently initiated it (started and received HD or PD within 90 days before randomization), had a screening blood Hb concentration of 8.0 to 10.5 g/dL					on Hb level as starting dose	Intravenous (Haemodialysis) 40 or 60 µg every 2 or 4 weeks